

**EDITORIAL BOARD**
**Editor-in-chief**

Carlos V. Serrano Jr.

**Co-editors**

 José Maria Soares Jr.  
 Wanderley M. Bernardo

**Administrative Co-editor**

Paula Jereissati

**Managing Editor**

César Teixeira

**Associated Editors**

 Albert Bousso  
 Anna Andrei  
 Auro Del Giglio  
 Daniel Deheinzelin  
 Edna Frasson de S. Montero  
 Eduardo F. Borba  
 Elias Jirjoss Ilias  
 Isabela Giuliano  
 José Maria Soares Jr.  
 José Mendes Aldrighi

**Lucia Pellanda**

 Nilson Roberto de Melo  
 Paulo Caramelli  
 Paulo Kassab  
 Rossana Pulcineli V. Francisco  
 Seizo Miyadahira  
 Werther Bruno W. de Carvalho

**International Editors**

 Andre D'Avila  
 Dimas Ikeoka

**Frida Leonetti**

 Geltrude Mingrone  
 Giuseppe Barbaro  
 Marcelo Marotti  
 Ruy Jorge Cruz Junior  
 Walter Ageno

**Junior Editor**

Gabriel Liguori

**ADVISORY BOARD**

 Alexandre Biasi Cavalcanti  
 Alvaro Atalah  
 Álvaro Petracco  
 Angelita Habr Gama  
 Anoi Castro Cordeiro  
 Antonio José Gonçalves  
 Carlos A. Cardim de Oliveira  
 Carlos Alberto Malheiros  
 Claudio Cohen  
 Cristina Muccioli  
 Davi Rumel  
 Décio Mion  
 Décio Matos  
 Durval Damiani

 Edmundo M. Ferraz  
 Eduardo de Souza  
 Eduardo Weltman  
 Emmanuel A. Burdmann  
 Gilberto Schwartzmann  
 Hillegonda M. Durithl Novaes  
 Ivan Ceconello  
 José Eduardo de Siqueira  
 Júlio Coelho  
 Luana Carandina  
 Luís Bahamondes  
 Luís Paulo Kowalski  
 Marcelo Gurgel C. da Silva  
 Márcia R. Pinho Makdisse

 Marco A. Borges Lopes  
 Marcos Roberto Tavares  
 Maria de Lourdes Brizot  
 Maurício Abrão  
 Milton A. Martins  
 Nilton Hideto Takiuti  
 Paulo A. Carvalho Fortes  
 Paulo Veiga Jardim  
 Pedro Luis Squilacci Leme  
 Pedro Paulo Pereira  
 Pedro Puech Leão  
 Raymundo S. Azevedo  
 Roberto Eduardo Bittar  
 Rodrigo Ruano

 Rogério Souza  
 Rolf Gemperli  
 Rosana P. V. Francisco  
 Roseane Mattar  
 Sérgio Nishioka  
 Sonia Mansoldo Dainesi  
 Valdir Golin  
 Victor Bunduki  
 Volnei Garrafa  
 Wagner Weidebach

**BRAZILIAN MEDICAL ASSOCIATION – MANAGEMENT BOARD – YEARS 2014-2017**
**President**

 Florentino de Araújo  
 Cardoso Filho

**Petrônio Andrade Gomes**

 José Luiz Weffort  
 Eduardo da Silva Vaz

**1<sup>st</sup> Vice-president**

Eleuses Vieira de Paiva

**Jurandir Marcondes**

Ribas Filho

**2<sup>nd</sup> Vice-president**

Lincoln Lopes Ferreira

**Aguiel José Bastian Junior**
**General Secretary**

Antônio Jorge Salomão

**Vice-presidents**

 Lairson Vilar Rabelo  
 Eduardo Francisco  
 de Assis Braga  
 Cléa Nazaré Carneiro Bichara  
 Salustiano José Alves  
 de Moura Junior  
 Álvaro Roberto Barros Costa

**1<sup>st</sup> Secretary**

Aldemir Humberto Soares

**1<sup>st</sup> Treasurer**

José Luiz Bonamigo Filho

**2<sup>nd</sup> Treasurer**

Miguel Roberto Jorge

**Directors**

 Giovanni Guido Cerri  
 (Scientific)

 Antonio Carlos Vieira Lopes  
 (DAP)

 Jane Maria Cordeiro Lemos  
 (Cultural)

 Emilio Cesar Zilli  
 (Professional Defense)

 Nívio Lemos Moreira Junior  
 (International Relations)

 Rafael Klee de Vasconcelos  
 (Medical Economics)

 Jorge Carlos Machado Curi  
 (Public Health)

 Diogo Leite Sampaio  
 (Communications)

 Edmund Chada Baracat  
 (Academic)

 Antonio Carlos Weston  
 (Member's Helpline)

 Márcio Silva Fortini  
 (Patient Protects)

 Carmelo Silveira Carneiro  
 Leão Filho (Marketing)

 José Luiz Dantas Mestrinho  
 (Parliamentary Affairs)



## **Brazilian Medical Association**

Address: Rua São Carlos do Pinhal, 324  
Bela Vista – São Paulo  
Postal Code: 01333-903  
Phone: (11) 3178-6800

**Editor-in-chief:** Carlos V. Serrano Jr.

**Managing Editor:** César Teixeira

**e-mail:** ramb@amb.org.br

**website:** www.ramb.org.br

The norms for publication are available on the website [www.ramb.org.br](http://www.ramb.org.br)



The Journal of the Brazilian Medical Association is affiliated to the ANATEC and indexed in Medline, SciELO, Science Citation Index Expanded, Journal Citation Reports, Index Copernicus, Lilacs, and Qualis B2 Capes databases, and licensed by Creative Commons®. Registered in the 1<sup>st</sup> Office of Registration of Deeds and Documents of São Paulo under n. 1.083, Book B, n. 2.

The Journal of the Brazilian Medical Association is an official publication of the Brazilian Medical Association (AMB), distributed exclusively to the medical community in Brazil and Latin America.

All rights reserved and protected by Law n. 9.610 – 2/19/1998. No part of this publication may be reproduced without prior written authorization of the AMB, whatever the means employed: electronic, mechanical, photocopying, recording or other.

## **Manole Publisher**

**Authorizing Editor:** Walter Luiz Coutinho

**Editor:** Karin Gutz Inglez

**Publishing production:** Juliana Penna, Fernanda Quinta, Juliana Morais e Cristiana Gonzaga S. Corrêa

**English version:** Graziella Risolia Gallo

**Cover:** Rafael Zemantauskas

**Graphic design and layout:** Sopros Design



**Manole**

The advertisements and opinions published in the *Ramb* are the sole responsibility of the advertisers and authors.

The AMB and Manole Publisher are not responsible for its content.

## SECTIONS

### EDITORIAL

#### Ramb: new pathways

CARLOS V. SERRANO JR..... 501

### HOMAGE

#### Adib Jatene, an immense legacy to Brazilian medicine

CÉSAR TEIXEIRA..... 502

### ACCREDITATION

#### Update on degenerative spondylolisthesis: surgical treatment

BERNARDO WM, BOTELHO RV, FONI NO, GOTFRYD AO, HERRERO CFPS, JEFFERSON D, MEVES R, MUDO ML, SIMÕES RS, ZYLBERSZTEIN S..... 505

#### Update on late-onset hypogonadism (LOH) or ADAM: treatment

BERNARDO WM, MARTINS AM, COSTA EMF, NARDI AC, NARDOZZA JR A, FACIO JR FN, FARIA G..... 506

### GUIDELINES IN FOCUS

#### Treatment with intensity-modulated radiation therapy (IMRT) for breast cancer

MARTA GN, HANNA SA, GADIA R..... 508

#### Stress fractures in the foot and ankle of athletes

ASANO LYJ, DUARTE JR. A, SILVA APS..... 512

### IMAGE IN MEDICINE

#### Giant sclerosing papilloma mimicking locally advanced breast carcinoma

RENÉ ALOISIO DA COSTA VIEIRA, SILVIA MARIA PRIOLI DE SOUZA SABINO, GUSTAVO ZUCCA MATTHES, ANAPÁULA HIDEMI UEMA WATANABE, LUCAS FARIA ABRAHÃO-MACHADO..... 518

### POINT OF VIEW

#### Bioethical conflicts of gene therapy: a brief critical review

JOSÉ EDNÉSIO DA CRUZ FREIRE, SUELEN CARNEIRO DE MEDEIROS, ANTÔNIO VIANA LOPES NETO, JOSÉ EDVAR MONTEIRO JÚNIOR, ANTÔNIO JUSCELINO SUDÁRIO SOUSA, ANTÔNIO JOSÉ ROCHA, LÉA MARIA BEZERRA DE MENEZES ..... 520

## ORIGINAL ARTICLES

#### Common mental disorders and associated factors among final-year healthcare students

EDMÉA FONTES DE OLIVA COSTA, MARGLEICE MARINHO VIEIRA ROCHA, ANA TERESA RODRIGUES DE ABREU SANTOS, ENALDO VIEIRA DE MELO, LUIZ ANTONIO NOGUEIRA MARTINS, TARCISIO MATOS ANDRADE ..... 525

#### Estimated glomerular filtration rate in patients with type 2 *diabetes mellitus*

PAULA CAITANO FONTELA, ELIANE ROSELI WINKELMANN, JOICE NEDEL OTT, DOUGLAS PRESTES UGGERI ..... 531

#### Doppler flowmetry of ophthalmic arteries for prediction of pre-eclampsia

LARISSA OLIVEIRA DE AQUINO, HENRIQUE VÍTOR LEITE, ANTÔNIO CARLOS VIEIRA CABRAL, AUGUSTO HENRIQUES F. BRANDÃO ..... 538

#### Profile and scientific production of the Brazilian Council for Scientific and Technological Development (CNPq) researchers in the field of Hematology/Oncology

MARIA CHRISTINA LOPES ARAUJO OLIVEIRA, DANIELLA REIS MARTELLI, ISABEL GOMES QUIRINO, ENRICO ANTÔNIO COLOSIMO, ANA CRISTINA SIMÕES E SILVA, HERCÍLIO MARTELLI JÚNIOR, EDUARDO ARAUJO DE OLIVEIRA..... 542

#### Single-site laparoscopy in gynecology: preliminary study of a series of 50 cases

ADMÁRIO SILVA SANTOS FILHO, MAURÍCIO BECHARA NOVIELLO, RACHEL CRUZ FRAGA DAMASCENO, EVILANE DO CARMO PATRÍCIO, LARA RODRIGUES FÉLIX, PAOLA GASTON GIOSTRI, AUGUSTO HENRIQUES F. BRANDÃO ..... 548

<b>Intake of antioxidants in patients with rheumatoid arthritis</b>	
BRUNA NOLASCO SIQUEIRA SILVA, ÍSIS LUCÍLIA SANTOS BORGES DE ARAÚJO, PEDRITA MIRELLA ALBUQUERQUE QUEIROZ, ANGELA LUZIA BRANCO PINTO DUARTE, MARIA GORETTI PESSOA DE ARAÚJO BURGOS.....	<b>555</b>
<b>Endometriosis is an important cause of pelvic pain in adolescence</b>	
MARINA DE PAULA ANDRES, SERGIO PODGAEC, KARINA BELICKAS CARREIRO, EDMUND CHADA BARACAT .....	<b>560</b>
<b>Space-time description of dengue outbreaks in Cruzeiro, São Paulo, in 2006 and 2011</b>	
RENATA MARZZANO DE CARVALHO, LUIZ FERNANDO COSTA NASCIMENTO .....	<b>565</b>
<b>Surgical treatment of clinically early-stage endometrial carcinoma without systematic lymphadenectomy</b>	
ARTUR LÍCIO ROCHA BEZERRA, THALES PAULO BATISTA, MÁRIO RINO MARTINS, VANDRÉ CABRAL GOMES CARNEIRO.....	<b>571</b>
<b>Psychogenic non-epileptic seizures and psychoanalytical treatment: results</b>	
NIRALDO DE OLIVEIRA SANTOS, GLÁUCIA ROSANA GUERRA BENUTE, ALESSANDRA SANTIAGO, PAULO EURÍPEDES MARCHIORI, MARA CRISTINA SOUZA DE LUCIA.....	<b>577</b>
<b>Intrauterine growth restriction in monochorionic-diamniotic twins</b>	
RITA DE CÁSSIA ALAM MACHADO, MARIA DE LOURDES BRIZOT, SEIZO MIYADAHIRA, ROSSANA PULCINELI VIEIRA FRANCISCO, VERA LÚCIA JORNADA KREBS, MARCELO ZUGAIB.....	<b>585</b>
<b>Distortion-product otoacoustic emission growth curves in neonates</b>	
TANIA ALVES BARBOSA, ALESSANDRA SPADA DURANTE, LÍDIO GRANATO .....	<b>591</b>

## **REVIEW ARTICLE**

<b>Diagnostic accuracy of respiratory diseases in primary health units</b>	
BRUNO PIASSI DE SÃO JOSÉ, PAULO AUGUSTO MOREIRA CAMARGOS, ÁLVARO AUGUSTO SOUZA DA CRUZ FILHO, RICARDO DE AMORIM CORRÊA .....	<b>599</b>

## Ramb: new pathways

### RAMB: NOVOS CAMINHOS

<http://dx.doi.org/10.1590/1806-9282.60.06.001>

The Brazilian Medical Association, understanding that the *Journal of the Brazilian Medical Association (Ramb)* should follow the worldwide trend among scientific periodicals, decided that, from 2015 on, the journal will be published in online format only.

To do so, the Board is taking measures to optimize the journal's website ([www.amb.org.br](http://www.amb.org.br)), aiming at modernizing it and making it more functional. Thus, in addition to submissions and follow-up of articles, which were already done through the website, starting next year, the editions will also include articles and sections presented in online format.

The *Ramb* website will provide immediate access to the latest journal issue finalized in PDF format, as well as previous volumes that will be available through the SciELO link. This link offers all the printed volumes since 1997, when the magazine was still quarterly, having been transformed into a bimonthly journal in 2004.

The submission process will not change: articles will only be submitted through the [www.amb.org.br](http://www.amb.org.br) page. After prior approval, they will be forwarded to peer review. Approved articles will follow the usual path for publication, that is, according to the order of submission. The process adopted for the printed format will continue so that, before the magazine is published online, the authors will receive a PDF of the article for review.

We also emphasize that this change is part of an editorial improvement process, in order to raise the journal's impact factor. On July 29 this year, Thomson Reuters released through its ISI Web Knowledge portal, the 2014 Journal Citation Reports (JCR) list with impact indicators for 2013 based on citation data statistics. *Ramb* is growing every year and, at present, has an impact factor of 0.915, above the 0.771 received in the previous classification.

This change will not affect the indexing of our journal, properly inserted in the most prestigious national and international databases. In addition to the previously cited JCR, it is indexed to other databases, including: SciELO, SCImago (SJR), Elsevier's Scopus, Lilacs, PubMed (Medline), Science Citation Index Expanded (ISI Web of Knowledge), Scopus, Qualis/Capes – B2.

We hope we can continue to count on the valuable collaboration of all those involved in this process in order to strengthen the *Journal of the Brazilian Medical Association*, which has a long, established and reputable history among Brazilian scientific publications, and is published continuously since 1954.

**Carlos V. Serrano Jr.**

Managing Editor

*Journal of the Brazilian Medical Association (Ramb)*

## Adib Jatene, an immense legacy to Brazilian medicine

<http://dx.doi.org/10.1590/1806-9282.60.06.002>

November 14, 2014, will be marked forever in the history of Brazil as the day that the national medicine lost one of its greatest references: cardiologist Adib Jatene.

Born in Xapuri, Acre, son of a Lebanese rubber tapper, he wrote one of the finest chapters in the history of Brazilian medicine. With a medical degree from University of São Paulo's Faculty of Medicine (FMUSP), awarded in 1953, where he also became professor *emeritus*, he accumulated positions at Hospital do Coração (HCor) and Instituto Dante Pazzanese, two national references in cardiology.

Jatene was a pioneer of heart surgery in the country. In addition to having created the first artificial lung-heart machine at Hospital das Clínicas, in the 1950s, he was responsible for the first bypass surgery in Brazil in 1968. His contributions in favor of techniques for the development of cardiology put his name among the most respected cardiac surgeons in the world. One of the procedures developed by him to correct transposed arteries in neonates became known worldwide as "Jatene's surgery", adding up to an impressive history of more than 20,000 operations and nearly 700 scientific papers published in the national and international literature as author or co-author. One of them, related to the intracavitary correction technique and published in *The Journal of Thoracic and Cardiovascular Surgery*, reached, in the medical literature only, over 400 citations.

### POLITICS

Even without joining any political party, Jatene took part on several occasions in the national political scene. He was state secretary of health in São Paulo, between 1979 and 1982, and twice minister of health in the administrations of Fernando Collor, for eight months, and Fernando Henrique Cardoso, from 1995 to 1996. It was in this last administration that he created the Provisional Contribution on Financial Transactions (CPMF), a tax intended solely to fund the national health sector. Ministry of Health officials remember one of his favorite habits in those days: enter the cafeteria queue or have breakfast with servers, seeking to gather opinions on our health system. Unmotivated, he left the ministry when he realized that the government started to divert health budget funds collected through the tax he envisioned.

Last year, he returned to the government to chair a committee of experts to create a project aiming at changes in medical education. He walked away again after the Dilma Rousseff administration launched, without any prior discussion, the More Doctors program. His main concerns in terms of national public health were proper medical education, health financing and the Family Health program, which was highlighted in a recent article published in *Folha de S.Paulo* newspaper: "Physicians must be experts in people," he wrote.

The *Journal of the Brazilian Medical Association (Ramb)* honors Professor Adib Jatene in recognition of his example as physician and public figure, his dedication to medicine, and unwavering integrity throughout his life. We are certain that this legacy will remain, inspiring professionals to defend medicine with honor, ethics and dignity, as he never gave up doing.

### TESTIMONIALS

"The Brazilian Medical Association mourns the passing of Prof. Dr. Adib Domingos Jatene, who worked hard for the sake of medicine and health. Medical science loses one of its icons, who has inspired generations. May the pain of loss be comforted by the important legacy he left as a doctor, teacher, researcher and citizen."

**Florentino Cardoso**, president of the Brazilian Medical Association.

"Permanent reason for inspiration for all those around him, Jatene managed to bring together the most absolute accuracy in medical procedures and a humane treatment, always maintaining a close relationship with each one of his patients. His ethical and fair stance was, and will be, a beacon shedding light on all medicine. I owe much of my career to him, who always had a friendly and encouraging word to offer. Working for years with him in the operating room and ICU was a lesson I will never forget. To be the director of the Faculty of Medicine at University of São Paulo, where Jatene received his medical degree, and to be in the position he held with both talent and dedication, fills me with pride and responsibility. I must also mention his career as an agent of public life, and key figure in the implementation of the Unified Health System, benefiting millions of patients. Brazil loses one of its most brilliant public figures."

**José Otavio Costa Auler Junior**, director of the University of São Paulo's Faculty of Medicine.

“Dr. Adib Jatene was the most talented man I met in medicine. He had the highest of the intellectual qualities: creativity. He was a great surgeon and tireless worker, who invented new and lasting things. He was righteous; he did not envy nor was vain; on the contrary, he recognized the value of others and encouraged careers. He had great administrative vision, not only about medical institutions, but also in relation to health in the country. He was a natural leader who indicated paths, led with courage, persuaded by example and thus conquered the trust of his colleagues. His judgments were wise. Dr. Adib deserves to be called a great man, an indelible mark in the history of Brazil.”

**Protásio L. da Luz**, Cardiology senior professor at Instituto do Coração, Faculty of Medicine, University of São Paulo.

“Dr. Adib was a person predestined to be all that he was. If he had been an engineer, he would have been the best of all; if he had been a lawyer, he also would have been the best of all; if he had chosen any other profession, I am sure he would have been the best of all because of his discipline and enormous capacity for work. Brazil has excellent surgeons, but few like him. Professionals like Dr. Adib do not appear that often.”

**Fulvio Pillegi**, professor *emeritus*, Faculty of Medicine, University of São Paulo.

“Prof. Adib Jatene left the Brazilian medicine a legacy of inestimable value, his contributions to cardiology and cardiac surgery were many. Besides being a brilliant physician and teacher, Dr. Adib acted with great skill as Health State Secretary and Minister.”

**Sérgio Almeida Oliveira**, professor *emeritus* of Thoracic and Cardiovascular Surgery, Faculty of Medicine, University of São Paulo

“On November 19<sup>th</sup>, cardiovascular surgery and the Brazilian medicine as a whole lost one of its greatest exponents. The life story of Adib Jatene is extraordinary, from Xapuri, Acre, where he was born until the time of his death, in São Paulo. Jatene was an innovative professional. He proposed and performed original techniques and also contributed to the development of the cardiac surgery products industry. His accomplishments allowed this medical specialty to gain international recognition, especially within Latin America.

Unfortunately, Professor Jatene is gone, but he left so much of himself, and took much of us who had the privilege of knowing him closely.”

**Noedir Stolf**, head of the cardiology team at Beneficência Portuguesa de São Paulo.

“Prof. Adib D. Jatene leaves a legacy not only to Hospital do Coração, but also to the entire Brazilian society and, dare I say, to the international medical and scientific community. Prof. Adib is one of those characters that will always be in our memories, whether because of his teachings, or for his achievements and developments, but mostly for his principles. The innovations he created in the area of cardiac surgery, with development of techniques for correction of congenital heart abnormalities, benefited thousands of children around the world, and opened the borders of the Brazilian medicine and specifically cardiology to first world countries. In the realm of education, he participated directly and indirectly in the formation of numerous cardiologists. Today, many of them have international recognition in their respective fields, planting good seeds in various places of our country and abroad. As a human being, he always attempted to develop sustainable social practices, focusing on the most vulnerable population, and promoting the return of family doctors in Brazil, in order to meet the needs of our public health system. As a politician, he served thinking in the sustainable development of the health of the Brazilian people, at municipal, state and federal levels. Last, as head of his family, he honored his wife, children, grandchildren and great-grandchildren with a personal history that will be recorded forever in the list of illustrious personalities of Brazilian society of all time. All those who had the pleasure of knowing him more closely will miss him greatly.”

**Carlos Alberto Buchpiguel**, superintendent physician at Hospital do Coração.

“Professor Adib Jatene was a master for all Brazilian physicians. His commitment to medicine and health guided his career, with great activism in favor of society. He has my gratitude forever for having done so much. I hope that his example will continue to guide all doctors, for as Euryclides Jesus Zerbini used to say, nothing and no one can resist work.”

**Carlos Vital Tavares Corrêa Lima**, president of the Federal Board of Medicine.

“‘Work does not kill. What kills is anger’, would say Professor Adib. Talking to him was always encouraging. Last year, while studying for a public competition to become full professor of cardiology at USP, I would sometimes feel a little tired, but all I needed was to enter his office and listen to his ideas on public health to feel extremely motivated once again.”

**Roberto Kalil Filho**, cardiologist.

---

“Adib Domingos Jatene, a recent loss to the cardiology and medicine, was a physician who had one of the most comprehensive and successful performances in Brazilian medicine, with meritocratic and clear visibility in all scenarios of his professional life. With undisputed talent, irreparable systemic view and didactics, professor Jatene consolidated the teaching of cardiovascular surgery in the main institutions of our country. Always dealing with healthcare, teaching and research in an inseparable and translational manner, he idealized, completed and accomplished much, products of his brilliance, perseverance and unparalleled capacity to work. Jatene’s surgery, one of those great examples, magnifies the Brazilian scientific literature since 1975 with this great contribution that is not only quoted in all databases, but is also the reference point of cardiovascular scientometrics in our country. His erudition, great systemic view, and especially his daily civil practice defined his management career from state secretary to minister of health. This very ability to manage and undertake consolidated institutions of excellence, such as the Dante Pazzanese Institute of Cardiology (IDPC) and Hospital do Coração (HCor) in São Paulo, also leading him to the higher ranks at University of São Paulo’s Faculty of Medicine (FMUSP). Aware of the importance of integrative medical societies, he was a leader in several organizations, and even president of the Brazilian Society of Cardiology in the biennium 1985-7. When we think of the great names in Brazilian

medicine, we think of physician Adib Jatene, a scientist, teacher, association leader, entrepreneur, manager and one of our greatest examples of comprehensive medical doctor. Noted for his immense contribution in the cardiovascular field and his immortal legacy of excellence, competence, transparency, tireless work and good citizenship, Jatene will always be a name of reference in our memories and our institutions.”

**Angelo A. V. de Paola**, president of the Brazilian Cardiology Society.

“Professor Adib Jatene was the first president and founder of the São Paulo State Cardiology Society, standing out with huge importance in the context of cardiology not only in São Paulo, but throughout Brazil. He was internationally immortalized thanks to his contributions and innovations in major surgical procedures, which revolutionized the cardiac specialty and which are now practiced by surgeons worldwide. For his work in support of cardiology, Socesp will honor Dr. Jatene permanently as of its next annual Congress, in June 2015, introducing a master lecture that will be named after him.”

**Francisco A. H. Fonseca**, president of the São Paulo State Cardiology Society.

**César Teixeira**

Head Writer

*Revista da Associação Médica Brasileira (Ramb)*

# Update on degenerative spondylolisthesis: surgical treatment

## ATUALIZAÇÃO EM ESPONDILOLISTESE DEGENERATIVA: TRATAMENTO CIRÚRGICO

BERNARDO WM, BOTELHO RV, FONI NO, GOTFRYD AO, HERRERO CFPS, JEFFERSON D, MEVES R, MUDO ML, SIMÕES RS, ZYLBERSZTEJN S

<http://dx.doi.org/10.1590/1806-9282.60.05.003>

- 1. Is the use of bone substitutes such as BMP (bone morphogenetic protein) safe and effective in lumbar arthrodesis?**
  - a. It is safe due to lack of complications.
  - b. Complications include osteolysis and heterotopic ossification.
  - c. The routine use is recommended in spondylolisthesis.
  - d. Clinical results with iliac grafts are superior.
  
- 2. Bone substitutes are equal or superior to autografts in this situation?**
  - a. The removal of autologous bone graft from the iliac bone is radiologically superior.
  - b. Bone substitutes are contraindicated in this clinical situation.
  - c. The association of local bone graft (from the posterior vertebral elements) and beta-tricalcium phosphate is a therapeutic option.
  - d. The removal of autologous bone graft from the iliac bone is clinically superior.
  
- 3. What is the most appropriate diagnostic study in this clinical context?**
  - a. In the presence of symptomatic lumbar stenosis, the most sensitive and specific radiologic examination is computed tomography (CT).
  - b. Plain radiographs in the standing position does not determine the diagnosis.
  - c. Magnetic Resonance Imaging (MRI) is more sensitive and specific in identifying the narrowing of the spinal canal.
  - d. The most appropriate diagnostic test in this situation is plain radiography.
  
- 4. Is it necessary to refer the patient to arthrodesis with use of rigid pedicle screws (non-dynamic)?**
  - a. Instrumentation does not increase fusion rate.
  - b. Instrumented fusion produces less progression and improved walking ability.
  - c. A side effect of fusion is increased radicular pain.
  - d. There is subjective improvement independent of solid fusion.
  
- 5. How long should conservative treatment (non-surgical) be maintained?**
  - a. In treatment failure after 1 year of therapy.
  - b. Medical and surgical treatments have similar results, differing in required time.
  - c. After 12 weeks of failure in conservative treatment.
  - d. Spondylolisthesis is an absolute indication for surgical treatment.

## Update on late-onset hypogonadism (LOH) or ADAM: treatment

### ATUALIZAÇÃO EM HIPOGONADISMO MASCULINO TARDIO (HMT) OU DAEM: TRATAMENTO

BERNARDO WM, MARTITS AM, COSTA EMF, NARDI AC, NARDOZZA JR A, FACIO JR FN, FARIA G

<http://dx.doi.org/10.1590/1806-9282.60.06.004>

#### 1. What is the role of androgen replacement therapy (ART) to restore bone mass, muscular strength and body composition?

- Increase in fat mass.
- Does not affect bone mass.
- Increase in muscle mass.
- Reduces the testicular volume.

#### 2. What is the role of androgen replacement therapy (ART) to restore libido and sexual function?

- Testosterone restores libido in men independent of the hormone's levels.
- Testosterone restores libido in men with low testosterone levels.
- The combination of testosterone and phosphodiesterase inhibitors produces no benefit.
- Dehydroepiandrosterone (DHEA) improves erectile dysfunction.

#### 3. What is the risk of ART in relation to exacerbating prostate disease?

- Increases the incidence of prostate cancer
- Cannot be used in patients treated for prostate cancer.
- Patients with a family history of prostate cancer should not use ART.
- Can increase PSA levels.

#### 4. How should ART be administered orally?

- 50 mg of DHEA orally twice a day, improves sexual function in men.
- Oral testosterone undecanoate (OTU), 160 mg/day, improves sexual function.
- Oral mucosa patches (containing 30 mg of testosterone), 3 times a day.
- It is strongly advised NOT to use oral testosterone formulations.

#### 5. What is the best form of ART?

- Injectable testosterone undecanoate depot (TUD) is the most physiologic.
- The oral route remains a quick and convenient way to ART.
- Skin patches at the maximum dose are not very effective.
- Subcutaneous testosterone implants can be used in our midst.

### ANSWERS TO CLINICAL SCENARIO: ANGLE-CLOSURE GLAUCOMA: TREATMENT [PUBLISHED IN RAMB 2014; 60(5)]

#### 1. On prophylactic laser iridotomy, in the contralateral eye, in a patient with acute primary angle closure in one eye, we can affirm that:

It can prevent similar episodes in many cases. (Alternative A)

#### 2. The differences between prophylactic laser iridotomy (PLI) and prophylactic surgical iridectomy include:

PLI costs less. (Alternative B)

#### 3. It is not a complication of PLI:

Clinical improvement of cataract. (Alternative C)

#### 4. Which anatomic situation of the cameral sinus is an indication for prophylactic laser iridotomy?

All cases diagnosed as primary angle closure. (Alternative B)

#### 5. Factors involved in the indication of PLI in cases of suspected primary angle closure include all of the following, except:

Lack of symptoms. (Alternative A)

**ANSWERS TO CLINICAL SCENARIO: LATE-ONSET HYPOGONADISM (LOH) OR ADAM: DIAGNOSIS [PUBLISHED IN RAMB 2014; 60(5)]**

- 1. The main signs and symptoms involved in late-onset male hypogonadism include the following, except:**

Anxiety. (Alternative B)

- 2. On the main instruments used in the definition and diagnostic assessment of male aging, we cannot affirm that:**

The use of the three instruments makes the diagnosis of HMT through functional and biochemical criteria unnecessary. (Alternative D)

- 3. What is the role of the *serum* and free testosterone (BAT) levels in the diagnosis of late-onset hypogonadism?**

TT (total testosterone) would not be the ideal measure to assess late-onset hypogonadism. (Alternative C)

- 4. Tests to be requested before the start of hormone replacement therapy (ART) include the following, except:**

Evaluation of renal function. (Alternative D)

- 5. How should prostate cancer be monitored?**

Ultrasound-guided prostate biopsy. (Alternative A)

# Treatment with intensity-modulated radiation therapy (IMRT) for breast cancer

## TRATAMENTO COM RADIOTERAPIA DE INTENSIDADE MODULADA (IMRT) PARA CÂNCER DE MAMA

**Authorship:** Sociedade Brasileira de Radioterapia

**Participants:** Marta GN, Hanna SA, Gadia R

**Final draft:** February 27, 2014

<http://dx.doi.org/10.1590/1806-9282.60.06.005>

*The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.*

*The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.*

### DESCRIPTION OF THE EVIDENCE COLLECTION METHOD

Through the development of four relevant clinical questions related with the proposed subject, we tried to present the main evidence for safety, toxicity and effectiveness using different radiotherapy techniques. The study population consisted of female patients of all ages with primary breast cancer treated with radiation therapy to the whole breast, regardless of histological type, staging, context of treatment (radical, adjuvant or palliative) and whether comorbidities were present or not. For this, a systematic review of the literature was performed in primary scientific research databases (Medline - Pubmed; Embase - Elsevier; Lilacs - Bireme; Cochrane Library - Central Register of Controlled Trials). All articles available until July 22, 2013, were included. The search strategy used for Medline research is described in Appendix. Articles were selected based on critical evaluation in search of the best available evidence. Recommendations were prepared based on discussion with the writing group, composed of three members of the Brazilian Society of Radiotherapy. The guideline was reviewed by an independent group specializing in evidence-based clinical guidelines. After completion, the guideline was made available for public consultation for 15 days and the suggestions forwarded to the writers for evaluation and consideration into the final text.

### GRADE OF RECOMMENDATION AND STRENGTH OF EVIDENCE

**A.** Experimental or observational studies of higher consistency.

**B.** Experimental or observational studies of lower consistency.

**C.** Case reports (non-controlled studies).

**D.** Opinions without critical evaluation, based on consensus, physiological studies, or animal models.

### OBJECTIVE

To assess the most appropriate method of radiation therapy for treating patients with primary breast tumors.

### CONFLICT OF INTEREST

No conflict of interest informed.

### INTRODUCTION

Breast cancer is the most common malignancy (except for non-melanoma skin tumors) and the leading cause of cancer death among women(**D**).<sup>1</sup> According to data from the National Cancer Institute, in Brazil, for the year 2012, 52,680 new cases were estimated, which corresponds to an estimated risk of 52 new cases per 100,000 women(**D**).<sup>2</sup>

Radical mastectomy, as proposed by Halsted in 1894, has been the standard treatment for breast cancer regardless of any associated factor. However, in the last 50 years, there has been a change in surgical approach, following the trend of breast conservation, whilst continuing to offer oncological safety. According to this rationale, adjuvant radiotherapy (RT) is fundamental to treat all patients with initial *in situ* and invasive tumors who undergo conservative surgery, as well as those with locally advanced

ced disease (tumor size > 5 cm, more than three lymph nodes affected, and more).

From the standpoint of the existing RT techniques, conventional planning (2D) is performed based on two dimensions (planar images such as X-ray) with dose distribution calculation in a single plane (contour) of the patient. The total volume irradiated is not considered, that is, the dose variation outside this contour is ignored (no accurate volumetric measurement of dose distribution). The combinations of the radiation beams are simple and there is a need for good margin coverage, in order to ensure complete coverage of the treatment target volume. Thus, critical structures (organs at risk) are often included in the treatment field, which contributes greatly to increased toxicity.

In the late 1980s, with the improvement of hardware and planning systems, it was possible to provide tools capable of assisting the evaluation of treatments that have become fully three-dimensional (conformal technique - 3D). In 3D RT for the breast, dose distribution is calculated over the total volume irradiated, with tissue inhomogeneity corrections, considering the contour of the patient's chest at different levels. The measurements of heart volume and lung volume, which are irradiated through field entries, are known for the calculation of dose-volume histograms. This is an important tool because it helps to assess the homogeneity of planning, as well as measures the dose to be received by each organ during treatment delivery. Ultimately, it is the tool used to determine whether a treatment is prohibitive due to the high chance of side effects, or if it is acceptable on account of greater sparing effect for the organs at risk.

As previously said, 3D RT offers better distribution of the prescribed dose at the target volume. However, dose deposition in tissues using the 3D technique is practically the same as in 2D RT. Thus, in the scope of treatment, the intensity of radiation is the same in each treatment beam, that is, the dose is uniformly delivered to both the tumor and normal adjacent tissues in the treatment target area.

In order to improve the intensity of non-uniform beams, a technique of beam intensity-modulated RT (IMRT) was developed. For this, an inverse planning is used, consisting in first defining the organs at risk and target volumes, and the dose that each structure should receive. As a result, a non-uniform deposition of dose is obtained within treatment area, which is achieved by

dividing the field into several sub-fields. In the case of breast cancer, in which the incidence of treatment beams is arranged tangentially to the chest wall, conventional beams end up generating inhomogeneous dose distributions in the breast, particularly in areas of lower thickness. Therefore, the treated area lacks dose homogenization, while IMRT, which usually allows a 'non-uniform deposition' of the dose at the treatment target, offers exactly the opposite: the homogenization of the dose in the breast.

Importantly, in practice, for the treatment of breast cancer with radiotherapy, the so-called IMRT involves the adoption of two distinct strategies:

1. the use of inverse planning, as mentioned above;
2. the use of a computerized planning system capable of evaluating the dose distribution in the overall volume. Through visualization of high-dose regions, field segmentation is carried out manually using collimation blocks or a multileaf collimator, resulting in a more homogeneous dose distribution (no need to use reverse planning).

### **IS DOSE DISTRIBUTION FOR BREAST IRRADIATION SUPERIOR WITH INTENSITY-MODULATED RADIATION THERAPY (IMRT) COMPARED TO CONVENTIONAL AND CONFORMAL RADIOTHERAPY?**

IMRT is the modality that provides best dose coverage at the treatment target (breast) compared to the conformal and conventional techniques (B).<sup>3,4</sup>

In addition, IMRT significantly reduces the dose delivered to organs at risk. The dose reduction in the contralateral breast can reach 50%, which reduces the likelihood of radiation-induced breast cancer especially in young women (B).<sup>5,6</sup> The same was noted with regard to other structures such as the heart and lungs (ipsilateral and contralateral), which can be associated with a reduced risk for chronic lung and heart disease (B).<sup>7-14</sup> This benefit was also demonstrated in patients undergoing mastectomy and adjuvant radiation therapy for plastron (B).<sup>7</sup>

#### **Recommendation**

Intensity-modulated radiation therapy (IMRT) is a modality that provides better dose distribution in breast irradiation.

## IS IT LESS TOXIC TO USE INTENSITY-MODULATED RADIATION THERAPY (IMRT) COMPARED TO CONVENTIONAL OR CONFORMAL RADIATION THERAPY FOR PRIMARY BREAST TUMORS?

Toxicity related to radiation therapy can be temporally divided into two sub-categories: acute and delayed.

When comparing IMRT with conventional or conformal radiation therapy of the breast, two studies had acute toxicity as the main outcome.

A phase III multicenter study including 358 patients showed that the rates of moist desquamation during radiotherapy and up to six weeks after treatment were 31.2% with IMRT, and 47.8% with conventional or conformal radiation therapy ( $p=0.002$ )(A).<sup>16</sup>

A recently published English study with median follow-up of five years and which included 1,145 treated patients showed that the use of IMRT reduces the rates of telangiectasia (OR 0.58, 95%CI: 0.36 – 0.92,  $p=0.021$ )(A)<sup>3</sup> (B).<sup>17</sup>

Regarding delayed toxicity, a minimum of five years for patient follow-up is required. Some institutional series reported a low rate of delayed toxicity related to radiation therapy: a study with 7.5 years of median follow-up reports rates of delayed skin toxicity grade II or higher at 39 *vs.* 52% ( $p=0.004$ ) with IMRT and conventional radiotherapy, respectively (D).<sup>18</sup> Rates of pneumonitis, lymphoedema, and tumor recurrence within the follow-up were not statistically different between the two groups (D).<sup>18</sup> A similar study showed after 4.7 years of median follow-up that the use of IMRT reduces the rates of acute and delayed toxicity, with respective rates of delayed breast edema grade II or higher at 6 *versus* 1% ( $p=0.009$ ) (B).<sup>19</sup> For patients with larger breasts (volume > 1,600cm<sup>3</sup>), the gains were more expressive with IMRT: chronic breast edema (3 *vs.* 30%,  $p=0.007$ ) and hyperpigmentation (3 *vs.* 41%,  $p=0.001$ )(B).<sup>19</sup>

### Recommendation

There is less acute toxicity with the use of intensity-modulated radiation therapy (IMRT) compared to conventional or conformal radiation therapy for primary breast tumors, especially regarding the rate of moist desquamation during radiotherapy. Delayed skin toxicity is less prevalent with IMRT, with a lower incidence of chronic breast edema, hyperpigmentation, and telangiectasia. These gains are also seen in larger breasts treated with this technique.

## IS THE QUALITY OF LIFE AFFECTED TO THE POINT OF JUSTIFYING THE USE OF INTENSITY-MODULATED RADIATION THERAPY (IMRT) OVER CONFORMAL OR CONVENTIONAL RADIATION THERAPY?

Quality of life is a difficult outcome to be measured, with many uncertainties, including the difficulty in defining

it and the subjectivity of measurements. For the treatment of breast cancer, quality of life was assessed in studies using specific tools such as questionnaires or through cosmetic evaluation of patients, which is intrinsically linked to quality of life and personal satisfaction.

Cosmesis was evaluated in two randomized studies as the primary outcome according to the use of IMRT.

306 women underwent cosmetic assessment by serial photographs after 1, 2 and 5 years of follow-up. The rate of change in the appearance of the breast was 58 *vs.* 40% ( $p=0.008$ ) for conventional radiotherapy and IMRT, respectively (B).<sup>4</sup>

The findings illustrated a 68% reduction in the risk of worsening of cosmesis using the RTOG scale after IMRT (OR=0.68; 95%CI, 0.48 to 0.96;  $p=0.027$ ) (B)<sup>3</sup> (A).<sup>17</sup>

Direct evaluation of the quality of life through scores or questionnaires was carried out in the study, which assessed patients based on two questionnaires: EORTC Quality of Life Questionnaire C-30 general module and BR-23 module self-assessment. During patient follow-up, there was a significant correlation between the two scores for quality of life and the presence of breast pain and radiodermatitis (A).<sup>16</sup>

### Recommendation

The use of intensity-modulated radiation therapy (IMRT) reduces the risk of worsening of cosmesis. There is no evidence for other outcomes related to quality of life.

## ARE THERE DIFFERENCES IN EFFECTIVENESS, LOCAL CONTROL OR OVERALL SURVIVAL AMONG THE TECHNIQUES OF INTENSITY-MODULATED RADIATION THERAPY (IMRT), CONFORMAL RT AND CONVENTIONAL RT?

In three phase III randomized trials comparing conventional or conformal RT with IMRT, effectiveness, local control and overall survival were not the main outcomes evaluated. The reason for this is that the hypothesis was not proposed because the prescribed doses and irradiated volumes were equal, regardless of the technique. In one of these studies, with five years of median follow up, the rate of local control in the group of women treated with IMRT and conventional RT in five years was 98.6 and 97.4%, respectively ( $p=0.36$ ) and the overall survival in five years was 92.5 and 91.7%, respectively ( $p=0.88$ )(A).<sup>17</sup>

### Recommendation

IMRT compared with conventional or conformal radiation therapy techniques for the breast has benefits in terms of dosage, toxicity and quality of life, while it does not affect local control and overall survival of patients.

## APPENDIX

### Medline search strategy

(Breast Neoplasms [Mesh] OR Breast Neoplasm OR Neoplasm, Breast OR Neoplasms, Breast OR Tumors, Breast OR Breast Tumors OR Breast Tumor OR Tumor, Breast OR Mammary Carcinoma, Human OR Carcinoma, Human Mammary OR Carcinomas, Human Mammary OR Human Mammary Carcinomas OR Mammary Carcinomas, Human OR Human Mammary Carcinoma OR Mammary Neoplasms, Human OR Human Mammary Neoplasm OR Human Mammary Neoplasms OR Neoplasm, Human Mammary OR Neoplasms, Human Mammary OR Mammary Neoplasm, Human OR Breast Cancer OR Cancer, Breast OR Cancer of the Breast OR Cancer of Breast) AND (Radiotherapy, Intensity-Modulated [Mesh] OR Intensity-Modulated Radiotherapies OR Intensity-Modulated Radiotherapy OR Radiotherapies, Intensity-Modulated OR Radiotherapy, Intensity Modulated OR IMRT OR Volumetric-Modulated Arc Therapy OR Arc Therapies, Volumetric-Modulated OR Arc Therapy, Volumetric-Modulated OR Therapies, Volumetric-Modulated Arc OR Therapy, Volumetric-Modulated Arc OR Volumetric Modulated Arc Therapy OR Volumetric-Modulated Arc Therapies OR Intensity-Modulated Arc Therapy OR Arc Therapies, Intensity-Modulated OR Arc Therapy, Intensity-Modulated OR Intensity Modulated Arc Therapy OR Intensity-Modulated Arc Therapies OR Therapies, Intensity-Modulated Arc OR Therapy, Intensity-Modulated Arc OR Helical Tomotherapy OR Helical Tomotherapies OR Tomotherapies, Helical OR Tomotherapy, Helical) AND (Radiotherapy, Conformal [Mesh] OR Conformal Radiotherapies OR Radiotherapies, Conformal OR Conformal Radiotherapy OR Radiotherapy Planning, Computer-Assisted OR Radiotherapy Dosage OR Radiotherapy Planning, Computer-Assisted OR 3D radiotherapy OR tridimensional radiotherapy OR 3D RT OR 3DRT OR 3DCRT OR CRT OR 3D-CRT) OR (Conventional radiotherapy OR 2D radiotherapy OR 2D RT OR 2DRT OR 2D-CRT OR standard radiotherapy OR two-dimensional radiotherapy).

Other guidelines at [www.projetodiretrizes.org.br](http://www.projetodiretrizes.org.br)

## REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55:74.
2. Ministério da Saúde do Brasil. Estimativas para o ano de 2012 de número de casos novos e de óbitos por câncer em mulheres, segundo localização pri-

mária. Access on 7/22/2013. Available from: <http://www.inca.gov.br/estimativa/2012/index.asp?ID=5>

3. Barnett GC, Wilkinson J, Moody AM, Wilson CB, Sharma R, Klager S, Hoole ACF, Twyman N, Burnet NG, Coles CE. A randomised controlled trial of forward-planned radiotherapy (IMRT) for early breast cancer: Baseline characteristics and dosimetry results. *Radiother Oncol* 2009;92:34-41.
4. Donovan E, Bleakley N, Denholm E, et al. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. *Radiother Oncol* 2007;82:254-64.
5. Burmeister J, Alvarado N, Way S, McDermott P, Bossenberger T, Jaenisch H, Patel R, Washington T. Assessment and minimization of contralateral breast dose for conventional and intensity modulated breast radiotherapy. *Med Dosim* 2008;33:6-13.
6. Bhatnagar AK, Brandner E, Sonnik D, Wu A, Kalnicki S, Deutsch M, Heron DE. Intensity modulated radiation therapy (IMRT) reduces the dose to the contralateral breast when compared to conventional tangential fields for primary breast irradiation. *Breast Cancer Res Treat* 2006;96:41-6.
7. Landau D, Adams EJ, Webb S, Ross G. Cardiac avoidance in breast radiotherapy: a comparison of simple shielding techniques with intensity-modulated radiotherapy. *Radiother Oncol* 2001;60:247-55.
8. Johansen S, Cozzi L, Olsen DR. A planning comparison of dose patterns in organs at risk and predicted risk for radiation induced malignancy in the contralateral breast following radiation therapy of primary breast using conventional, IMRT and volumetric modulated arc treatment techniques. *Acta Oncol*. 2009;48:495-503.
9. Stillie AL, Kron T, Herschtal A, Hornby C, Cramb J, Sullivan K, Chua B. Does inverse-planned intensity-modulated radiation therapy have a role in the treatment of patients with left-sided breast cancer? *J Med Imaging Radiat Oncol* 2011;55:311-9.
10. Ercan T, Idem S, Alço G, Zengin F, Atilla S, Dinçer M, Okkan S. Dosimetric comparison of field in field intensity-modulated radiotherapy technique with conformal radiotherapy techniques in breast cancer. *Jpn J Radiol* 2010;28:283-9.
11. Fong A, Bromley R, Beat M, Vien D, Dineley J, Morgan G. Dosimetric comparison of intensity modulated radiotherapy techniques and standard wedged tangents for whole breast radiotherapy. *J Med Imaging Radiat Oncol* 2009;53:92-9.
12. Schubert LK, Gondi V, Sengbusch E, Westerly DC, Soisson ET, Paliwal BR, Mackie TR, Mehta MP, Patel RR, Tomé WA, Cannon GM. Dosimetric comparison of left-sided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and tomotherapy. *Radiother Oncol* 2011;100:241-6.
13. Baycan D, Karacetin D, Balkanay AY, Barut Y. Field-in-field IMRT versus 3D-CRT of the breast. Cardiac vessels, ipsilateral lung, and contralateral breast absorbed doses in patients with left-sided lumpectomy: a dosimetric comparison. *Jpn J Radiol* 2012;30:819-23.
14. Coon AB, Dickler A, Kirk MC, Liao Y, Shah AP, Strauss JB, Chen S, Turian J, Griem KL. Tomotherapy and multifield intensity-modulated radiotherapy planning reduce cardiac doses in left-sided breast cancer patients with unfavorable cardiac anatomy. *Int J Radiat Oncol Biol Phys* 2010;78:104-10.
15. Rudat V, Alaradi AA, Mohamed A, Ai-Yahya K, Altuwaijri S. Tangential beam IMRT versus tangential beam 3D-CRT of the chest wall in post-mastectomy breast cancer patients: a dosimetric comparison. *Radiat Oncol* 2011;06:26 AM.
16. Pignol JP, Olivetto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J Clin Oncol* 2008;26:2085-92.
17. Mukesh MB, Barnett GC, Wilkinson JS, Moody AM, Wilson C, Dorling L, Chan Wah Hak C, Qian W, Twyman N, Burnet NG, Wishart GC, Coles CE. Randomized Controlled Trial of Intensity-Modulated Radiotherapy for Early Breast Cancer: 5-Year Results Confirm Superior Overall Cosmesis. *J Clin Oncol*. 2013 Sep 16. [Epub ahead of print]
18. McDonald MW, Godette KD, Butker EK, Davis LW, Johnstone PAS. Long-Term Outcomes of IMRT for Breast Cancer: A Single-Institution Cohort Analysis. *Int J Radiat Oncol Biol Phys* 2008; 72:1031-1040.
19. Harsolia A, Kestin L, Grills I, Wallace M, Jolly S, Jones C, Lala M, Martinez A, Schell S, Vicini FA. Intensity-Modulated Radiotherapy Results in Significant Decrease in Clinical Toxicities Compared with Conventional Wedge-Based Breast Radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;68:1375-1380.

## Stress fractures in the foot and ankle of athletes

### FRATURA POR ESTRESSE NO PÉ E TORNOZELO DE ATLETAS

**Authors:** Asano LYJ, Duarte Jr. A, Silva APS

<http://dx.doi.org/10.1590/1806-9282.60.06.006>

*The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.*

*The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.*

### DESCRIPTION OF THE EVIDENCE COLLECTION METHOD

To develop this guideline, the Medline electronic database (1966 to 2012) was consulted via PubMed, as a primary base. The search for evidence came from actual clinical scenarios and used keywords (MeSH terms) grouped in the following syntax: “Stress fractures”, “Foot”, “Ankle”, “Athletes”, “Professional”, “Military recruit”, “Immobilization”, “Physiotherapy”, “Rest”, “Rehabilitation”, “Conventional treatment”, “Surgery treatment”. The articles were selected by orthopedic specialists after critical evaluation of the strength of scientific evidence, and publications of greatest strength were used for recommendation. The guidelines were drawn from group discussion. The entire text was reviewed by a group specializing in evidence-based clinical guidelines.

### GRADE OF RECOMMENDATION AND STRENGTH OF EVIDENCE

- A.** Experimental or observational studies of higher consistency.
- B.** Experimental or observational studies of lower consistency.
- C.** Case reports (non-controlled studies).
- D.** Opinions without critical evaluation, based on consensus, physiological studies, or animal models.

### OBJECTIVE

The target audience of this guideline includes orthopedists, physiatrists and sports doctors in order to guide the diagnosis and treatment of athletes with stress fractures in the foot and ankle.

### CONFLICT OF INTEREST

No conflict of interest informed.

### INTRODUCTION

Stress fractures were described for the first time in 1855 by Breihaupt among soldiers reporting plantar pain and edema following long marches.<sup>1</sup> For athletes, the first clinical description was given by Devas in 1958, based solely on the results of simple X-rays.<sup>2</sup> Stress injuries are common among athletes and military recruits, accounting for approximately 10% of all orthopedic injuries.<sup>3</sup>

It is defined as a solution for partial or complete continuity of a bone as a result of excessive or repeated loads, at submaximal intensity, resulting in greater reabsorption faced with an insufficient formation of bone tissue.<sup>1</sup>

Although stress fractures may affect all types of bone tissue, they are more common in bones that support body weight, especially those in the lower limbs (tibia, 49%; tarsal bones, 25%; metatarsals, 9%).<sup>3</sup> Studies on runners reveal a higher incidence of stress fractures in the tibia, followed by the metatarsals, fibula, femur and navicular bone.<sup>4,5</sup>

The locations of stress fractures vary from sport to sport. Runners may develop a stress fracture of the medial malleolus, the distal end of the fibula, calcaneus, lesser metatarsal, and medial sesamoid bone. Classical ballet, aerobic gymnastics, tennis and volleyball athletes mainly present stress fractures in the navicular and sesamoid bones. Basketball athletes have a prominence of the medial malleolus, navicular bone and metatarsal stress fractures, while for footballers lesser metatarsal fractures are more common.<sup>6,7,8</sup>

From a biomechanical point of view, fatigue fractures are the result of specific, cyclical and repetitive muscle action until exhaustion, with load transfer to the bone exceeding its adaptation capacity.<sup>8,10</sup> The shear and compression forces stimulate bone transformation according to Wolff's law, that is, the compression forces promote osteoblast activity and bone deposition leading to a strengthening of bone structures, adapting to the applied load, while shear forces lead to the reverse process of bone resorption by stimulating osteoclast activity. As a result, the majority of stress fractures are located in the areas of shear stress.<sup>4,5,8</sup>

## WHEN SHOULD WE SUSPECT A STRESS FRACTURE IN THE FOOT?

Suspected injury is based on the details from the medical history, general physical examination and orthopedic physical examination. It is important to establish the relationship between the start of painful symptoms and physical activity, generally performed repetitively, abrupt changes in the amount of training and the presence of risk factors **(D)**.<sup>8,11,12</sup>

Initially, pain emerges at the end of the exercises and intensifies over some weeks; it may occur during the entire activity, and be constant during walking. Pain worsens and transforms training into suffering. Training becomes increasingly painful and difficult to continue. Even after some days of rest, returning to activities too early leads to recurrence of the pain **(D)**.<sup>4,6,8</sup>

### Recommendation

Stress fractures in the feet of athletes should be suspected in the presence of insidious pain associated with increased exercise intensity.

## WHICH COMPLEMENTARY EXAMS SHOULD BE REQUESTED FOR THE DIAGNOSIS?

After the medical history and clinical exam, plain radiography, bone scintigraphy, computerized tomography and magnetic resonance imaging have been used to aid the diagnosis **(D)**.<sup>8,11</sup> Despite its low sensitivity, simple radiography is recommended to start the investigation **(D)**.<sup>12</sup> In more advanced cases, cortical or medullary fracture lines, regional osteopenia, sclerosis and callus formation may be noted. Unfortunately, radiographs are initially negative in 70% of stress fractures and might not show evidence of injury for 2 to 4 weeks after the start of symptoms **(C)**<sup>13</sup> **(B)**.<sup>14</sup>

Rupture of the bone cortex can be demonstrated through computerized tomography and evidence of periostitis can also be detected in this manner. The sensitivity of computerized tomography is higher than radiography; however, compared with bone scintigraphy and magnetic resonance injury, the sensitivity for revealing stress fractures is low, resulting in a higher rate of false negatives **(C)**.<sup>16</sup> Owing to the high rate of false negatives using radiographs at the start of the course of stress fractures, additional diagnostic imaging is often necessary. Bone scintigraphy has traditionally been the test of choice in this situation, but has been supplanted by magnetic resonance imaging **(B)**.<sup>17,18</sup> Despite its sensitivity, bone scintigraphy is not specific and may produce false positive results in 13 to 24% of cases **(C)**.<sup>13</sup>

Magnetic resonance imaging has numerous practical advantages over scintigraphy. It provides precise anatomical resolution, can differentiate a stress reaction from a stress fracture, as well as being a noninvasive, multiplanar exam that does not require radiation. It is more sensitive and specific, provides greater information and is capable of detecting pre-radiographic bone changes. The disadvantages include the higher cost, contraindications relating to claustrophobic patients and those with metal implants or surgical materials **(C)**.<sup>13</sup>

Follow-up using computerized tomography or magnetic resonance imaging may also be useful to monitor healing of the stress fractures and determining if there is a delay in healing that could require surgical intervention **(D)**.<sup>6</sup>

### Recommendation

In cases of suspected stress fractures, plain radiography of the site of pain should be requested, with diagnosis in the majority of cases via more sensitive and specific imaging exams (magnetic resonance imaging).

## WHAT ARE THE FACTORS THAT FAVOR STRESS FRACTURES?

Various factors contribute to the pathogenesis of the disease, which may be classified into 2 sub-types: intrinsic and extrinsic. In general, extrinsic factors are related to the type and rhythm of training, the use of unsuitable footwear and sports equipment, precarious physical conditioning, the training location, environmental temperature and insufficient recovery time of previous injuries. Intrinsic factors include age, sex, race, bone density and structure, hormonal, menstrual, metabolic and nutritional balance, sleep pattern and collagen diseases **(D)**<sup>4,5,8</sup> **(C)**.<sup>19,20</sup>

Prospective and retrospective studies show a higher incidence among Caucasians. When compared to American black and Hispanic individuals, white individuals are more susceptible to stress fractures **(D)**.<sup>22</sup> The same occurs with age: older individuals present a higher incidence of such fractures **(B)**.<sup>7</sup> Stress fractures are less common in children than adolescents and adults **(D)**.<sup>23</sup> In relation to sex, some studies have shown that military women have an incidence 5 to 10 times higher than men **(B)**.<sup>7</sup>

With regard to genetic factors, studies on identical twin military recruits submitted to the same treatment in quantity, duration and intensity reveal fatigue fractures in the metatarsal bones in both **(B)**.<sup>7</sup>

In relation to biomechanical factors, a high longitudinal arch of the foot, difference in the length of the lower limbs and a marked varus foot associated with multiple stress fractures have been observed **(B)**<sup>15,21</sup> **(C)**.<sup>19,20,24</sup>

Cavovarus feet have recently been gaining more attention as being a significant risk factor for various conditions of overuse, especially stress fractures. This shape of foot is known for being relatively rigid, with weak capacity for attenuating shock (C).<sup>25,26</sup> Supination and pronation of the feet are associated with a significant increase in the risk of stress injuries (B).<sup>27</sup>

#### Recommendation

In cases of suspected stress fractures, intrinsic and extrinsic factors that favor the occurrence of injury should be investigated. The investigation of these risk factors aids diagnosis and treatment.

### WHAT IS THE DIFFERENTIAL DIAGNOSIS?

The main diseases that should be discarded are those resulting from repetitive and excessive effort and that affect the soft tissues that surround the area of bone affected, such as muscle injuries, bursitis, tendinopathy, splints, infections, cancer and compartment syndrome (C)<sup>28</sup>(B).<sup>29</sup>

### DOES FEMALE ATHLETE TRIAD AFFECT STRESS FRACTURES?

Female athletes are more likely to developing stress fractures (C).<sup>19</sup> The growing increase of this pathology among female athletes is related to factors that characterize female athlete triad: eating disorders, menstrual disturbances and low bone density (D).<sup>4,5,8</sup> Greater prevalence of eating disorders (such as bulimia, anorexia nervosa, ingestion of laxatives and diuretics) has been found among female athletes (D).<sup>30</sup> Irregularities in the menstrual cycle (hypoestrogenism) correlate with early bone loss, reduced mineralization of the osteoid and, consequently, the prevalence of stress fractures in women (D).<sup>22</sup>

### HOW SHOULD STRESS FRACTURES BE TREATED?

The treatment of stress fractures varies according to some of the fracture's characteristics, such as location, type, and evolution time. A general plan can be established divided into two phases: phase I, or modified rest, is characterized by pain control through the use of anti-inflammatory drugs, physiotherapy methods for analgesia and kinesiotherapy, weight-bearing permitted in daily activities and maintenance of aerobic fitness without causing abnormal stress responses in the affected segment. Activities such as cycling, swimming or running in water are alternatives for maintaining the athlete's physical conditioning.

Phase II begins from the moment in which the athlete no longer presents complaints of pain, which generally

occurs within 10 to 14 days from the start of symptoms. A gradual return to the sport is allowed based on the correction of intrinsic and extrinsic factors (D).<sup>3</sup>

Most stress fractures can be treated conservatively. This implies immobilization in a boot, without sustaining the foot until the symptoms have disappeared, generally around 6 to 8 weeks. Impact activities are avoided, but low impact workouts such as swimming, cycling, and elliptical machines can be continued to maintain aerobic fitness. Frequent physical exams are useful to identify the resolution of symptoms. Nutritional considerations are important as dietary deficiencies may contribute to the development of stress fractures. Recent data recommends early surgical treatment of fractures with a high risk of stress to elite athletes owing to the high risk of dislocation and non-consolidation. Early surgical treatment is also associated with a quicker return to the sport (B)<sup>15</sup>(C)<sup>49,50</sup>(D).<sup>31</sup>

Electrical stimulation has also been used for the treatment of stress fractures with satisfactory results (C).<sup>32</sup>

#### Recommendation

The treatment of stress fractures in the feet and ankles of athletes is, in most cases, conservative, through the use of analgesic methods, relative rest, not bearing weight, immobilization of the limb, maintaining physical condition with low impact exercise and correcting risk factors.

### WHAT ARE THE INDICATIONS FOR SURGICAL TREATMENT?

Despite greater awareness about this injury, the treatment of stress fractures in the foot and ankle continue to be a particularly problematic issue, including the navicular bone, fifth metatarsal and medial malleolus. These injuries are often not diagnosed and may occur at a higher frequency than that actually observed. For example, the navicular bone has a risk of delayed healing because of the poor areas of blood supply, and stress fractures of the medial malleolus have a high rate of dislocation and lack of consolidation. These injuries frequently require surgical stabilization (D).<sup>8,33</sup>

Stress fractures in the navicular bone are often difficult to diagnose. If untreated, they can result in osteoarthritis and delayed consolidation (C)<sup>34-36</sup>(B).<sup>37</sup> A large number of stress fractures in the navicular bone may show differences in the outcomes of surgical and nonsurgical treatments for various types of injuries. Given that the published data reveals a high occurrence of delayed consolidation, importance should be given to immediate surgical treatment, especially when the fracture extends to the navicular body or up to the second cortex of the navicular bone (B).<sup>38</sup> Surgical

treatment consists in percutaneous screw fixation with or without exposure of the fracture site. Generally, bone grafts are reserved for chronic fractures and delayed consolidation and nonunions (C).<sup>36</sup> Partially threaded solid or cannulated compression screws measuring 4 mm are used (D).<sup>31</sup>

A stress fracture in the fifth metatarsal diaphysis is defined as a stress fracture of the proximal zone of the bone immediately distal to the anatomical area of the Jones fracture (C)<sup>41</sup> (B).<sup>42</sup> These fractures frequently occur in athletes and are included in the 'high risk' group owing to the difficulty of obtaining consolidation and the high rate of nonunion and refracture. These fractures may have a prolonged healing time of 21 months, and nonunion may developed in up to 25% of patients treated conservatively (C).<sup>41,44</sup> Therefore, many authors currently favor surgical intervention for this fracture, especially in athletes (D)<sup>8,31,43</sup> (C).<sup>44</sup> Compared to conservative treatment, surgical treatment offers a quicker healing time, a shorter time for returning to full sports activity, and a lower rate of complications (C).<sup>40</sup>

Various surgical treatment methods (bone grafts (C),<sup>24,41</sup> tension bands (D)<sup>23</sup> and intramedullary screws) have been proposed. Fixation with intramedullary screws is the method recommended for the treatment of stress fractures by the majority of authors in the literature (C)<sup>44,47</sup> (B).<sup>45,46</sup> The hybrid technique (fixation with intramedullary screws associated with autogenous cancellous bone graft) seems to be a reasonable treatment for primary intramedullary fixation (C)<sup>24</sup> (D).<sup>39</sup> A recent systematic review (B)<sup>59</sup> concluded that intramedullary fixation with screws promotes successful union in all types of Jones fractures when compared to non-surgical treatments.

The treatment of stress fractures in the medial malleolus, and the distal end of the fibula depends on several factors. The presence of a fracture line, deviated fracture and athletic participation in the season may influence treatment decisions (D).<sup>48</sup> There are numerous reports of surgical intervention for the treatment of stress fractures in the medial malleolus. The presence of a fracture line detectable via radiography, especially in high level athletes, or deviation of the fracture is reported as an indication for surgical intervention. Surgical treatment consists in closed or open reduction and internal fixation with screws (B)<sup>15</sup> (C).<sup>58</sup> The present authors believe there are no reports in the literature of surgical fixation of distal fibular stress fractures.

#### Recommendation

Surgical treatment is indicated in cases where the fracture occurs in the shear zone, the location most disposed to delayed consolidation, nonunion or refractures.

## HOW CAN STRESS FRACTURES IN ATHLETES BE PREVENTED?

The best manner of treating stress fractures is prevention. The attending physician is responsible for knowing their athlete well, seeking to detect concurrent intrinsic and extrinsic factors for the injuries caused by microtrauma from repetition, and correcting them (D).<sup>11</sup>

The prevention of injuries and prognosis are of particular importance to competitive athletes as the objective is not only to start participating again, but to compete at a high level, preventing long term consequences. Injury prevention strategies and programs are a vital part of the education and training of athletes at all levels (C).<sup>51</sup>

It is important to educate athletes that continuous pain lasting 3 weeks is a warning sign for the body, and that early diagnosis leads to quicker recovery (B).<sup>52</sup>

Changes in footwear and the surface for practicing training may help to reduce the number and severity of injuries in relation to the feet and ankles of athletes (D).<sup>33</sup>

Worn footwear may have a role in increased injury rates. Use of light and flexible shoes with less support of the midfoot may place the athlete at risk, as these may offer less protection against potentially harmful forces in the foot (A).<sup>53</sup>

A Cochrane review in 1999 declared that 'the use of shock absorbing inserts in footwear probably reduces the incidence of stress fractures in military personnel' (A).<sup>54</sup> Another Cochrane review found evidence that custom-made orthoses for feet were effective in the treatment of cavus foot pain (A).<sup>55</sup>

Running shoes with neutral insoles have recently demonstrated a statistically significant reduction in plantar pressure in athletes with cavus feet (A).<sup>56</sup>

In relation to refracture, it is well known that returning to sport early is an important risk, therefore athletes should be warned about the complication (C).<sup>47,57</sup> In high level athletes, computerized tomography or magnetic resonance imaging should be considered before returning to training in order to avoid refracture (C).<sup>57</sup>

#### Recommendation

The prevention of stress fractures in athletes is based on a suitable physician/patient relationship in order to identify the characteristics of the athlete, correct risk factors and guide them in relation to symptoms and the importance of correct treatment to avoid new fractures.

## WHEN CAN THE PATIENT RETURN TO SPORT?

The decision to return to sport is based on the location of the injury and its corresponding potential for healing

and risk of significant complication (D).<sup>60</sup> It is useful to divide stress injuries into high and low grades. This simplification provides an approximate assessment of the healing time, with high reliability (C)<sup>35</sup> (D).<sup>8,9</sup>

Healing time is defined as the time required to return to full activity without any symptoms. This time was significantly greater in scintigraphy with high grade stress injuries compared with low grade ones. This grading of stress injury provided by scintigraphy was a significant indicator for the time until full recovery (B).<sup>29</sup>

Low risk stress fractures generally heal when the athlete is limited to activities without pain, over a period of 4 to 8 weeks. This healing period is an ideal time to assess the modifiable risk factors that could decrease the change of injuries recurring. A gradual increase in activity (daily life activities) should begin after the athlete is free from pain and the site is not injured (D).<sup>61</sup> In a study by Arendt and Griffith (D),<sup>62</sup> returning to full activity from initial stress injuries (3.3 to 5.5 weeks) was significantly quicker than for more serious injuries (11.4 to 14.3 weeks).

For stress fractures in the navicular bone, the time for returning to sports activities and condition for returning to competitions is around 4 months (B).<sup>38</sup> Khan et al. (B)<sup>37</sup> reported on the time to returning to full activity among 55 patients with stress fractures of the navicular bone treated conservatively. The treatment of 6 weeks without bearing weight enabled 86% of the patients to return to full activity in an average period of 5.6 months after injury.

Considerations related to returning to training for athletes with high risk stress fractures are more difficult than in low risk fractures. In general, returning should only be recommended after suitable treatment and when the injury has completely healed, given that high risk fractures have the most frequent complications, such as delayed consolidation and refracture (D).<sup>8,60</sup>

### Recommendation

Returning to practicing sports should be conducted gradually after consolidation of the fracture, which depends on the grade and location of the fracture, with greater rest time required for high risk fractures.

**Other guidelines at [www.projetodiretrizes.org.br](http://www.projetodiretrizes.org.br)**

### REFERENCES

1. Fitch KD. Stress fractures of the lower limbs in runners. *Australian Fam Phys* 1984;13:511-5.
2. Reeder MT, Dick BH, Atkins JA, Pribis, AB. Stress fractures. Current concepts of diagnosis and treatment. *Sports Med* 1996;22(3):198-212.
3. Matheson GO, Clement DB, McKenzie DC, et al. Stress fractures in athletes: a study of 320 cases. *Am J Sports Med*. 1987;03:46 PM-58.
4. Bennell KL. Epidemiology and site specificity of stress fractures. *Clin. Sports Med* 1997;16:179-196.
5. Amatuizzi MM, Carazzato JG. *Medicina do esporte*. 1, ed. Ver. São Paulo: Roca 2004;38:363-369.
6. Haverstock BD. Foot and Ankle Imaging in the Athlete. *Clin Podiatr Med Surg* 2008;25:249-262.
7. Bennell KL, Malcolm AS, Thomas AS. Risk factors for stress fractures in track and field athletes: A twelve-month prospective study. *Am J Sports Med* 1996;24:810-8.
8. Boden BP, Osbahr DC. High-risk stress fractures: evaluation and treatment. *J Am Acad Orthop Surg* 2000;8:344-53.
9. Boden BP, Osbahr DC, Jimenez C. Low-risk stress fractures. *Am J Sports Med* 2001;29:100-111.
10. Sonoda N, Chosa E, Totoribe K, Tajima N. Biomechanical analysis stress fractures of the anterior middle third of the tibia in athletes: nonlinear analysis using a three-dimensional finite element method. *J Orthop Sci* 2003;8(4):505-13.
11. Verma RB, Sherman O. Athletic stress fractures: part I. History, epidemiology, physiology, risk factors, radiography, diagnosis and treatment. *Am J Orthop* 2001;30(11):798-806.
12. Knapp TP. Stress fractures: general concepts. *Clin. Sports Med* 1997;16:339-356.
13. Steinbronn DJ, Bennett GL, Kay DB. The use of magnetic resonance imaging in the diagnosis of stress fractures of the foot and ankle: four case reports. *Foot Ankle Int* 1994;15(2):80-3.
14. Kiuru MJ, Pihlajamaki HK, Hietanen HJ, et al. MR imaging, bone scintigraphy, and radiography in bone stress injuries of the pelvis and the lower extremity. *Acta Radiol* 2002;43:207-212.
15. Kor A, Saltzman AT, Wempe PD. Medial malleolar stress fractures: literature review, diagnosis, and treatment. *J Am Podiatr Med Assoc* 2003;93(4):292-7.
16. Murcia M, Brennan RE, Edeiken J. Computed tomography of stress fracture. *Skeletal Radiol* 1982;8(3):193-5.
17. Hodler J, Steinert H, Zanetti M, et al. Radiographically negative stress related bone injury. MR imaging *versus* two-phase bone scintigraphy. *Acta Radiol* 1998;39:416-420.
18. Gaeta M, Minutoli F, Scribano E, et al. CT and MR imaging findings in athletes with early tibial stress injuries: comparison with bone scintigraphy findings and emphasis on cortical abnormalities. *Radiology* 2005;235:553-561.
19. Korpelainen R, Orava S, Karpakka J, Siira P, Hulkko A. Risk factors for recurrent stress fractures in athletes. *Am J Sports Med* 2001;29(3):304-10.
20. Blivin SJ, Martire JR, McFarland EG. Bilateral midfibular stress fractures in a collegiate football player. *Clin J Sport Med* 1999;9(2):95-7.
21. Giladi M, Milgrom C, Simkin A, et al. Stress fractures: identifiable risk factors. *Am J Sports Med* 1991;19(6):647-52.
22. Monteleone GP. Stress fractures in the athletes. *Orthopedic clinics of north america* 1995;26(3):423-432.
23. Hulkho A, Orava S. Stress fractures in athletes. *Int J Sports Med* 1987;8:221-226.
24. Popovic N, Jalali A, Georis P, et al. Proximal fifth metatarsal diaphyseal stress fracture in football players. *Foot Ankle Surg* 2005;11:135.
25. Pearce CJ, Brooks JH, Kemp SP, Calder JD. The epidemiology of foot injuries in professional rugby union players. *Foot Ankle Surg* 2011;17(3):113-8.
26. Raikin SM, Slenker N, Ratigan B. The association of a varus hindfoot and fracture of the fifth metatarsal metaphyseal-diaphyseal junction: the Jones fracture. *Am J Sports Med* 2008;36:1367.
27. Cain LE, Nicholson LL, Adams RD, Burns J. Foot morphology and foot/ankle injury in indoor football. *J Sci Med Sport* 2007;10(5):311-9.
28. Aoki Y, Yasuda K, Tohyama H, Ito H, Minami A. Magnetic resonance imaging in stress fractures and shin splints. *Clin Orthop* 2004;421:260-7.
29. Dobrindt O, Hoffmeyer B, Ruf J, Steffen JG, Zarva A, Richter WS, et al. Blinded-Read of Bone Scintigraphy, The Impact on Diagnosis and Healing Time for Stress Injuries With Emphasis on the Foot. *Clin Nucl Med* 2011;36:186-191.
30. Barrow GW, Saha S. Menstrual irregularity and stress fractures in collegiate female distance runners. *Am J Sports Med* 1988;16:209-216.
31. Brockwell J, Yeung Y, Griffith JF. Stress fractures of the foot and ankle. *Sports Med Arthrosc* 2009;17(3):149-159.
32. Benazzo F, Mosconi M, Beccarisi G, Galli U. Use of capacitive coupled electric fields in stress fractures in athletes. *Clinical Orthopaedics and Related Research* 1995;310:145-149.

33. Robert B, Anderson MD, Kenneth J, Hunt MD, Jeremy J, McCormick MD. Management of Common Sports-related Injuries About the Foot and Ankle. *J Am Acad Orthop Surg* 2010;18: 546-556.
34. Lee A, Anderson R. Stress fractures of the tarsal navicular. *Foot Ankle Clin* 2004;9:85-104.
35. Saxena A, Fullem B, Hannaford D. Results of treatment of 22 navicular stress fractures: a new proposed radiographic classification system. *J. Foot Ankle Surg* 2000;39:96-103.
36. Torg J, Pavlov H, Cooley L, et al. Stress fractures of the tarsal navicular: a retrospective review of twenty-one cases. *J. Bone Joint Surg* 1982;64:700-712.
37. Khan K, Fuller P, Brukner P, Kearney C, Burry H. Outcome of conservative and surgical management of navicular stress fractures in athletes. Eighty-six cases proven with computerized tomography. *Am J Sports Med* 1992;20:657-666.
38. Saxena A, Fullem B. Navicular stress fractures. A prospective study on athletes. *Foot Ankle Int* 2006;27(11):917-21.
39. Rosenberg GA, Sfera JJ. Treatment strategies for acute fractures and nonunions of the proximal fifth metatarsal. *J Am Acad Orthop Surg* 2000;8:332.
40. Chuckpaiwong B, Queen RM, Easley ME, et al. Distinguishing Jones and proximal diaphyseal fractures of the fifth metatarsal. *Clin Orthop Relat Res* 2008;466:1966.
41. Dameron TB. Fractures and anatomical variations of the proximal portion of the fifth metatarsal. *J Bone Joint Surg Am* 1975;57:788.
42. Landorf KB. Clarifying proximal diaphyseal fifth metatarsal fractures: the acute fracture versus the stress fracture. *JAPMA* 1999;89:398.
43. Brown SR, Bennett CH. Management of proximal fifth metatarsal fractures in the athlete. *Curr Opin Orthop* 2005;16:95.
44. Kavanaugh JH, Brower TD, Mann RV. The Jones fracture revisited. *J Bone Joint Surg Am* 1978;60:776.
45. Pecina MD, et al. Surgical treatment of diaphyseal stress fractures of the fifth metatarsal in competitive athletes. Long-term follow-up and computerized pedobarographic analysis. *J Am podiatr med assoc* 2011;101(6):517-522.
46. Kelly IP, Glisson RR, Fink C, et al. Intramedullary screw fixation of Jones fractures. *Foot Ankle Int* 2001;22:585.
47. Larson CM, Almekinders LC, Taft TN, et al. Intramedullary screw fixation of Jones fractures: analysis of failure. *Am J Sports Med* 2002;30:55. Sherbondy, PS. Sebastianelli, WJ. Stress Fractures of the Medial Malleolus and Distal Fibula. *Clin Sports Med* 2006;25:129-137.
48. Miller MD, Marks PH, Fu FH. Bilateral stress fractures of the distal fibula in a 35-year-old woman. *Foot Ankle Int* 1994;15(8):450-3.
49. Palamarchuk HJ, Sabo M. Fibular stress fracture in a female runner: a case report. *J Am Podiatr Med Assoc* 1998;88(1):34-6.
50. Hootman JM, Dick R, Agel J. Epidemiology of collegiate injuries for 15 sports: Summary and recommendations for injury prevention initiatives. *J Athl Train* 2007;42(2):311-319.
51. Ohta-Fukushima M, Mutoh Y, Takasugi S, Iwata H, Ishii S. Characteristics of stress fractures in Young athletes under 20 years. *J Sports Med Phys Fitness* 2002;42(2):198-206.
52. Schwellnus MP, Jordaan G, Noakes TD. Prevention of common overuse injuries by the use of shock absorbing insoles: A prospective study. *Am J Sports Med* 1990;18(6):636-641.
53. Rome K, Handoll HHG, Ashford R. Interventions for preventing and treating stress fractures and stress reactions of bone of the lower limbs in young adults. *Cochrane Database of Systematic Reviews* 2005;18(2):CD000450.
54. Hawke F, Burns J, Radford JA, du Toit V. Custom-made foot orthoses for the treatment of foot pain. *Cochrane Database of Systematic Reviews* 2008;16(3):CD006801.
55. Wegener C, Burns J, Penkala S. Effect of neutral-cushioned running shoes on plantar pressure loading and comfort in athletes with cavus feet: a crossover randomized controlled trial. *The American Journal of Sports Medicine* 2008;36:2139-46.
56. Wright RW, Fischer DA, Shively RA, et al. Refracture of proximal fifth metatarsal (Jones) fracture after intra-medullary screw fixation in athletes. *Am J Sports Med* 2000;28:732.
57. Shabat S, Sampson KB, Mann G, et al. Stress fractures of the medial malleolus: review of the literature and report of a 15-year-old elite gymnast. *Foot Ankle Int* 2002;23(7):647-50.
58. Roche AJ, Calder JD. Treatment and return to sports following a Jones Fracture of the fifth metatarsal: a systematic review. *Knee Surg Sports Traumatol Arthrosc* 2012.
59. Jason J, Diehl MD, Thomas M, Best MD, Christopher C, Kaeding MD. Classification and Return-to-Play Considerations for Stress Fractures. *Clin Sports Med* 2006;25:17-28.
60. Brukner P, Bradshaw C, Bennell K. Managing common stress fractures: let risk level guide treatment. *Physician Sports Med* 1998;26(8):39-47.
61. Arendt E, Griffiths HJ. The use of MR imaging in the assessment and clinical management of stress reactions of bone in high-performance athletes. *Clin Sports Med* 1997;16:291-306.

# Giant sclerosing papilloma mimicking locally advanced breast carcinoma

## PAPILOMA ESCLEROSANTE GIGANTE MIMETIZANDO CARCINOMA DE MAMA LOCALMENTE AVANÇADO

RENÉ ALOISIO DA COSTA VIEIRA<sup>1\*</sup>, SILVIA MARIA PRIOLI DE SOUZA SABINO<sup>2</sup>, GUSTAVO ZUCCA MATTHES<sup>1</sup>,

ANAPAUOLA HIDEMI UEMA WATANABE<sup>2</sup>, LUCAS FARIA ABRAHAO-MACHADO<sup>3</sup>

<sup>1</sup>Department of Mastology and Reconstructive Surgery, Barretos Cancer Hospital – Pio XII Foundation, Barretos, SP

<sup>2</sup>Department of Radiology Breast Image Division, Barretos Cancer Hospital – Pio XII Foundation, Barretos, SP

<sup>3</sup>Department of Pathology, Barretos Cancer Hospital – Pio XII Foundation, Barretos, SP

Study conducted at Barretos Cancer Hospital – Pio XII Foundation, Barretos, SP

**\*Correspondence**

Address: Rua Antenor Duarte Villela, 1331

Bairro Dr Paulo Prata

Postal Code: 14784 – 400

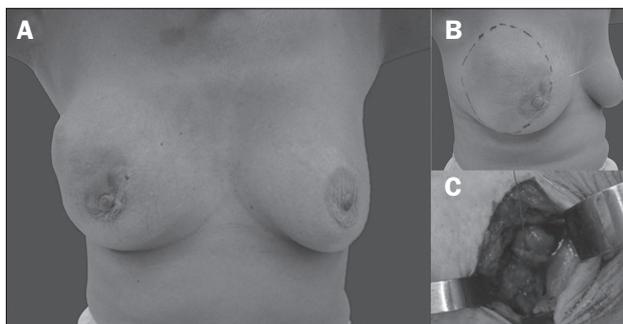
Barretos – SP

posgrad@hcancerbarretos.com.br

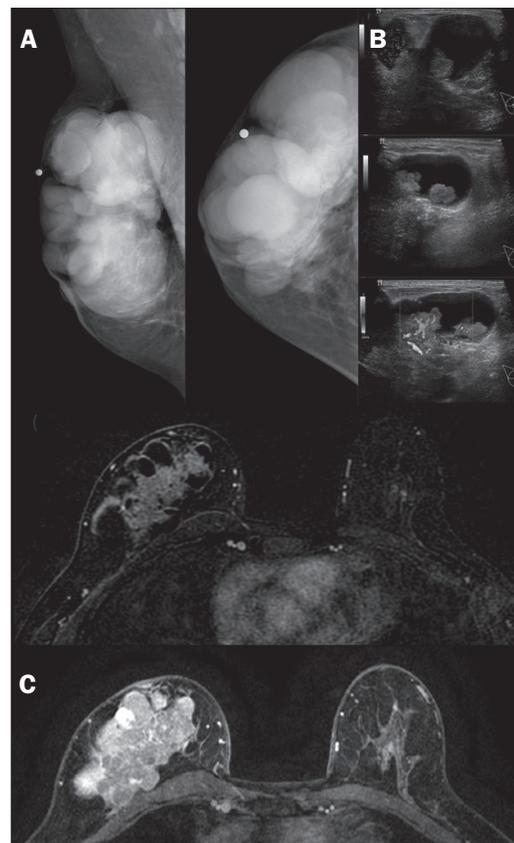
<http://dx.doi.org/10.1590/1806-9282.60.06.007>

**Conflict of interest:** none

The patient was a 54-year-old Brazilian woman presenting a progressive mass in the right breast. The clinical exam showed a 9 x 8 cm tumor and a hardened axillary lymph node. It was clinically considered a T3N1M0 breast tumor (Figure 1A). Mammography showed multiple oval formations, occupying the whole breast (Figure 2A). Ultrasonography showed the presence of multiple cysts, many of which containing vegetating lesions with intense vascular flow (Figure 2B) and absence of axillary lesion. Magnetic resonance imaging showed multiple oval cysts associated with vegetative lesions, a 4.7cm infiltrative area near the pectoral muscle (Figure 2C), and normal enlarged lymph node. As findings highly suspicious of malignancy were noted, radiological staging was performed. Abdominal ultrasound, bones scan and thoracic radiography showed absence of metastatic disease.

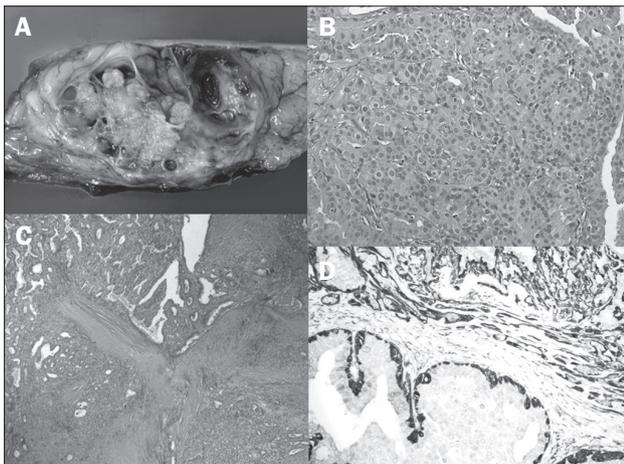


**FIGURE 1** Clinical exam. (A) lump in right breast; (B) marked area showing clinical localization; (C) open biopsy.



**FIGURE 2** Radiologic findings. (A) Mammography: multiple round image in the whole right breast; (B) breast ultrasound: cystic mass with intense vascular flow; (C) MRI findings: infiltrative solid mass with intense early enhancement and washout kinetic curve associated with multiple cysts occupying the right breast.

The core biopsy showed a benign complex papillary lesion. Since the radiologic and pathologic divergence did not allow a definitive diagnosis of malignancy, an ultrasound-guided stereotactic needle biopsy was scheduled. The open biopsy was performed in a vegetative intracystic lesion (Figures 1B and 1C) and pathologic findings showed a papillary neoplasia with atypical cells. Due to atypical findings and the necessity to evaluate the whole lesion,<sup>1-4</sup> the patient underwent a simple mastectomy with sentinel lymph node dissection. No reconstructive surgery was considered because of the lesion size and tumor characteristics. The macroscopic assessment showed a 7.5 x 6.0 cm solid-cyst lesion, with a 3.8 cm solid component (Figure 3A). The microscopy revealed a sclerosing papilloma harboring ductal carcinoma *in situ* in about 30% of the lesion (Figures 3B and 3C), with free margins and absence of lymph node metastasis. Immunohistochemistry for myoepithelial cells was performed in order to exclude *foci* of invasion in the periphery of the lesion (Figure 3D).



**FIGURE 3** Pathologic findings. Macroscopic finding: (A) Gross examination showed a large solid-cystic tumor. Microscopic findings: (B) papillary neoplasia with sclerotic stroma (HE, 40x); (C) areas containing carcinoma *in situ* (HE, 200x); (D) Immunohistochemistry positive for myoepithelial cells (Calponin, 200x).

Mammary extensive papillomatous lesions represent a clinical challenge, especially when observing a highly suspicious malignant tumor based on clinical and radiological findings.<sup>5</sup> As core biopsy showed a benign lesion, an open biopsy in the vegetative intracystic lesion was performed to improve material sampling. So, when a definitive diagnosis of malignancy cannot be done because of discordant findings, sampling limitations of a core biopsy<sup>5</sup> or open biopsy, or limited sensibility of breast images,<sup>5,6</sup> resection of the entire lesion is mandatory<sup>1-4,6</sup> due to high association with malignancy.<sup>1,2,4</sup> The open biopsy was an attempt to improve the pathological results that were hindered by limitation of diagnostic procedures and discordant findings. Also, the indication for diagnostic mastectomy,<sup>7</sup> as seen in this case, is a fact that must be thoroughly discussed with the patient.

## REFERENCES

1. Sydor MK, Wilson JD, Hijaz TA, Massey HD, Paredes ESS. Underestimation of the presence of breast carcinoma in papillary lesions initially diagnosed at core-needle biopsy. *Radiology* 242(1):58-62.
2. Liberman L, Tornos C, Huzjan R, Bartella L, Morris EA, Dershaw DD. AJRIs surgical excision warranted after benign, concordant diagnosis of papilloma at percutaneous breast biopsy? *ARJ*. 2006; 186(5):1328-1334.
3. Ueng SH, Mezzeti T, Tavassoli FA. Papillary neoplasms of the breast. *Arch Pathol Lab Med*. 2009; 133(6):893-907.
4. Youk JH, Kin EK, Kwak JY, Son EJ. Atypical papilloma diagnosed by sonographically guided 14-gauge core needle biopsy of breast mass. *AJR*. 2010;194(5):1397-492.
5. Lam WWM, Chu MCW, Tang APY, Tse G, Ma TKF. Role of radiologic features in the management of papillary lesions of the breast. *AJR* 2006;186(5):1322-1327.
6. Eliada R, Chong H, Lylmarni S, Goldberg F, Muradai S. Papillary lesions of the breast: MRI, ultrasound, and mammographic appearances. *AMJ J Roentgenol*. 2012; 183(2): 264-71.
7. Fenoglio C, Raffaele L. Sclerosing papillary proliferations in the female breast. A benign lesion often mistaken for carcinoma. *Cancer* 1974; 33(3): 691-700.

# Bioethical conflicts of gene therapy: a brief critical review

## CONFLITOS BIOÉTICOS DA TERAPIA GÊNICA: UMA BREVE OPINIÃO CRÍTICA

JOSÉ EDNÉSIO DA CRUZ FREIRE<sup>1\*</sup>, SUELEN CARNEIRO DE MEDEIROS<sup>2</sup>, ANTÔNIO VIANA LOPES NETO<sup>1</sup>, JOSÉ EDVAR MONTEIRO JÚNIOR<sup>3</sup>, ANTÔNIO JUSCELINO SUDÁRIO SOUSA<sup>1</sup>, ANTÔNIO JOSÉ ROCHA<sup>1</sup>, LÉA MARIA BEZERRA DE MENEZES<sup>4</sup>

<sup>1</sup>Department of Biochemistry and Molecular Biology, Federal University of Ceará (UFC), Fortaleza, CE, Brazil

<sup>2</sup>Department of Clinical and Toxicology Analysis, Federal University of Ceará (UFC), Fortaleza, CE, Brazil

<sup>3</sup>Biology Department, Federal University of Ceará (UFC), Fortaleza, CE, Brazil

<sup>4</sup>Faculty of Pharmacy, Odontology and Nursing, Federal University of Ceará (UFC), Fortaleza, CE, Brazil

### SUMMARY

Methods and techniques employed in gene therapy are reviewed in parallel with pertinent ethical conflicts. Clinical interventions based on gene therapy techniques preferentially use vectors for the transportation of therapeutic genes, however little is known about the potential risks and damages to the patient. Thus, attending carefully to the clinical complications arising as well as to security is essential. Despite the scientific and technological advances, there are still many uncertainties about the side effects of gene therapy. Moreover, there is a need, above all, to understand the principles of bioethics as both science and ethics, in accordance with its socioecological responsibility, in order to prioritize the health and welfare of man and nature, using properly natural resources and technology. Therefore, it is hard to determine objective results and to which extent the insertion of genes can affect the organism, as well as the ethical implications of it.

**Keywords:** gene transfer techniques, gene therapy, bioethics, ethics, clinical.

Study conducted at the Federal University of Ceará, Fortaleza, CE

Article received: 3/26/2014

Accepted for publication: 6/3/2014

\*Correspondence:

Address: Universidade Federal do Ceará,  
Centro de Ciências, Departamento de  
Biologia  
Laboratório de Genética Molecular  
Bloco 906, Campus do Pici  
Av. Humberto Monte, s/n, PICI  
Postal Code: 60455-970  
Fortaleza – CE

<http://dx.doi.org/10.1590/1806-9282.60.06.008>

Conflict of interest: none

### INTRODUCTION

The first scientific work involving gene transfer was described in 1944 and involved two strains of *Pneumococcus*, one pathogenic and the other nonpathogenic.<sup>1</sup> However, only in the 1950s the three-dimensional structure of DNA was elucidated, allowing the emergence of what we now know as genetic engineering. Since then, the possibility of using the genes or gene fragments for different scientific purposes emerged.<sup>2</sup>

About 10 years later, in 1963, the idea of anticipating the *in vitro* culture of germ cells genetically engineered to obtain direct control of these cells by selecting and integrating specific genes in human chromosomes arises.<sup>3</sup> Since then, numerous experimental designs in order to establish safe methodologies to insert healthy genes into defective cells were initiated.

However, the first successful *in vitro* gene correction in mammalian cells occurred in 1977, using a viral vector as vehicle to transport the genetic material.<sup>4</sup> The first clinical trial of human gene therapy was performed in 1989 using a viral vector in five patients with metastatic melanoma.<sup>5</sup> This pioneering study in humans established

a number of important experimental designs for future clinical interventions using gene transfer.

The method stimulated intense research in subsequent decades in an effort to optimize viral vectors for the insertion of therapeutic DNA, leading to the possibility of clinical applications in humans.<sup>6-8</sup> The choice of viral vectors for the purpose occurred because these beings possess the ability to recognize and infiltrate naturally in the cell nucleus, and thus transfer the therapeutic DNA into the host cell.<sup>9</sup>

Moreover, with the advent of human genome sequencing and the development of new software tools for comparing genes, the diagnosis of almost all human diseases related to genetic defects became possible. Thus, gene therapy is currently the most efficient and promising clinical tool available, being capable to predict with a high level of accuracy if someone will develop a disease, as well as to cure it.<sup>10</sup>

In general, gene therapy can be organized according to its cellular target, being called somatic gene therapy when the target is limited to somatic cells.<sup>11</sup> This thera-

peutic method can also be considered an *ex vivo* system, since tissue samples or cells from the patient must be collected for biopsy with subsequent reimplantation after the cells are reprogrammed genetically allowing the correct synthesis of desired gene products.<sup>12</sup> Another widely used method involves germ cell lineages generated after collection; the genes of interest are reprogrammed so that the new features will be perpetuated for future generations of cells from the patient.<sup>13</sup>

From the *ex vivo* application, it was possible to develop a method of *in vivo* gene therapy based on mRNA interference (RNAi). The scientific reports on RNAi date from 1998, initially identified in the nematode *Caenorhabditis elegans*,<sup>14</sup> and, since then, this mechanism has been identified in many species,<sup>15,16</sup> included in all eukaryotic phyla.<sup>17</sup>

The term RNAi refers to a set of small sequences of double-strand RNA (dsRNA), with size from 21 to 28 nucleotides, capable of inhibiting the expression of messenger RNA target sequences with high specificity.<sup>18,19</sup> After the discovery of these molecules, the possibility to use these sequences as a new therapeutic approach, especially for humans, was seen.<sup>20</sup> As such, RNAi-based gene therapy represents today the most advanced form of intervention in genetic diseases among the methods used in gene therapy, with very promising results.<sup>21-23</sup>

Nevertheless, thorough attention must be given to clinical complications arising from the use of gene therapy,<sup>24</sup> as well as to safety certification tests. Human clinical trials based on gene therapy are first carried out in animals and, sometimes, there is not a concrete correlation between the animal models used and the actual human biochemical and physiological conditions.<sup>24</sup>

Despite the scientific and technological advances regarding gene therapy, there are still many uncertainties about the side effects of treatment. Furthermore, the lesser-known effects, such as long-term expression of the introduced genes, the lack of control of the expression of these genes and genetic modification of germ cells, are now ignored.<sup>25</sup> There is no doubt that the main problem to be overcome is currently the high immunogenicity of viral vectors introduced into the patient,<sup>26,27</sup> as well as problems related to efficacy, toxicity and inflammatory response.

Other methods of gene therapy include the injection of genetic material directly into the target tissue,<sup>28</sup> and a variety of natural, synthetic and inorganic nanoparticles, including liposomes, micelles, exosomes, synthetic organic polymers, carbon nanotubes, quantum dots, gold nanoparticles and more, which have been conjugated to nucleic acids and used in gene therapy.<sup>29</sup>

Therefore, the aim of this paper is to present the fundamentals of using gene therapy as a practice of clinical intervention under the scope of bioethics, as well as its implications for the patient.

## BIOETHICAL AND LEGAL ISSUES OF GENE THERAPY

The success of gene therapy led to a boom in the development of several studies with prospects for therapeutic use of genes. And soon after April 14, 2003, the day that the mapping of the human genome was completed, it became possible to diagnose and treat many diseases of genetic origin before they progress,<sup>30</sup> using gene therapy. However, these findings have triggered a series of bioethical controversies about the safety of genetic engineering and the likelihood of its use for the purposes of eugenics.<sup>31</sup>

Gene therapy is a therapeutic strategy characterized by the transfer of genetic material in order to rearrange the genome of target cells to enable expression of the inserted gene or inhibit the expression of a specific gene.<sup>32</sup> Among the methodologies used in gene therapy, there is the application of RNAi, widely used in biomedical research in recent years,<sup>33</sup> due to its relative ease of handling.<sup>23</sup>

Quality of life is a concept that has been extensively studied in recent years, and integrates different fields of knowledge, especially those included in health sciences such as medicine, psychology and biology, and more. In this context, medicine presents itself as a primary mediator in order to prevent diseases and to maintain good health of the patient; science cannot afford to use a still unfinished therapy such as gene therapy at this time, since it is still experimental.

With the advances made in biotechnology in recent decades, the clinical responsibility of medical practitioners and of the debates about intervention methods used by them has inevitably increased. The participation of everyone in order to contribute their views on bioethical issues inherent in aiming at analyzing the risks and expected benefits of gene therapy is indispensable. So, today, to be part of that context and help to guide better decisions, rules of deontological ethics are not enough, and there is the need for plural and interdisciplinary reflections, always focused on human dignity.

Although the advantages of sequencing the human genome have been widely accepted, there are still ethical concerns regarding those benefits,<sup>34</sup> and several problems were encountered in clinical protocols, making it clear that we still have a long way to go before employing technology RNAi in modern medicine.<sup>31</sup>

From the perspective of bioethics, the use of gene therapy appears to be closely related to several negative factors. Among which, can be cited: economic difficulties,<sup>35</sup> particularly with regard to wealth distribution, political and cultural conflicts, as well as the scarcity of studies evaluating the impacts of the use of gene therapy on human health (clinical dilemmas and legal issues).<sup>2, 36, 37</sup>

Some methods, including RNAi, are associated with the use of pathogenic (however attenuated) viruses as transport vectors. The initial proposal for the use of viruses as carriers to transport and introduce genes into a patient seems to be very simple; however, some of them are associated with severe human disease, such as viruses causing pharyngitis, conjunctivitis, leukemia and AIDS. The use of viruses belonging to the lentivirus family, which includes HIV, seems very dangerous, because with the exception of African communities, the global population does not have antibodies against this pathogen.

Overall, gene therapies are new procedures that are still in the experimental stage. This is a very risky therapy, since many vehicles are viruses with genetic material consisting of RNA and, therefore, they can more readily undergo genetic recombination and become more virulent. From the point of view of bioethics, the main obstacle to the application of RNAi-based gene therapy is the fact that the safer non-viral vectors currently available are still inefficient or have very limited application. Therefore, studies that evaluate the effects in experimental models and in preclinical trials are needed in order to validate the potential effectiveness of this type of therapeutic intervention. It is necessary to evaluate the actual benefits as well as to detect the potential risks of implementing this therapy so that both safety and human health are preserved, and worse health problems than those we have today are avoided.

The speed and effectiveness of some of the protocols used in gene therapy have not allowed much scientific and legal discussion about experimental regulation and commercialization, or about the long-term effects of this new therapeutic approach.<sup>38</sup> This decade, it is essential to further understanding about the side effects arising from clinical trials, in order to intervene if necessary. New experimental designs to determine the faults and dangers arising from the use of gene therapy before their deliberation and hence the application as routine technique in hospitals and health centers are, therefore, timely and indispensable.

In 2008, the number of clinical trials using gene therapy as an intervention method reached 118 and since

then there has been a decrease in these experiments. Probably be due to temporary restrictions, omitted flaws in the protocols, or even bioethical issues. Over the past four years, clinical trials using gene as a therapeutic mechanism were recorded in more than 33 countries, with representatives from all continents, although the American continent is responsible for over 50% of the trials currently in progress. It is worth saying that the numbers may be underestimated due to the scarcity of information made available and the omission of data in some countries.

The vast majority of clinical trials using gene therapy is currently connected to cancers (64.3%) with a total of 1,223 trials; monogenic hereditary diseases (8.8%) with 1,667 trials; heart disease (8.3%), 158 trials; infectious diseases (8%) with 153 trials; neurological diseases (1.9%) with 36 trials; optical diseases (1.5%) with 28 trials; inflammatory diseases (0.7%) with 13 trials; and other negative factors associated with genetic disorders (6.5%), 119 trials.

In the global legal context, the use of experimental trials with the inclusion of intrinsic parts of animals, plants or other organisms including DNA, RNA and stem cells in humans was always challenged to face dilemmas, insecurity, especially about the consequences of the development of biomedical sciences and biotechnology. This idea is defended in both the international sphere as in the constitution of many countries, in addition to statutory law involving the subject.

In this context, it is vital, above all, to understand the principles of bioethics and ethical science aligned with their socio-ecological responsibility, so as to prioritize the health and welfare of man and nature, in order to properly utilize the natural resources and technology. Among the fundamental principles of bioethics and biolaw are respect for life in all its forms and manifestations, and the quality of the environment, to ensure the maintenance of life and vital processes, with an ongoing commitment to transparency and the dissemination of knowledge involving biological and medical sciences.

The law relating to the use of gene therapy is rarely debated in scientific circles, because of great resistance on the use of these clinical trials, despite numerous prospects for curing different diseases. However, such perspectives are submerged in dubious methods, and the effects of the projects now under study are not predictable. On the one hand, men are entitled to life and health, as stated in the Universal Declaration of Human Rights; on the other hand, there is the question of to what extent we

can risk this right on behalf of still unfinished scientific research.

As in other areas of research, validation of new therapeutic methods is closely related to the development of clinical trials, and prior approval by local, national and international ethics committees is, therefore, required. Some types of vectors, notably adenoviral and retroviral vectors, have produced serious and even fatal side effects and, therefore, security seems to be the main obstacle for the application of this type of clinical intervention in hospitals and other public health care centers particularly in underdeveloped areas or countries.

Not so far from the new technological possibilities applied to modern medicine, many matters involving moral and ethics were raised with heated debate, especially on the behavior of the professionals involved - including doctors, researchers, patients and other people involved with the problems of medicine and public health.

## CONCLUSION

The main difficulties faced by researchers dealing with gene therapy are the following: (1) efficiency during gene transfer, which requires greater effort by researchers in order to optimize vectors that can transfer DNA to target cells as planned; (2) Amplifying and expressing the heterologous gene naturally as seen with resident genes, so that the patient can undertake a single treatment; (3) Minimizing the biological risk caused by viral vectors currently used, adopting more meticulous safety assessments and studies, especially in the case of virulent genes to target cells; (4) Preventing unwanted expression of the heterologous gene or vector, since this may trigger immunological responses in individuals under treatment.

## RESUMO

Conflitos bioéticos da terapia gênica: uma breve opinião crítica.

Métodos e técnicas empregadas na terapia gênica são revisados em paralelo a conflitos éticos pertinentes. Intervenções clínicas com base em técnicas de terapia gênica são usadas preferencialmente em vetores para o transporte de genes terapêuticos; porém, pouco se sabe sobre os possíveis riscos e danos para o paciente, sendo necessário atender cuidadosamente às complicações clínicas resultantes, bem como à segurança. Apesar dos avanços científicos e tecnológicos relacionados à terapia gênica, ainda há muitas incertezas sobre os efeitos colaterais do

uso dessa terapia. Além disso, é necessário, acima de tudo, compreender os princípios da bioética como uma ética da ciência para com a responsabilidade socioecológica, a fim de priorizar a saúde e o bem-estar do homem e da natureza, utilizando adequadamente recursos naturais e tecnologia. Portanto, é difícil afirmar qual é o rendimento real, bem como os resultados do aumento da genética inserida no organismo e as implicações éticas.

**Palavras-chave:** técnicas de transferência genética; terapia gênica; bioética; ética clínica.

## REFERENCES

1. Avery OT, MacLleod CM, McCarty M. Studies on the chemical nature of the substance inducing transformation of pneumococcal types. *J Exp Med.* 1944;79(2):137-58.
2. Folayan MO, Oyedeji KS, Fatusi OA. Community Members' Engagement with and Involvement in Genomic Research: Lessons to Learn from the Field. *Dev World Bioeth.* 2013 Apr 17. [Epub ahead of print]
3. Lederberg J. Molecular biology, eugenics and euphenics. *Nature.* 1963;198(4879):428-9.
4. Wigler M, Silverstein S, Lee LS, Pellicer A, Cheng YC, Axel R. Transfer of purified herpes virus thymidine kinase gene to cultured mouse cells. *Cell.* 1977;11(1):223-32.
5. Rosenberg SA, Aebersold P, Cornetta K, Kasid A, Morgan RA, Moen R, et al. Gene transfer into humans - immunotherapy of patients with advanced melanoma, using tumor-infiltrating lymphocytes modified by retroviral gene transduction. *N Engl J Med.* 1990;323(9):570-8.
6. Obbard DJ, Gordon KHJ, Buck AH, Jiggins FM. The evolution of RNAi as a defence against viruses and transposable elements. *Philos. Trans Royal Soc Lond B Biol Sci.* 2009;364(1513):99-115.
7. Burney TJ, Davies JC. Gene therapy for the treatment of cystic fibrosis. *Appl Clin Genet.* 2012;05:29 AM-36.
8. Liu Y, Chang Y, Zhang C, Wei Q, Chen J, Chen H, et al. Influence of mRNA features on sRNAi Interference efficacy. *J Bioinform Comput Biol.* 2013;11(3):1341004.
9. Heilbronn R, Weger S. Viral vectors for gene transfer: current status of gene therapeutics. *Handb Exp Pharmacol.* 2010;(197):143-70.
10. Millan MJ. An epigenetic framework for neurodevelopmental disorders: from pathogenesis to potential therapy. *Neuropharmacology.* 2013;68:2-82.
11. Xu Y, Wei X, Wang M, Zhang R, Fu Y, Xing M, et al. Proliferation rate of somatic cells affects reprogramming efficiency. *J Biol Chem.* 2013;288(14):9767-78.
12. Naldini L. Ex vivo gene transfer and correction for cell-based therapies. *Nat Rev Genet.* 2011;12(5):301-15.
13. Rives N, Milazzo JP, Perdrix A, Castanet M, Joly-Hélas G, Sibert L, et al. The feasibility of fertility preservation in adolescents with Klinefelter syndrome. *Hum Reprod.* 2013;28(6):1468-79.
14. Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature.* 1998;39(6669):806-11.
15. Kim DH, Rossi JJ. Strategies for silencing human disease using RNA interference. *Nat. Rev. Genet.* 2007;8(3):173-84.
16. Borgio JF. RNA interference (RNAi) technology: a promising tool for medicinal plant research. *J Med Plants Res.* 2009;3(13):1176-83.
17. Moazed D. Small RNAs in transcriptional gene silencing and genome defence. *Nature.* 2009;457(7228):413-20.
18. Almeida R, Allshire RC. RNA silencing and genome regulation. *Trends Cell Biol.* 2005;15(5):251-8.
19. Ramachandran PV, Ignacimuthu S. RNA interference-a silent but an efficient therapeutic tool. *Appl Biochem Biotechnol.* 2013;169(6):1774-89.
20. Duchaine TF, Slack FJ. RNA interference and micro RNA-oriented therapy in cancer: rationales, promises, and challenges. *Curr Oncol.* 2009;16(4):61-6.

21. Chen C, Mei H, Shi W, Deng J, Zhang B, Guo T, Wang H, Hu Y. EGFP-EGF1-conjugated PLGA nanoparticles for targeted delivery of siRNAi into injured brain microvascular endothelial cells for efficient RNA interference. *PLoS One*. 2013;8(4):e60860.
22. Halasi M, Gartel AL. Targeting FOXM1 in cancer. *Biochem Pharmacol*; 2013;85(5):644-52.
23. Lin T, Chen Y, Ding Z, Luo G, Liu J, Shen J. Novel insights into the synergistic interaction of a thioredoxin reductase inhibitor and TRAIL: the activation of the ASK1-ERK-Sp1 pathway. *PLoS One*. 2013;8(5):e63966.
24. Fallahi A, Ravasi A, Farhud D. Genetic doping and health damages. *Iran J Public Health*. 2011;40(1):1-14.
25. Haisma HJ, Hon O. Gene doping. *Int J Sports Med*. 2006;27(4):257-66.
26. Maersch S, Huber A, Büning H, Hallek M, Perabo L. Optimization of stealth adeno-associated virus vectors by randomization of immunogenic epitopes. *Virology*. 2010;397(1):167-75.
27. Louis Jeune V, Joergensen JA, Hajjar RJ, Weber T. Pre-existing anti-adeno-associated virus antibodies as a challenge in AAV gene therapy. *Hum Gene Ther Methods*. 2013;24(2):59-67.
28. Onodera M, Ariga T, Kawamura N, Kobayashi I, Ohtsu M, Yamada M, et al. Successful peripheral T-lymphocyte-directed gene transfer for a patient with severe combined immune deficiency caused by adenosine deaminase deficiency. *Blood*. 1998;91(1):30-6.
29. Shen H, Sun T, Ferrari M. Nanovector delivery of siRNAi for cancer therapy. *Cancer Gene Ther*. 2012;19(6):367-73.
30. Wieacker P, Steinhard J. The prenatal diagnosis of genetic diseases. *Dtsch Arztebl Int*. 2010;107(48):857-62.
31. Menck CFM, Ventura AM. Manipulando genes em busca de cura: o futuro da terapia gênica. *Rev USP*. 2007;(75):50-61.
32. Petrocca F, Lieberman J. Promise and challenge of RNA interference - based therapy for cancer. *J Clin Oncol*. 2011;29(6):747-54.
33. Angaji SA, Hedayati SS, Poor RH, Madani S, Poor SS, Panahi S. Application of RNA interference in treating human diseases. *J Genet*. 2010;89(4):527-37.
34. Wonkam A, Kenfack MA, Muna WFT, Ouwe-Missi-Oukem-Boyer O. Ethics of human genetic studies in sub-saharan Africa: the case of Cameroon through a bibliometric analysis. *Dev World Bioeth*. 2011;11(3):120-7.
35. Cobucci RNO, Duarte LMCP. Bioética , assistência médica e justiça social. *Rev Bioética*. 2013;21(1):62-6.
36. Deakin CT, Alexander IE, Kerridge I. Accepting risk in clinical research: is the gene therapy field becoming too risk-averse? *Mol Ther*. 2009;17(11):1842-8.
37. Perrey C, Wassenaar D, Gilchrist S, Ivanoff B. Ethical issues in medical research in the developing world: a report on a meeting organised by Fondation Mérieux. *Dev World Bioeth*. 2009;9(2):88-96.
38. Edelstein ML, Abedi MR, Wixon J. Gene therapy clinical trials worldwide to 2007 - an update. *J Gene Med*. 2007;9(10):833-42.

# Common mental disorders and associated factors among final-year healthcare students

EDMÉA FONTES DE OLIVA COSTA<sup>1\*</sup>, MARGLEICE MARINHO VIEIRA ROCHA<sup>2</sup>, ANA TERESA RODRIGUES DE ABREU SANTOS<sup>3</sup>,

ENALDO VIEIRA DE MELO<sup>4</sup>, LUIZ ANTONIO NOGUEIRA MARTINS<sup>5</sup>, TARCISIO MATOS ANDRADE<sup>6</sup>

<sup>1</sup>Adjunct Professor of Psychiatry, Department of Medicine; Federal University of Sergipe (DME/UFES); Doctorate in PPGMS/UFBA

<sup>2</sup>Graduate in Medicine (DME/UFES); Masters student, professional in Neurology of University of São Paulo of Ribeirão Preto (USP-RP)

<sup>3</sup>Medical Coordinator of Mental Health Juvenile Service of the teaching Hospital and the Psycho Pedagogic assistance service to medical students of the UFBA; Masters in PPGMS/UFBA

<sup>4</sup>Assistant professor at the department of medicine at the Federal University of Sergipe (UFES)

<sup>5</sup>Associate professor of psychiatry at the Federal University of São Paulo (UNIFESP)

<sup>6</sup>Associate professor of the Faculty of Medicine of Bahia and supervisor of the first and third authors in the postgraduate program in health and medicine at the Federal University of Bahia (PPGMS/UFBA)

## SUMMARY

**Objective:** to assess the prevalence of common mental disorder (CMD) and to identify potential associated factors among medical, dental and nursing students.

**Method:** a cross-sectional study conducted in a public university in Northeast Brazil with 172 undergraduate students of the last three semesters of the medicine, dentistry and nursing courses, in February 2010, using the Self Reporting Questionnaire (SRQ-20) and a structured questionnaire developed by the authors. Logistic regression was performed for data analysis.

**Result:** the prevalence of CMD was 33.7%. The courses presented no differences in CMD prevalence. The logistic regression analysis showed a strong association of the following variables with CMD: female (OR=4.34), lack of good expectations regarding the future (OR=5.83), course as not a source of pleasure (OR=7.52) and feeling emotionally tense (OR=11.23).

**Conclusion:** the high prevalence suggests that immediate preventive measures should be implemented, such as the setting up of psycho-pedagogic support services for students, and teacher development programs.

**Keywords:** mental health, mental disorders, students, dental, students, medical students, nursing, occupational health.

Study conducted at the Department of Medicine of the Federal University of Sergipe, Aracajú, SE

Article received: 3/18/2014

Accepted for publication: 6/3/2014

\*Correspondence:

Universidade Federal de Sergipe  
Campus da Saúde  
Address: Rua Cláudio Batista, s/n  
Bairro Sanatório  
Postal Code: 49055-520  
Aracajú – SE  
edmeaolivacosta@gmail.com

Financial support: none

<http://dx.doi.org/10.1590/1806-9282.60.06.009>

Conflict of interest: none

## INTRODUCTION

Common mental disorders (anxiety, depressive and somatoform disorders), also known as minor psychiatric disorders, are mild psychic troubles that, throughout the years, may cause great biopsychic and social impact.<sup>1</sup> These disorders have symptoms such as: fatigue, insomnia, forgetfulness, difficulty in concentrating, irritability and somatic complaints.<sup>2</sup> They also indicate relevant psychic suffering and may lead to the development of more serious mental disorders, which seems particularly important in the case of healthcare professionals for their role in assisting the population.<sup>3-5</sup>

Medicine, dentistry and nursing are traditionally recognized as being some of the most strenuous courses at university level as they demand great physical, intellectual and emotional effort from students. In the last year of

the undergraduate program, emotional exhaustion becomes more evident and ends up predisposing the students to common mental disorder.<sup>3,6-11</sup>

We know from the literature that the prevalence of common mental disorder in industrialized countries ranges from 7 to 30%.<sup>4</sup> Similar studies drawn from the Brazilian population, showed that this prevalence varied from 22 to 35%.<sup>12,13</sup>

At the same university, a recent study including only medical students revealed a high prevalence of common mental disorder (42.5%).<sup>14</sup> To date, in this institution, there are no published researches on the mental health of nursing and dental students. National and international studies assessing this kind of population are also scarce.

Several studies have showed that institutions responsible for the training of health professionals should take cognizance of their students' weaknesses regarding the educational process.<sup>15-18</sup>

This study aims to assess the prevalence of common mental disorder among the students of the last three semesters of the medicine, dentistry and nursing courses in a public university in Northeast Brazil and to identify the potential factors associated with this disorder.

## METHODS

The authors conducted a cross-sectional study in February 2010, in a public university from Northeast Brazil. The number of students per class when they were admitted into the university was: 40 for medicine, 20 for dentistry and 20 for the nursing course.

The medicine course follows the Brazilian traditional model for medical teaching comprised of 12 semesters: Basic Sciences Cycle (1<sup>st</sup> to 4<sup>th</sup>), Preparatory Clinical Cycle (5<sup>th</sup> to 9<sup>th</sup>), and Internship (10<sup>th</sup> to 12<sup>th</sup>).

The dentistry course presents 10 semesters: Basic Sciences Cycle (1<sup>st</sup> to 4<sup>th</sup>), Preparatory Clinical Cycle (5<sup>th</sup> to 10<sup>th</sup>) and the Supervised Training Cycle (9<sup>th</sup> and 10<sup>th</sup>).

The Nursing course includes 9 semesters: Basic Sciences Cycle (1<sup>st</sup> to 4<sup>th</sup>), Preparatory Clinical Cycle (5<sup>th</sup> to 8<sup>th</sup>) and the Supervised Training Cycle (9<sup>th</sup> semester).

All the 220 students of medicine, dentistry and nursing regularly enrolled in the last three semesters of college at the time of this survey were invited to participate, and 175 accepted the research terms.

Participants were required to answer two self-administered questionnaires in the classrooms: the Self Reporting Questionnaire (SRQ-20)<sup>1</sup> and a specific questionnaire developed by the authors.

Before that, the teaching staff in each of the three courses received letters from the researchers informing that a survey would be carried out, and asking their permission to have the questionnaires applied during class time.

Every classroom was approached at least twice in order to get the maximum adhesion of the students to the survey. Students who did not return their questionnaires were considered missing.

The SRQ-20 is an assessment scale of anxious, depressive and somatoform symptoms developed by the World Health Organization (WHO). It was introduced by Harding, in 1980, for screening minor psychiatric disorders in basic attention and was validated in Brazil by Mari.<sup>1,4</sup> It is a self-administered instrument with 20 binary response questions related to psycho-emotional symptoms, which showed satisfactory indexes in the studies conducted by

Mari, with sensibility and specificity equal to 85 and 80%, respectively.<sup>1</sup> The students answered the questionnaire based on what they felt during the last 30 days. Scores higher or equal to 6 for men and higher or equal to 8 for women are considered as probable cases. This cutoff, according to the SRQ-20, was determined based on several studies.<sup>1,8,14</sup> Although, this score does not implicate in formal diagnosis, it indicates relevant psychic suffering that draws attention to the mental health of healthcare professionals.

The structured self-administered questionnaire developed and tested by the authors in an earlier pilot study consisted of 54 questions related to socio-demographic features, educational process and personal aspects.

The data analysis was performed using the SPSS statistics software version 16.0. The analysis was done in three stages:

- 1<sup>st</sup> Population description through descriptive statistics (inferential statistics is not suitable for this study, since the authors studied the population instead of a random sample);
- 2<sup>nd</sup> Bivariate and simple analysis, including the construction of tables and calculation of crude odds ratio (OR) instead of prevalence ratio (PR) since OR is the measure obtained in the logistic regression (final step of our analysis) and can also be used in this type of study;
- 3<sup>rd</sup> Analysis of multiple variables by logistic regression. The variables' selection criteria are based on the variable's importance in the literature, on the authors' experience, and on the magnitude of the OR. The variables showing association with CMD >30% were kept in the final model.

The outcome variable (common mental disorder) was adjusted to the following predictive variables: sex, having a steady partner, religion, income, having another occupation, course (socio-demographic features); satisfaction with the course choice, attitude toward the course, thoughts about dropping out the course, self-assessment of academic performance, self-assessment of skill acquisition needed to become a good professional, satisfaction with the teaching strategies, attitude toward the course's activities, course as a source of pleasure (educational process); presence of physical disease, presence of mental disease, feeling emotionally stressed, reaction to conflicts, leisure time, emotional support, expectations about the future and feeling of happiness (personal aspects).

This study was approved by our institutional Ethics Committee of Research on Humans Beings (0018.0.107.000-06 protocol number). Study participants signed a confidentiality agreement authorizing disclosure of data but

concealing identity throughout the study period, including during the completion of questionnaires.

## RESULTS

From all the 220 students enrolled in the last three semesters of the courses, 175 (79.5%) took part in the research: medicine (113), dentistry (47) and nursing (60). Three participants did not answer the SRQ-20, thus being excluded from the study.

According to the cutoff point pre-established for male and female, the studied common mental disorder presented a general prevalence of 33.7% (Table 1).

**TABLE 1** Distribution of health care students according to socio-demographic variables and prevalence of common mental disorder; Public University, Northeast, Brazil, 2010

Variables	N	%	CMD(%)	Crude OR
Total	172	100	33.7	
<b>Sex</b>				
Female	108	62.8	43.5	3.71
Male	64	37.2	17.2	1
<b>Steady partner</b>				
Yes	117	70.5	35.9	1.27
No	49	29.5	30.6	1
Missing	6			
<b>Religion</b>				
Yes	126	73.3	33.3	1
No	46	26.7	34.8	1.06
<b>Family income (Minimum wage)</b>				
1 to 5	12	7.9	41.7	1.87
6 to 10	54	35.5	42.6	1.95
11 to 15	38	25	28.9	1.07
16 to 20	19	12.5	31.6	1.21
More than 20	29	19.1	27.6	1
Missing	20			
<b>Have other occupation</b>				
Yes	27	15.7	40.7	1.43
No	145	84.3	32.4	1

The studied population comprised predominantly female (62.8%) and young (average age  $23.5 \pm 1.6$ ) students. The majority (70.5%) had a steady partner, 73.3% practiced a religion, and 90.5% lived with relatives.

The majority (84.3%) did not have any other occupation apart from being a student in that course, and most of them (35.5%) had a family income of 6 to 10 minimum wages (Table 1).

Concerning variables related to the educational process, 77.6% of the students considered the course to be a source of pleasure, and 79.1% believed that their academic performance was good or excellent. Although 87.7% thought that they were acquiring the skills necessary to become good professionals, only 29.3% were satisfied with the teaching strategies used. In total, 94.7% of the students were satisfied with their career choices, but 35.1% were uncomfortable with course activities and more than a half (56.4%) had thought of dropping out the course at least once.

With regards to personal issues, around half of the students dedicated less than 6 hours per week to leisure activities (50%), reacted aggressively or retracted themselves in situations of conflict (51.5%), and considered themselves emotionally stressed (44.4%).

In terms of a personal support network, 80.2% reported that they were receiving the emotional support they needed, 82% had good expectations for the future, and 92.4% reported feeling happy.

On bivariate analysis of variables related to the educational process, those students that had already thought of dropping out the course (OR=2.52) or felt uncomfortable in academic activities (OR=3.33) presented a greater association with the development of common mental disorders.

Concerning personal aspects, the probability of developing a common mental disorder was higher among the students who considered themselves emotionally stressed (OR=10.60), who reacted to conflicts in a retracted or aggressive way (OR=2.89), who referred the presence of physical disease (OR=3.21), or mental disorder diagnosed by a psychiatrist (OR=2.73).

The probability of developing CMD increased among the students who reported absence of suitable emotional support (OR=2.82), feeling unhappy (OR=13.11), and not so good expectations for the future (OR=8.71).

There were no significant statistical differences in the prevalence of CMD among students of medicine (30.1%), dentistry (36.8%) and nursing (39%) (Table 2).

**TABLE 2** Distribution of health care students according to course and prevalence of common mental disorder; Public University, Northeast, Brazil, 2010

Variables	n	CMD(%)	Crude OR
Total	172	33.7	
<b>Course</b>			
Medicine	93	30.1	1
Dentistry	38	36.8	1.35
Nursing	41	39	1.49

After adjustment using multiple logistic regression analysis, the following variables were associated with common mental disorder: female sex, not having good expectations for the future, not seeing the course as a source of pleasure and considering oneself emotionally tense (Table 3).

**TABLE 3** Outcome of the logistic regression for related variables and common mental disorder in healthcare students; Public University, Northeast, Brazil, 2010

Variables	Crude OR	Adjusted OR
Total	170	
<b>Sex</b>		
Female	3.71	4.34
Male	1	
<b>How do you consider yourself emotionally?</b>		
Calm	1	
Tense	10.61	11.23
<b>Course as a source of pleasure</b>		
Yes	1	
No	2.07	7.52
<b>Expectations for the future</b>		
Good	1	
Not so good	8.71	5.83

## DISCUSSION

The general prevalence of common mental disorder among the students was higher than the rates found in general populations studied in industrialized countries.<sup>4</sup>

A survey carried out in Campinas, Brazil, using SQR-20, revealed a common mental disorder prevalence of 17% in the urban population.<sup>19</sup> In Olinda, Brazil, a study using the same instrument revealed a 35% CMD rate among individuals aged 15 years or older.<sup>13</sup>

A study at the Pernambuco University-Brazil (UPE) among students of some health care courses found a general prevalence of CMD of 34.1%. The prevalence by course was: physical education (25%), nursing (31.8%), dentistry (33.3%), and medicine (42.6%).<sup>8</sup> These results were similar to those found in our survey. Nevertheless, after comparing only medicine courses in Brazil, we found that the prevalence of CMD in students of the course surveyed (30.1%) was smaller than the results of another earlier study by the author in the same university (42.5%) than those found at UPE (42.6%) and UNESP Botucatu (44.7%)<sup>8,14,19</sup> but similar to those found at the Bahia Federal University (29.6%) and Santa Maria-Rio Grande do Sul University (31.7%).<sup>20,21</sup> We believe that similarities or differences

in the courses' infra-structure and the educational models adopted contributed to these results.

Four variables that showed strong association with common mental disorder were identified after adjustment by multiple logistic regression analysis.

In the international literature, having low income, being female, not having a steady partner, being unemployed and practicing no religion are socio-demographic variables that may be identified as factors associated with common mental disorder.<sup>13,22,23</sup>

In this study, only females showed a strong association with common mental disorder after logistic regression. This finding coincides with the literature that asserts that women have higher prevalence of mental disorders and that CMD is the third health problem among females in developed countries and the fifth in undeveloped countries.<sup>13,24</sup>

Studies performed with others university students corroborate with these data. In medical schools in Tehran, female students were likely to develop psychic suffering in the same way that those who had very precarious financial conditions.<sup>25</sup> On the other hand, in Turkey, a high association with depression among female and older students is seen.<sup>26</sup>

In other studies, CMD are more diagnosed in females because they look for health services more than males.<sup>22,24</sup> In our study, the female sex variable showed strong association with CMD after logistic regression, but the female frequency was also greater than male.

Other variables in our study that demonstrated strong association with CMD were: 'not having good expectations for the future', 'not seeing the course as a source of pleasure' and 'feeling emotionally stressed'. This may be explained by the inherent features of the academic atmosphere including tests and tight deadlines that are mainly sources of stress for the students. This finding coincides with the literature which points out emotional stress as an important associated factor to common mental disorder.<sup>15,17,27</sup>

The healthcare courses present certain peculiarities in the educational process that impact negatively the student's physical and psychological health, cognitive function and learning. These stressful factors include the proximity of death and innumerable pathological processes, excessive workload, competitiveness, fear of making mistakes, late financial independence and disappointment with the course, as well as privation of the family convivality and leisure.<sup>18,23,28,29</sup> Sleep problems have been associated with deficits in attention and academic performance,

drowsiness during classes, risk-taking behavior and depression, impaired social relationships, and poorer health.<sup>30-32</sup>

Frequency of experiencing chronic illness, depression, anxiety disorder, seasonal affective disorder, mononucleosis, and sleep difficulties were significant stress predictors.<sup>31-33</sup> Students of medicine, dentistry and nursing represent a population with high educational level that is constantly exposed to this inhospitable environment, which may predispose them to a higher risk of developing common mental disorder.<sup>9,14,16</sup>

Due to the workload of study and training that these courses require, students are also more inclined to develop burnout syndrome.<sup>9,32,34-36</sup>

Despite the high prevalence of CMD among the students assessed, only a small percentage (10.5%) had any mental trouble diagnosed by a psychiatrist. In the same way, in a universe of 7,357 students from 36 medical schools of South Korea, 689 students presented depression and, out of these, only 9.7% were diagnosed and submitted to psychiatric treatment.<sup>37</sup>

This situation of under diagnosis may be motivated by the lack of a support service to the mental health of students in the universities.

Even the students of medicine, dentistry and nursing courses that studied with the most recognized health teams from the best universities in Brazil had their mental health very neglected by these institutions since no healthcare and psycho-pedagogical support service was made offered to the students.<sup>5</sup> Many medical schools, especially in South and Southeast Brazil, have established psycho-pedagogical support services in the last years; however, in Northeast Brazil, this hasn't occurred in the same proportion.<sup>28</sup>

In the USA, most colleges and universities have now developed mental health and counseling programs commensurate with the size of their student bodies, although yet in 1957 the American College Health Association formed a Mental Health Section to serve mental health professionals, 37 years after the American Student Health Associations annual meeting in 1920 had identified "mental hygiene" as critical for college campuses to assist students to reach their highest potential. Indeed, the first student health service is credit to Amherst College in 1861.<sup>38</sup>

Regarding the issues of the educational process, we can observe that, although most students feel satisfied with their course choices and feel comfortable with their courses' activities, more than half of them is not satisfied with the teaching strategy and at least once considered to drop out the course. Nevertheless, these variables did not maintain a strong association with CMD after logistic regression.

The cross-sectional design of our study has a limitation, which is the simultaneous analysis of both exposure and outcome, preventing us from establishing causal relations among the associations found. On the other hand, the purpose of this study was restricted to assess the answers given to the questionnaires that aim to detect symptoms of CMD and not to establish a formal diagnosis. For this reason, further longitudinal studies including a qualitative stage with psychiatric interview are required for a more accurate definition of the problem outcome found in our study. Despite these limitations, the study suggests hypotheses and supplies important data for preventive measures to be adopted.

## CONCLUSION

Considering all the above, it is evident that the mental health of those who will soon become healthcare suppliers for the population needs more attention.

There was no difference regarding CMD prevalence among the students of medicine, dentistry and nursing in the university surveyed. This population showed a high prevalence of CMD and more than its half was discontent with the teaching strategies adopted, having thought at least once about dropping out the course. Furthermore, the majority considered the course chosen as a source of pleasure and had good expectations for the future.

The high prevalence of common mental disorder found by the researchers suggests that preventive measures must be immediately implemented such as: psycho-pedagogical support services for students and lecturers, development courses for the teaching staff, and a healthier environment to improve interpersonal relationships. In addition, we also suggest the raising of awareness among future healthcare professionals regarding the importance of maintaining their physical and mental well-being, which impact positively in the patient assistance.

Longitudinal studies assessing this theme at the researched university and other universities that have a population with similar profile are necessary aiming to identify the causal factors of common mental disorder among students from health-related courses.

## RESUMO

Transtornos mentais comuns e fatores associados entre estudantes de saúde do último ano.

**Objetivo:** determinar a prevalência de transtorno mental comum (TMC) e identificar potenciais fatores associados entre estudantes de medicina, odontologia e enfermagem.

**Métodos:** estudo transversal realizado em uma universidade pública no Nordeste do Brasil com 172 alunos de graduação dos últimos três semestres de Medicina, Odontologia e Enfermagem, em fevereiro de 2010, utilizando o Self Reporting Questionnaire (SRQ-20) e um questionário estruturado desenvolvido pelos autores. A análise dos dados foi realizada por regressão logística.

**Resultados:** a prevalência de TMC foi de 33,7%. Os cursos não apresentaram diferenças na prevalência de TMC. A regressão logística mostrou uma forte associação entre as seguintes variáveis com TMC: sexo feminino (OR=4,34), não ter boas expectativas em relação ao futuro (OR=5,83), curso não ser uma fonte de prazer (OR=7,52) e sentir-se emocionalmente tenso (OR=11,23).

**Conclusão:** a alta prevalência de TMC sugere que medidas preventivas imediatas devam ser implementadas, como: a criação de serviços de apoio psicopedagógico para alunos e programas de desenvolvimento docente.

**Palavras-chave:** saúde mental, estudantes de odontologia, saúde do trabalhador, estudantes de medicina, estudantes de enfermagem, transtornos mentais.

## REFERENCES

- Mari JJ, Williams P. A validity study of a psychiatric screening questionnaire (SRQ-20) in primary care in the city of Sao Paulo. *Br J Psychiatry*. 1986;148:23-6.
- Goldberg DP, Huxley P. Common mental disorders a bio-social model. London: Tavistock/Routledge; 1992.
- Birks Y, McKendree J, Watt I. Emotional intelligence and perceived stress in healthcare students: a multi-institutional, multi-professional survey. *BMC Med Educ*. 2009;9(1):61.
- Harding TW, de Arango MV, Baltazar J, Climent CE, Ibrahim HH, Ladrigo-Ignacio L, et al. Mental disorders in primary health care: a study of their frequency and diagnosis in four developing countries. *Psychol Med*. 1980;10(2):231-41.
- Meleiro AM. [Suicide among physicians and medical students]. *Rev Assoc Med Bras*. 1998;44(2):135-40.
- Benjakul P, Cheunarrom C. Student adjustment problems in two dental schools in Thailand. *J Dent Educ*. 2000;64(5):365-9.
- Burnard P, Haji Abd Rahim HT, Hayes D, Edwards D. A descriptive study of Bruneian student nurses perceptions of stress. *Nurse Educ Today*. 2007;27(7):808-18.
- Facundes VL, Ludermir AB. Common mental disorders among health care students. *Rev Bras Psiquiatr* 2005;27(3):194-200.
- Gorter R, Freeman R, Hammen S, Murtoomaa H, Blinkhorn A, Humphris G. Psychological stress and health in undergraduate dental students: fifth year outcomes compared with first year baseline results from five European dental schools. *Eur J Dent Educ*. 2008;12(2):61-8.
- Heath JR, Macfarlane TV, Umar MS. Perceived sources of stress in dental students. *Dent Update*. 1999;26(3):94-8,100.
- Tysen R, Vaglum P, Gronvold NT, Ekeberg O. Factors in medical school that predict postgraduate mental health problems in need of treatment. A nationwide and longitudinal study. *Med Educ*. 2001;35(2):110-20.
- Lima MS, Beria JU, Tomasi E, Conceição AT, Mari JJ. Stressful life events and minor psychiatric disorders: an estimate of the population attributable fraction in a Brazilian community-based study. *Int J Psychiatr Med*. 1996;26(2):211-22.
- Ludermir AB, Melo Filho DA. [Living conditions and occupational organization associated with common mental disorders]. *Rev Saúde Pública*. 2002;36(2):213-21.
- Costa EF, Andrade TM, Silvano Neto AM, Melo EV, Rosa AC, Alencar MA, et al. Common mental disorders among medical students at Universidade Federal de Sergipe: a cross-sectional study. *Rev Bras Psiquiatr*. 2010;32(1):11-9.
- Divaris K, Barlow PJ, Chendea SA, Cheong WS, Dounis A, Dragan IF, et al. The academic environment: the students perspective. *Eur J Dent Educ*. 2008;12(Suppl 1):120-30.
- Lloyd C, Musser LA. Psychiatric symptoms in dental students. *J Nerv Ment Dis*. 1989;177(2):61-9.
- Seyedfatemi N, Tafreshi M, Hagani H. Experienced stressors and coping strategies among Iranian nursing students. *BMC Nurs*. 2007;6:11.
- Wexler M. Mental health and dental education. *J Dent Educ*. 1978;42(2):74-7.
- Lima MC, Domingues MS, Cerqueira AT. [Prevalence and risk factors of common mental disorders among medical students]. *Rev Saúde Pública*. 2006;40(6):1035-41.
- Almeida AM, Godinho TM, Bitencourt AGV, Telles MS, Silva AS, Fonseca DC, et al. Common mental disorders among medical students. *J Bras Psiquiatr*. 2007;56(4):245-51.
- Benvenú LA, Deitos F, Copette FR. Problemas psiquiátricos menores em estudantes de medicina da Universidade Federal de Santa Maria, RS. *Rev Psiquiatr Rio Gde Sul*. 1996;18(3):229-233.
- Marin-Leon L, Oliveira HB, Barros MB, Dalgallarrondo B, Botega NJ. Social inequality and common mental disorders. *Rev Bras Psiquiatr*. 2007;29(3):250-3.
- Omigbodun OO, Odugogbe AT, Omigbodun AO, Yusuf OB, Bell TT, Olayemi O, et al. Stressors and psychological symptoms in students of medicine and allied health professions in Nigeria. *Soc Psychiatry Psychiatr Epidemiol*. 2006;41(5):415-21.
- Rodrigues-Neto JF, Figueiredo MFS, Faria AAS, Fagundes M. Transtornos mentais comuns e o uso de práticas de medicina complementar e alternativa: estudo de base populacional. *J Bras Psiquiatr*. 2008;57(4):233-9.
- Shariati M, Yunesian M, Vash JH. Mental health of medical students: a cross-sectional study in Tehran. *Psychol Rep*. 2007;100(2):346-54.
- Kaya M, Genc M, Kaya B, Pehlivan E. [Prevalence of depressive symptoms, ways of coping, and related factors among medical school and health services higher education students]. *Turk Psikiyatri Derg*. 2007;18(2):137-46.
- Compton MT, Carrera J, Frank E. Stress and depressive symptoms/dysphoria among US medical students: results from a large, nationally representative survey. *J Nerv Ment Dis*. 2008;196(12):891-7.
- Millan LR, Arruda PC. [Psychological assistance to medical students: 21 years of experience]. *Rev Assoc Med Bras*. 2008;54(1):90-4.
- Finger G, Silva ER, Falavigna A. Use of methylphenidate among medical students: a systematic review. *Rev Assoc Med Bras*. 2013;59(3):285-9.
- Gaultney JF. The prevalence of sleep disorders in college students: impact on academic performance. *J Am Coll Health*. 2010;59(2):91-7.
- Costa EF, Santana YS, Santos AT, Martins LA, Melo EV, Andrade TM. [Depressive symptoms among medical intern students in a Brazilian public university]. *Rev Assoc Med Bras*. 2012;58(1):53-9.
- Leao PB, Martins LA, Menezes PR, Bellodi PL. Well-being and help-seeking: an exploratory study among final-year medical students. *Rev Assoc Med Bras*. 2011;57(4):379-86.
- Dusselier L, Dunn B, Wang Y, Shelley MC 2<sup>nd</sup>, Whalen DF, et al. Personal, health, academic, and environmental predictors of stress for residence hall students. *J Am Coll Health*. 2005;54(1):15-24.
- Baldassin S, Silva N, de Toledo Ferraz Alves TC, Castaldelli-Maia JM, Bhugra D, Nogueira-Martins MC, et al. Depression in medical students: Cluster symptoms and management. *J Affect Disord*. 2012;150(1):110-4.
- Costa EF, Santos SA, Santos AT, Melo EV, Andrade TM. Burnout syndrome and associated factors among medical students: a cross-sectional study. *Clinics*. 2012;67(6):573-80.
- De Abreu Santos AT, Grosseman S, de Oliva Costa EF, da Andrade TM. Burnout syndrome among internship medical students. *Med Educ*. 2011;45(11):1146.
- Roh MS, Jeon HJ, Kim H, et al. Factors influencing treatment for depression among medical students: a nationwide sample in South Korea. *Med Educ*. 2009;43(2):133-9.
- Kraft DP. One hundred years of college mental health. *J Am Coll Health*. 2011;59(6):477-481.

# Estimated glomerular filtration rate in patients with type 2 diabetes mellitus

PAULA CAITANO FONTELA<sup>1</sup>, ELIANE ROSELI WINKELMANN<sup>2\*</sup>, JOICE NEDEL OTT<sup>3</sup>, DOUGLAS PRESTES UGGERI<sup>4</sup>

<sup>1</sup>Physiotherapy undergraduate student, Regional University of the Northwest of Rio Grande dos Sul State (Unijuí), PIBIC/CNPq grant recipient, Ijuí, RS, Brazil

<sup>2</sup>PhD - lecturer at the Regional University of the Northwest of Rio Grande do Sul State (Unijuí), Ijuí, RS, Brazil

<sup>3</sup>Pharmaceutical biochemist - responsible for the Clinical Analysis Laboratory at UNIJUÍ (UNILAB), Ijuí, RS, Brazil

<sup>4</sup>Physician specialized in nephrology - physician at the Ijuí Charity Hospital (HCI), Ijuí, RS, Brazil

## SUMMARY

**Objective:** to estimate the glomerular filtration using the Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, and *serum* creatinine in the screening of reduced renal function in patients with type two diabetes (T2DM) enrolled in the Family Health Strategy (ESF, Brazilian federal health-care program).

**Methods:** a cross-sectional descriptive and analytical study was conducted. The protocol consisted of sociodemographics, physical examination and biochemical tests. Renal function was analyzed through *serum* creatinine and glomerular filtration rate (GFR) estimated according to the CG, MDRD and CKD-EPI equations, available on the websites of the Brazilian Nephrology Society (SBN) and the (NKF).

**Results:** 146 patients aged 60.9±8.9 years were evaluated; 64.4% were women. The prevalence of *serum* creatinine > 1.2 mg/dL was 18.5% and GFR < 60 mL/min/1.73m<sup>2</sup> totaled 25.3, 36.3 and 34.2% when evaluated by the equations CG, MDRD and CKD-EPI, respectively. Diabetic patients with reduced renal function were older, had long-term T2DM diagnosis, higher systolic blood pressure and higher levels of fasting glucose, compared to diabetics with normal renal function. Creatinine showed strong negative correlation with the glomerular filtration rate estimated using CG, MDRD and CKD-EPI (-0.64, -0.87, -0.89) equations, respectively.

**Conclusion:** the prevalence of individuals with reduced renal function based on *serum* creatinine was lower, reinforcing the need to follow the recommendations of the SBN and the National Kidney Disease Education Program (NKDEP) in estimating the value of the glomerular filtration rate as a complement to the results of *serum* creatinine to better assess the renal function of patients.

**Keywords:** type 2 diabetes mellitus, kidney function tests, kidney failure, chronic, public health.

Study conducted at the Regional University of the Northwest of the State of Rio Grande do Sul, Ijuí, RS.

Article received: 4/1/2013

Accepted for publication: 3/31/2014

\*Correspondence:

Address: RS 155, Km 06, Vila Santana,  
Mail Box: 383  
Postal Code: 98700-000  
Ijuí - RS  
elianew@unijuí.edu.br

<http://dx.doi.org/10.1590/1806-9282.60.06.010>

Conflict of interest: none

## INTRODUCTION

Assessment of renal function in individuals with *diabetes mellitus* (DM) is extremely important since diabetic nephropathy (DN) constitutes a major cause of chronic kidney disease in the world, which makes DM the most frequent cause of end-stage renal disease.<sup>1,2</sup> Approximately 40% of all diabetic patients develop DN,<sup>3</sup> which is the most common diagnosis among individuals in renal replacement programs, accounting for up to 44% of cases.<sup>4</sup>

In Brazil, in 2010, 27.5% of patients on dialysis had DN, and it is likely that in the coming years a significant increase in the number of diabetic patients undergoing dialysis therapy occurs.<sup>5</sup>

Early identification and appropriate management of chronic kidney disease (CKD) are important measures to slow its progression. In clinical practice, measurement of plasma creatinine has been the method most often used

to assess renal function. However, it has been demonstrated that “apparently normal” *serum* creatinine levels may be accompanied by loss of renal function, making this a relatively late parameter for lesion detection.<sup>6</sup> Although the measurement of the calculated creatinine clearance is considered the reference standard for determining the glomerular filtration, its methods are laborious, expensive and require specialized equipment and personnel, making them impractical in daily practice.<sup>7</sup> Therefore, some formulas to estimate GFR were developed, and the most employed and analyzed equations are Cockcroft and Gault (CG),<sup>8</sup> Modification of Diet in Renal Disease (MDRD)<sup>9</sup> and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).<sup>10</sup>

The SBN and the NKDEP have recommended informing the amount of estimated glomerular filtration rate as a complement to results of *serum* creatinine.<sup>11</sup> Currently, the American Diabetes Association (ADA) recommends annual screening of DN with evaluation of the urinary excretion of albumin and GFR estimated using equations that include *serum* creatinine,<sup>12</sup> while the NKF recommends that the MDRD equation should be used to estimate GFR.<sup>13</sup>

That said, the present study aimed at estimating the filtration rate by using the CG, MDRD and CKD-EPI equations, and *serum* creatinine as methods for screening reduced renal function in patients with T2DM enrolled in the ESF program.

## METHODS

A cross-sectional descriptive and analytical study was conducted, including a sample of patients with type 2 *diabetes mellitus*, enrolled in the Family Health Strategy and living in the urban area of the municipality of Ijuí, state of Rio Grande do Sul (Brazil). The exclusion criteria were: individuals older than 75 years, difficulty understanding the proposed procedures, bedridden individuals, or impairments during ambulation.

The sample size was calculated according to population data from 2009, in which the city of Ijuí had a total of 819 diabetics enrolled in nine ESF centers, in urban areas. The StatCalc application of Epi Info 3.5.3 software was used; considering a prevalence of nonspecific outcome of 50%, 95% confidence interval, and 5% alpha-type error, we obtained a sample size of 269 patients, including 5% for possible losses, leaving a sample size of 283 patients. Later, we contacted the head nurse of each ESF center to conduct a meeting with the community health workers to present the project and decide which patients would be evaluated, which was done randomly by sortition.

The invitation to participate in the study was done to patients during home visits in the company of community health workers, whenever possible. On these occasions, the research project was explained to the patients, and the clinical and laboratory evaluations of the patients who agreed to participate were scheduled. The evaluations were performed, in the Physiotherapy Clinic at the Regional University of the Northwest of the State of Rio Grande do Sul (Unijuí), and the clinical analyses laboratory of Unijuí (Unilab), respectively, being performed by health professionals properly trained to standardize the assessments.

To analyze the social habits and health status of patients with T2DM a structured interview that sought to identify cardiovascular risk factors was performed. Every patient who claimed to be a smoker at the time of the evaluation, regardless of the number of cigarettes, was classified as a smoker; likewise, those who reported drinking alcohol during the study period in any quantity and frequency were classified as drinkers. Excessive salt intake and stress were considered according to the patient's own perception. Individuals who reported exercising at least three times per week, each session lasting 30 minutes, were classified as physically active. The others were considered sedentary.

At the same time, systolic (SBP) and diastolic blood pressure (DBP) were measured in millimeters of mercury (mmHg),<sup>14</sup> using aneroid sphygmomanometer with the patient seated; blood pressure measurement was standardized in the right upper limb. The evaluation of anthropometric data was also performed. Weight (in kilograms) was measured using a digital scale (Toledo®), and height (in meters) using a stadiometer (Toledo®), according to recommended techniques.<sup>15</sup> The ideal body weight for each patient was calculated using the CG and Lorenz' formulas, which estimate the ideal weight in terms of the individual's height in centimeters. The Body Mass Index (BMI) was calculated using the ratio of body weight and height squared (Kg/m<sup>2</sup>) and classified according to the criteria used by the World Health Organization (WHO).<sup>16</sup> Waist circumference (WC) was measured at the midpoint between the last rib and the iliac crest, whereas hip circumference (HC) was measured over the iliac crest, using standard measuring tape, flexible and non-extensible, accurate to 1 mm.<sup>17</sup>

Date and time of lab test appointments were scheduled at the end of the interview and clinical evaluation. Patients were personally informed about the procedures for sample collection, and instructed to fast for at least eight

hours before blood collection, in addition to receiving written instructions and containers for collection of first morning urine.

Renal function was assessed based on the result of *serum* creatinine, obtained from biochemical test, and GFR estimated using CG, MDRD and CKI-EPI equations, calculated using the formulas provided in the SBN and NKF websites. Values above 1.2 mg/dL for *serum* creatinine<sup>18</sup> and below 60 mL/min/1.73m<sup>2</sup> for GFR estimated by CG, MDRD and CKI-EPI,<sup>19,20</sup> were regarded as impaired renal function, since glomerular filtration rate below 60 mL/min/1.73m<sup>2</sup> represents a decrease of approximately 50% in normal renal function, which, below this level, increases the prevalence of complications of CKD.<sup>21</sup>

For data processing, we used the statistical Package for Social Science – SPSS software (18.0 version, Chicago, IL, USA). In the statistical analysis, all variables were tested for normality using the test Kolmogorov-Smirnov (K-S). Qualitative variables are presented as frequencies and percentages, and quantitative variables as mean and standard deviation (mean ± SD). We used Mann-Whitney test for comparison of two independent groups with non-normal distribution and the Student's *t* test for variables with normal distribution in order to verify variable differences per gender, and between individuals with normal and reduced renal function. The Spearman correlation coefficient was used to evaluate the correlation between clinical/biochemical parameters and GFR estimated using CG, MDRD and CKD-EPI equations. We considered statistically significant *p* < 0.05. All tests were applied with a confidence interval (CI) of 95%.

The research project was approved by the Research Ethics Committee (CEP) at Unijuí, after consolidated opinion n° 91/2010.

## RESULTS

283 patients with T2DM who met the study's criteria were selected for a home visit and invitation to participate, based on information collected by ESF health workers or gathered from medical records kept at nine ESF centers in the urban area of the municipality of Ijuí, state of Rio Grande do Sul. Out of this total, 64 patients were excluded from the study because they either did not attend the visit, did not accept the invitation to join the study, did not identify the address provided, or did not sign the Free and Informed Consent form. Of the 219 diabetic participants, we excluded 73 (33.33%) due to insufficient data to assess renal function, since they did not perform biochemical tests for *serum* creatinine; this led to a total sample of 146 patients with T2DM in the present study.

Patients had a mean age of 60.9 ± 8.9 years; 64.4% (94/146) were female. Time of T2DM diagnosis, body mass, height, systolic blood pressure, *serum* creatinine and GFR by CG, MDRD and CKD-EPI equations were greater on average among men, while among women body mass index, waist circumference, hip circumference, *serum* blood glucose, total cholesterol and triglycerides were higher. Waist circumference, time of type 2 diabetes' diagnosis, diastolic blood pressure, fasting blood glucose, total cholesterol and GFR according to the CG equation were variables that did not differ statistically (*p* > 0.05) (Table 1).

**TABLE 1** Clinical profile of patients with type 2 diabetes mellitus

Variables	F (n=94)	M (n=52)	p
	M±DP	M±DP	
Age (years)	59.7±9.2	63.3±8.1	0.04*£
Body mass (Kg)	78.3±16.1	81.9±12.2	0.04*£
Height (cm)	155.0±5.7	169.2±6.3	0.000**£
BMI (Kg/m <sup>2</sup> )	32.5±6.3	28.7±4.1	0.000**£
WC (cm)	105.8±14.5	103.8±10.2	0.18£
HC (cm)	108.9±13.3	101.9±10.2	0.001**£
TD-T2DM (years)	6.9±7.2	8.2±7.4	0.21£
SBP (mmHg)	132.0±16.6	138.9±15.3	0.005**£
DBP (mmHg)	82.7±10.8	82.5±14.8	0.45£
Fasting blood glucose (mg/dL)	127.1±53.8	122.2±48.2	0.78£
Total cholesterol (mg/dL)	179.6±44.1	169.9±52.2	0.23?
Triglycerides (mg/dL)	196.9±105.6	165.2±95.2	0.04*£
<i>Serum</i> creatinine (mg/dL)	1.0±0.29	1.1±0.35	0.03*£
CG (mL/min/1.73 m <sup>2</sup> )	80.6±32.0	85.7±30.5	0.16£
MDRD (mL/min/1.73 m <sup>2</sup> )	66.2±22.1	79.3±26.4	0.001**£
CKD-EPI (mL/min/1.73 m <sup>2</sup> )	66.5±20.4	74.5±20.5	0.01**£

\*: *p* < 0.05; \*\*: *p* < 0.01; F: female; M: male; M±DP: mean±standard deviation; £: Mann-Whitney test; ?: Student's *t* test; kg: kilogram; cm: centimeters; Kg/m<sup>2</sup>: kilograms per square meter; WC: waist circumference; HC: hip circumference; TD-T2DM: time of diagnosis of T2DM; SBP: systolic blood pressure; mmHg: millimeters of mercury; DBP: diastolic blood pressure; mg: milligrams; dL: deciliter; CG: Cockcroft-Gault; mL: milliliter; min: minute; m<sup>2</sup>: square meter; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

With regard to the social habits and medical history of the patients with T2DM, we observed that most diabetics were older (58.2%), considered overweight (35%) or class I obese (30.1%), referred the absence of hypersodic diet (82.9%) and had high blood pressure (73.3%) associated with T2DM. The prevalence of smoking and drinking habits in the population studied was 15.8% and 6.8%, respectively. Almost ¾ of the sample (73.1%) said that they did not exercise regularly.

The assessment of renal function, according to *serum* creatinine and GFR calculated using GC MDRD and CKD-EPI equations, shows that the prevalence of *serum*

creatinine above 1.2 mg/dL was 18.5%. In the case of GFR below 60 mL/min/1.73m<sup>2</sup>, one can observe a decrease in renal function of 25.3, 36.3 and 34.2% when assessed by CG, MDRD and CKD-EPI equations, respectively. This classification was used to categorize individuals according to demographic, anthropometric, clinical and laboratory characteristics of T2DM patients (Table 2).

According to the screening methods for reduced renal function in patients with T2DM used in this study, patients with impaired renal function are older, have diag-

nosed their condition for longer times, and show higher values for SBP and fasting blood glucose (Table 2).

In Table 3, the correlations between clinical and biochemical parameters and GFR estimated based on the equations were negative for *serum* creatinine, age and time of diagnosis of T2DM, and positive between body/mass BMI and GFR estimated using CG equation. In spite of having achieved statistical significance, we point out that the correlations found between GFR, according to the equations, and the clinical pa-

**TABLE 2** Evaluation of demographic, anthropometric, clinical and laboratory characteristics according to the criteria adopted for assessment of renal function in T2DM

Variables	Serum creatinine		CG		MDRD		CKD-EPI	
	Normal (n=119)	Impaired (n=27)	Normal (n=109)	Impaired (n=37)	Normal (n=93)	Impaired (n=53)	Normal (n=96)	Impaired (n=50)
Gender (F:M)	83:36	11:16	68:41	26:11	53:40	41:12*	57:39	37:13
Age (years)	60.4±9.3	63.8±6.7*	58.9±8.4	67.1±7.8**	59.9±9.3	62.9±8.1*	59.2±9.4	64.4±6.9**
TD-T2DM (years)	6.8±6.7	9.8±9.1	6.7±6.5	9.6±8.5*	6.4±6.1	9.0±8.7*	6.4±6.0	9.2±9.0
BMI (Kg/m <sup>2</sup> )	31.3±6.0	30.3±5.0	32.3±5.7	27.7±4.8**	30.6±5.3	32.0±6.8	30.7±5.5	32.0±6.4
WC (cm)	104.8±13.3	106.4±12.7	107.5±11.8	98.1±14.3**	104.5±10.9	106.3±16.3	104.3±11.7	106.7±15.5
HC (cm)	106.8±13.2	104.9±10.2	108.8±12.0	99.2±12.2**	105.9±12.7	107.3±12.8	105.8±13.2	107.6±11.7
SBP (mmHg)	132.7±15.2	142.2±19.5*	134.1±16.3	135.6±17.3	133.0±16.1	137.0±17.1	132.6±15.9	138.0±17.0*
DBP (mmHg)	81.7±11.2	86.7±15.9	82.8±12.8	82.4±10.7	82.1±13.0	83.7±11.1	81.9±12.8	84.1±11.2
TC (mg/dL)	175.6±45.5	178.4±55.1	178.7±47.1	168.7±47.3	178.1±45.7	172.8±49.9	178.3±46.6	172.1±48.5
Trig. (mg/dL)	186.2±104.9	183.0±94.4	188.1±98.3	178.2±116.1	182.8±95.7	190.5±115.0	185.1±105.5	186.5±98.4
FG (mg/dL)	120.0±45.0	148.7±71.3	124.9±48.3	126.4±61.6	121.2±43.8	132.5±63.3	123.7±46.5	128.5±61.1

Mann-Whitney test. \*: p<0,05; \*\*: p<0,01; F: female; M: male; CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; TD-T2DM: Time of diagnosis of T2DM; BMI: body mass index; Kg/m<sup>2</sup>: kilograms per square meter; WC: waist circumference; cm: centimeters; HC: hip circumference; SBP: systolic blood pressure; mmHg: millimeters of mercury; DBP: diastolic blood pressure; TC: total cholesterol; mg: milligrams; dL: deciliter; Trig.: triglycerides; FG: fasting blood glucose.

**TABLE 3** Correlation coefficients between clinical/biochemical parameters and glomerular filtration rate, estimated by the CG, MDRD, CKD-EPI equations for patients with T2DM enrolled in the ESF program

	GFR CG	GFR MDRD	GFR CKD-EPI
	r	r	r
Age (years)	-0.57***	-0.20*	-0.30***
TD-T2DM (years)	-0.29***	-0.18*	-0.21**
Body mass (Kg)	0.44***	0.16	-0.02
Body mass index (kg/m <sup>2</sup> )	0.38***	-0.07	-0.08
Fasting blood glucose (mg/dL)	0.07	-0.04	-0.02
Total cholesterol (mg/dL)	-0.01	-0.02	-0.00
Triglycerides (mg/dL)	-0.05	-0.14	-0.11
Serum creatinine (mg/dL)	-0.64***	-0.87***	-0.89***

Spearman Correlation Test; \*: p<0.05; \*\*: p<0.01; \*\*\*: p<0.001; ; CG: Cockcroft-Gault; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; TD-T2DM: Time of diagnosis of T2DM; BMI: body mass index; Kg/m<sup>2</sup>: kilograms per square meter; WC: waist circumference; cm: centimeters; HC: hip circumference; SBP: systolic blood pressure; mmHg: millimeters of mercury; DBP: diastolic blood pressure; TC: total cholesterol; mg: milligrams; dL: deciliter; Trig.: triglycerides; FG: fasting blood glucose.

rameters were not considered strong, unlike that observed with *serum* creatinine.

## DISCUSSION

From the results of this study, we highlight the lower prevalence of impaired renal function observed through *serum* creatinine. This supports the literature findings that indicate that *serum* creatinine alone is not a sensitive method to assess renal function in asymptomatic CKD patients.<sup>22</sup>

Following the recommendations of the SBN and the NKDEP, the value of GFR is estimated as a complement to the results of *serum* creatinine to better assess a patient's renal function. In this study, the prevalence of impaired renal function estimated by GFR calculation, using the CG, MDRD and CKD-EPI equations, was homogeneous (25.3, 36.3 and 34.2%). There is, however, greater similarity between the results of the MDRD and CKD-EPI equations, and a more marked difference (11%) compared to the CG equation, which resulted in prevalence almost twice greater than the change in renal function estimated through *serum* creatinine.

The literature reports that both equations show excellent correlation with the calculated GFR.<sup>21</sup> However, studies indicate that the MDRD equation proves more effective in detecting changes in patients with early renal disease,<sup>23</sup> as seen in the present study, where the prevalence of decreased renal function was greater in diabetic patients assessed by MDRD.

In this context, we draw attention to the fact that the formulas most commonly used and known to estimate GFR were validated in studies with target populations, thus presenting singularities. The CG formula was the first of these equations to gain acceptance, estimating creatinine clearance. When originally described, the CG equation was based on urinary creatinine excretion of hospitalized Caucasian men, aged 18-92 years and with normal renal function. The calculation was not standardized for a body surface area of 1.73m<sup>2</sup> and a correction was necessary for women.<sup>8</sup> It systematically overestimates the GFR, because tubular creatinine secretion and the increase in weight due to obesity or fluid overload are not taken into consideration.<sup>24</sup>

The MDRD equation to estimate GFR was originally developed based on data from a study entitled *Modification of Diet in Renal Disease*, which included CKD patients and not healthy individuals. The gold standard used to develop the MDRD equation was that of 125I-iothalamate clearance, which estimates GFR in mL/min/1.73m<sup>2</sup>, and not creatinine clearance.<sup>9</sup> In its original version, the MDRD equa-

tion requires the determination of *serum* albumin and *urea* nitrogen. Currently, the abbreviated MDRD formula with four variables has been recommended, because its performance is as good as the initial equation's.<sup>25</sup> GFR as calculated using MDRD and the actual GFR are very close to each other for results below 60 mL/min/1.73m<sup>2</sup>, while the GFR exceeds the estimated rate by a small difference when the result is greater than 60 mL/min/1.73m<sup>2</sup>.<sup>26</sup>

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) group has recently developed, based on a cohort study that included individuals with and without CKD, a new equation which is a variation of the MDRD formula.<sup>10</sup> The equation, called CKD-EPI, uses the same four variables adopted by the MDRD equation, but comparatively has better performance and risk prediction.

Using the results of this practical study to calculate GFR estimated by MDRD, which is considered more effective,<sup>23</sup> 36.3% of the patients were found to present levels below 60 mL/min/1.73m<sup>2</sup>. This represents an approximate decrease of 50% in normal kidney function.<sup>21</sup> Of these patients 77.4% (41/53) were women. According to the literature, levels of glomerular filtration rate below that show increased prevalence of complications of CKD. The minimum value found in this study was 20, 21 and 25.40 mL/min/1.73m<sup>2</sup>, estimated using the CKD-EPI, MDRD and CG equations, respectively. When the GFR reaches very low values, less than 15 mL/min/1.73m<sup>2</sup>, the so-called functional renal failure occurs, that is, the most advanced stage of progressive functional loss observed in CKD, which was never observed in the present study.

The mean estimated GFR according to CG equation for men and women in this study (85.7±30.5 and 80.6±32.0mL/min, respectively) had similar results to those found in the study by Guimarães et al.<sup>27</sup> that also assessed a population of diabetic patients, finding the estimated creatinine clearance at 71.67±30.85 mL/min/1.73m<sup>2</sup>, using the CG calculation. The latter also compared the GFR results determined by radioisotope methods and equivalent levels for GFR estimated using creatinine clearance. They came to the conclusion that the creatinine clearance underestimates the clearance of DTPA-Tc99m, particularly when the values for GFR are higher. Nevertheless, they claim that the CG formula is useful when GFR is below 100 mL/min/1.73m<sup>2</sup>, phase in which it is more accurate since the repeated use of a radioisotope method becomes impractical.<sup>27</sup>

It is possible, therefore, to observe that the use of formulas to determine GFR has been widely adopted and correlated well with radioisotope methods to measure glomerular filtration, especially when it is decreased

(< 60 mL/min/1.73m<sup>2</sup>).<sup>9</sup> Using these equations to estimate GFR has lower cost and greater convenience in clinical practice,<sup>8,9</sup> facilitating early screening and diagnosis of CKD in diabetics in primary care.

The various formulas were created to calculate the GFR more accurately, and they include not only the *serum* concentration of creatinine, but also correction factors, which allow for a greater individualization of the results, increasing the test's sensitivity aiming at detecting deficits in renal function.<sup>28</sup> But we cannot forget that, in elderly patients, glomerular filtration may decrease as part of the body's aging process, and it can be difficult to differentiate the age-related decrease in glomerular filtration from that seen in renal dysfunction in the elderly. Therefore, for purposes of stratification and intervention, the diagnosis of renal dysfunction should not be solely based on the estimate of GFR, but also the presence of other markers of kidney disease.<sup>29</sup>

The present study did not use any gold standard marker (insulin or iothalamate clearance) for comparison due to high cost, extended time for the procedure, and difficult access for patients followed in primary care. Given this bias, *serum* creatinine is the most widely used method because of its low cost and accessibility to users of public services. Another limitation of the study is the lack of association between the drugs taken by the patients and their GFR, since the drug therapy may interfere with the glomerular filtration rate and lipid profile.

But more than the comparison of formulas, we stress the importance of early diagnosis to improve the health and enhance the quality of life of diabetic patients. From routine screening and the application of calculations to estimate the GFR, it is possible to determine the renal function in these individuals earlier, and thus try to reduce the prevalence and incidence of renal failure through the adoption of intervention measures. This is most relevant since, currently, CKD is considered a global public health problem, DM being the most common cause of CKD in the world and the second most common etiology among dialysis patients in Brazil.

Also important forms of intervention are actions guided to change the patients' lifestyle, which is crucial to halt the progression of CKD. Dieting, exercising, controlling blood pressure and blood glucose, controlling dyslipidemia and obesity are all measures more effective than oral hypoglycemic agents.

After analyzing the results, we conclude that the prevalence of individuals with reduced renal function based on serum creatinine was lower, reinforcing the need to follow the recommendations of the SBN and the NKDEP, which is estimating the value of glomerular filtration as

a complement to the results of *serum* creatinine to better assess the patients' renal function. Diabetic patients with reduced renal function were older, had their T2DM diagnosis for a longer time, higher systolic blood pressure and higher levels of fasting blood glucose, compared to diabetics with normal renal function.

## ACKNOWLEDGEMENTS

The support was provided by the Rio Grande do Sul State Research Foundation (Fapergs), the National Council of Scientific and Technological Development (CNPq) and the Regional University of the Northwest of the State of Rio Grande do Sul (Unijuí) through the granting of scientific initiation scholarships.

**Conflict of interest:** the authors declare no conflicts of scientific interest regarding this study.

## RESUMO

Estimativa da taxa de filtração glomerular em pacientes com *diabetes mellitus* tipo 2.

**Objetivo:** estimar a taxa de filtração glomerular por meio das equações Cockcroft e Gault (CG), Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) e da creatinina sérica na triagem da função renal reduzida em pacientes com *diabetes mellitus* tipo 2 (DM2), adscritos em estratégia de saúde da família (ESF).

**Métodos:** foi realizado um estudo transversal, descritivo e analítico. O protocolo foi constituído de dados socio-demográficos, exame físico e dosagens bioquímicas. A função renal foi analisada pela creatinina sérica e pela taxa de filtração glomerular (TFG) estimada segundo as equações CG, MDRD e CKD-EPI, disponibilizadas nos *websites* da Sociedade Brasileira de Nefrologia (SBN) e da National Kidney Foundation (NKF).

**Resultados:** foram avaliados 146 pacientes com média de idade de 60,9±8,9 anos; 64,4% eram mulheres. A prevalência de creatinina sérica >1,2 mg/dL foi de 18,5%, e a TFG < 60 mL/min/1,73 m<sup>2</sup> foi de 25,3%, 36,3% e 34,2% quando avaliadas pelas equações CG, MDRD e CKD-EPI, respectivamente. Os pacientes diabéticos com função renal reduzida eram idosos, apresentavam maior tempo de diagnóstico de DM2, pressão arterial sistólica mais elevada e níveis superiores de glicemia de jejum, quando comparados a diabéticos com função renal normal. A creatinina apresentou correlação negativa e forte com a taxa de filtração glomerular estimada pelas equações CG, MDRD e CKD-EPI (-0,64; -0,87; -0,89, respectivamente).

**Conclusão:** a prevalência de indivíduos com função renal reduzida a partir dos valores de creatinina sérica foi inferior, reforçando a necessidade de seguir as recomendações da SBN e do National Kidney Disease Education Program (NKDEP) em estimar o valor do ritmo de filtração glomerular como complemento ao resultado da creatinina sérica para melhor avaliar a função renal dos pacientes.

**Palavras-chave:** *diabetes mellitus* tipo 2; testes de função renal; falência renal crônica; saúde pública.

## REFERENCES

- Atkins RC, Zimmet P. World Kidney Day 2010: diabetic kidney disease-act now or pay later. *Am J Kidney Dis.* 2010;55:205-8.
- Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC Public Health.* 2008;8:117.
- Murussi M, Campagnolo N, Beck MO, Gross JL, Silveiro SP. High-normal levels of albuminuria predict the development of micro and macroalbuminuria and increased mortality in Brazilian Type 2 diabetic patients: an 8-year follow-up study. *Diabet Med.* 2007;24:1136-42.
- US Renal Data System, USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda; 2010.
- Tratamento e acompanhamento do diabetes mellitus. Diretrizes da Sociedade Brasileira de Diabetes. Diagraphic; 2007.
- Salgado JV, Neves FA, Bastos MG, França AK, Brito DJ, Santos EM, et al. Monitoring renal function: measured and estimated glomerular filtration rates - a review. *Braz J Med Biol Res.* 2010;43:528-36.
- Stevens LA, Levey AS. Measured GFR as a confirmatory test for estimated GFR. *J Am Soc Nephrol.* 2009;20:2305-13.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from *serum* creatinine. *Nephron.* 1976;04:31 PM-41.
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from *serum* creatinine: a new prediction equation. *Ann Intern Med.* 1999;130:461-70.
- Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604-12.
- Pereira AB, Nishida SK, Kirsztajn GM. Como avaliar o ritmo de filtração glomerular. *J Bras Nefrol.* 2006;28(Suppl 1):15-8.
- American Diabetes Association. Standards of Medical Care in Diabetes - 2010. *Diabetes Care.* 2010;33:11-61.
- Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med.* 2003;139:137-47.
- Sociedade Brasileira de Nefrologia. VI Diretrizes Brasileiras de Hipertensão Arterial. *J Bras Nefrol.* 2010;32(supl 1):1-64.
- Kamimura MA, Baxmann A, Sampaio LR, Cuppari L. Avaliação nutricional. In: Cuppari L. Guia de nutrição: nutrição clínica no adulto. São Paulo: Manole; 2005. p.71-108.
- WHO. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. Geneva: WHO; 2005.
- Heyward VH, Stolarczyk LM. Avaliação da composição corporal aplicada. São Paulo: Manole; 2000. p.73-97.
- Di Napoli Filho M, Burmeister JE, Miltersteiner DR, Campos BM, Costa MG. Estimativa da função renal pela fórmula de Cockcroft e Gault em pacientes com sobrepeso ou obesidade. *J Bras Nefrol.* 2008;30:185-91.
- Magacho EJC, Pereira AC, Mansur HN, Bastos MG. Nomograma para a estimação da taxa de filtração glomerular baseado na Fórmula CKD-EPI. *J Bras Nefrol.* 2012;34:313-5.
- National Kidney Foundation - NKF. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis.* 2002;39(2 Suppl 1):1-266.
- Bastos MG, Bregman R, Kirsztajn GM. Doença renal crônica: frequente e grave, mas também prevenível e tratável. *Rev Assoc Med Bras.* 2010;56:248-53.
- Shemesh O, Golbetz H, Kriss JP, Meyers BD. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int.* 1985;28:830-8.
- Sodré FL, Costa JCB, Lima JCC. Avaliação da função e da lesão renal: um desafio laboratorial. *J Bras Patol Med Lab.* 2007;43:329-37.
- Bastos MG, Kirsztajn GM. Doença Renal Crônica: importância do diagnóstico precoce, encaminhamento imediato e abordagem interdisciplinar estruturada para melhora do desfecho em pacientes ainda não submetidos à diálise. *J Bras Nefrol.* 2011;33:93-108.
- Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from *serum* creatinine. *J Am Soc Nephrol.* 2000;11:A0828.
- Chronic Kidney Disease Epidemiology Collaboration. Using standardized *serum* creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006;145:247-54.
- Guimarães J, Bastos M, Melo M, Carvalheiro M. Nefropatia diabética: taxa de filtração glomerular calculada e estimada. *Acta Med Port.* 2007;20:145-50.
- Kirsztajn GM. Avaliação do ritmo de filtração glomerular. *J Bras Patol Med Lab.* 2007;43:257-66.
- Nogueira CS, Oliveira CRD. Disfunção renal: definição e diagnóstico. São Paulo: SAESP; 2006/2007. Cap. 64, p. 87-125.

# Doppler flowmetry of ophthalmic arteries for prediction of pre-eclampsia

LARISSA OLIVEIRA DE AQUINO<sup>1</sup>, HENRIQUE VÍTOR LEITE<sup>2</sup>, ANTÔNIO CARLOS VIEIRA CABRAL<sup>3</sup>, AUGUSTO HENRIQUES F. BRANDÃO<sup>4\*</sup>

<sup>1</sup>Physician at the Hospital das Clínicas, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil

<sup>2</sup>Adjunct Professor at the Department of Gynecology and Obstetrics, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil

<sup>3</sup>Full Professor at the Department of Gynecology and Obstetrics, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil

<sup>4</sup>Professor at the Postgraduate Program in Women's Health, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil

## SUMMARY

**Background:** central nervous system (CNS) hyperperfusion is one of the events that constitute the pathophysiological basis for the clinical manifestations and complications of pre-eclampsia (PE). Detecting the increased flow in the CNS through Doppler flowmetry of the ophthalmic artery might precede the clinical onset of PE and could be used as a marker for subsequent development of PE.

**Objective:** to evaluate the ophthalmic artery resistive index (OARI) values in the second trimester of pregnancy for prediction of the clinical manifestations of PE.

**Methods:** a total of 73 patients with risk factors for the development of PE were selected from the prenatal service at the HC-UFMG. They were submitted to ophthalmic artery Doppler flowmetry between 24 and 28 weeks of pregnancy and monitored until the end of the pregnancy to verify the occurrence of PE. ROC curves were created to determine the predictive characteristics of the OARI.

**Results:** fourteen of the patients selected developed PE and 59 remained normotensive until the postpartum period. Patients with subsequent development of PE presented OARI values lower than patients that remained normotensive ( $0.682 \pm 0.028$  X  $0.700 \pm 0.029$ ,  $p=0.044$ ). Considering the development of PE as an outcome, the area under the OARI curve was 0.694 (CI 0.543 to 0.845), with no points obtaining good values of sensitivity or specificity.

**Conclusion:** Doppler flowmetry of ophthalmic arteries between 24 and 28 weeks of pregnancy did not present itself as a good exam for predicting PE.

**Keywords:** vascular endothelium, pre-eclampsia, hypertension, laser Doppler flowmetry.

Study conducted at the Federal University of Minas Gerais – Hospital das Clínicas  
Belo Horizonte, MG

Article received on 4/9/2014

Accepted for publication on 4/12/2014

\*Correspondence:

Universidade Federal de Minas Gerais  
(UFMG) - the Otto Cime Maternity  
Hospital-HC

Address: Av. Professor Alfredo Balena 110  
4<sup>th</sup> floor

Postal Code: 30320-030

Belo Horizonte – MG

augustohfbrandao@hotmail.com

Financial support: Minas Gerais State  
Research Foundation (FAPEMIG)

<http://dx.doi.org/10.1590/1806-9282.60.06.011>

Conflict of interest: none

## INTRODUCTION

Hypertensive disorders in pregnancy are considered a major cause of maternal mortality, particularly in developing countries, including Brazil.<sup>1</sup> Pre-eclampsia (PE) is a syndrome of multifactorial etiology,<sup>1</sup> and its comorbidities account for a significant portion of these deaths, justifying major investment in research aiming to predict the clinical manifestations and complications of PE.<sup>2</sup>

Despite being considered a disease of the second half of the pregnancy, since the clinical manifestations of PE occur only after the twentieth week, the pathophysiological process of this syndrome begins early in the pregnancy,<sup>3</sup> and alterations may be identified from the first gestational trimester.<sup>4</sup> Assessing these events is of immense clinical

interest given that, if detected, they can be considered as markers of increased risk for developing this disease.<sup>5</sup>

Although its etiology is unknown, accumulated evidence implies that the placenta is the first site in the genesis of pre-eclampsia.<sup>6</sup> An exacerbated inflammatory process associated with local oxidative stress causes impairment of the placental angiogenesis process, preventing proper trophoblast invasion and remodeling of the uterine spiral arteries.<sup>7</sup>

The first and most studied of these events was placental perfusion, assessed using Doppler flowmetry of the uterine arteries.<sup>3</sup> With increased knowledge about other pathophysiological processes, such as endothelial

dysfunction and hyperperfusion of the central nervous system (CNS), new perspectives have emerged.<sup>8</sup>

In the CNS, endothelial injury alters the self-regulating blood flow system in this region, which culminates in hyperflow and cerebral edema, a direct cause of tonic-clonic seizures that characterize eclampsia.<sup>9</sup>

The assessment of CNS perfusion can be realized indirectly by Doppler flowmetry of the ophthalmic artery, using its resistance index (RI). Patients with signs of central hyperflow present a lower resistance index compared to normotensive patients.<sup>10</sup>

This study has the objective of assessing the ophthalmic artery resistive index (OARI) values in the second trimester of pregnancy for the prediction of the clinical manifestations of PE.

## MATERIALS AND METHODS

### Patients

A total of 73 pregnant women between 24 and 28 weeks that presented risk factors for the development of PE were selected by the Prenatal Service at the Hospital das Clínicas, Federal University of Minas Gerais. Subsequently, they were submitted to Doppler flowmetry of the ophthalmic arteries and were monitored up to the postpartum period for the diagnosis of PE.

PE diagnosis was performed according to criteria defined by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000. According to this classification, PE is defined as high blood pressure after 20 weeks of pregnancy (blood pressure  $\geq 140 \times 90$  mmHg for two measurements with an interval of six hours), accompanied by *proteinuria* (one or more on the *proteinuria* strip or 24 hour *proteinuria*  $> 0.3$  g).<sup>11</sup>

All of the patients selected presented risk factors for the development of PE. 26 (35.6%) had a history of developing early PE (before 34 weeks of pregnancy); 18 (24.7%) were *primigravidae* with a family history of PE; 21 (28.8%) were *primigravidae* and obese (pre-pregnancy body mass index greater than 35 Kg/m<sup>2</sup>); 8 (10.9%) were suffering from *diabetes mellitus* before pregnancy.

Patients with comorbidities such as chronic hypertension, kidney failure, heart diseases and infectious diseases were excluded.

The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais' Hospital das Clínicas (HC-UFGM). The patients selected to participate in the study were informed at the time of collection and signed the free and informed consent form.

After consenting, the patients were submitted to the Doppler flowmetry exam of the ophthalmic arteries between 24 and 28 weeks of pregnancy. All of the exams were conducted by the same professional at the HC-UFGM, trained and certificate in ultrasonography.

### Doppler flowmetry of the ophthalmic arteries

The color Doppler imaging of the orbit was obtained from a trained examiner blinded for the clinical information of the patients. The exams were conducted using a high resolution, color Doppler scanner, the Medison 8800 with a 7.5 MHz linear transducer, applied to closed eyes covered with methylcellulose gel. The exams were conducted with the patient in supine position, with an average duration of five minutes. A complete evaluation of the vessels of the orbit was obtained, identifying the ophthalmic artery and its branches. The anterior branch of the ophthalmic artery was assessed, approximately 10 mm from the posterior wall of the sclera, nasal location in relation to the optic nerve. The OARI was obtained from the right eye of the patients, after a minimum cycle of three consecutive similar waves.

### Statistical analysis

All of the numerical variables were explored to verify the normality criteria of the sample. Comparisons between the 2 groups (patients who developed PE and patients who remained normotensive) were performed using Student's *t*-test for parametric samples and the Mann-Whitney U test for nonparametric samples. Differences were considered with statistical significance when  $p < 0.05$ .

An ROC curve was created to determine the sensitivity and specificity values of the OARI in predicting PE. To create the curve, the lower the values encountered, the more positive the test was considered.

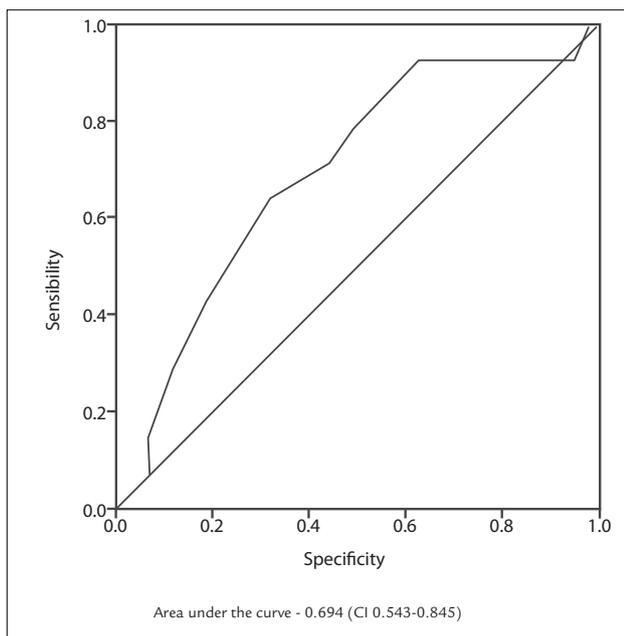
## RESULTS

Fourteen of the patients selected developed PE and 59 remained normotensive until the postpartum period. Demographic characteristics relating to pregnancy and OARI values for both groups (patients who subsequently developed PE and patients who remained normotensive) are expressed in Table 1. Patients with subsequent development of PE presented OARI values lower than patients that remained normotensive ( $0.682 \pm 0.028$  X  $0.700 \pm 0.029$ ,  $p = 0.044$ ). Considering the development of PE as an outcome, the area under the OARI curve was 0.694 (CI 0.543 to 0.845) (Figure 1), with no points obtaining good values of sensitivity or specificity (Table 2).

**TABLE 1** Characteristics of the groups of patients that developed pre-eclampsia and who remained normotensive

	Normotensive	Pre-eclampsia	p Value
Mother's age (years)	28.5 ± 5.9	30.2 ± 4.8	ns*
Pregnancies	2.3 ± 1.7	2.9 ± 1.5	ns**
Pre-pregnancy weight (Kg)	63.6 ± 14.8	65.8 ± 12.4	ns**
Body Mass Index (Kg/m <sup>2</sup> )	23.87 ± 5.63	24.75 ± 4.45	ns**
Mean arterial pressure between 24 and 28 weeks	83.50 ± 7.46	88.57 ± 7.81	ns*
Gestational age of delivery (weeks)	39.3 ± 1.1	35.1 ± 2.0	p<0.001**
Weight of the newborn (Kg)	3102.74 ± 268.37	2505.00 ± 588.47	P=0.003**
Ophthalmic artery resistive index between 24 and 28 weeks	0.700 ± 0.029	0.682 ± 0.028	P=0.044*

ns= not significant. \* Student's t test \*\* Mann-Whitney U test

**FIGURE 1** ROC Curve – Ophthalmic Artery Resistive Index between 24 and 28 weeks of pregnancy and prediction of pre-eclampsia.

## DISCUSSION

Damage to the vascular endothelium, clinically characterized as endothelial dysfunction, has been extensively demonstrated in patients with PE by means of biophysical methods, particularly testing for brachial artery flow-mediated vasodilation (FDM).<sup>12,13</sup> Abnormal values in this test have been demonstrated in patients who subsequently developed PE, indicating that the test can be used to predict the clinical manifestations of PE and thus the endothelium injuries precede the clinical manifestations of the disease.<sup>14,15</sup>

Endothelial dysfunction precedes the clinical manifestations of PE and persists up to one year after childbirth, which also generates the pathophysiological basis for explaining the higher incidence of cardiovascular complications in women with a history of PE.<sup>16</sup> Hyperperfusion of

**TABLE 2** Values of sensitivity and specificity for predicting pre-eclampsia with the ophthalmic artery resistive index (OARI) between 24 and 28 weeks of pregnancy

OARI cutoff value	Sensitivity (%)	Specificity (%)
0.65	7	93
0.66	14	93
0.67	29	88
0.68	43	81
0.69	64	68
0.70	71	56
0.71	79	51
0.72	93	37
0.73	93	22
0.74	93	8
0.75	93	5
0.76	100	2

the CNS, expressed by lower OARI values, has also been demonstrated in patients with PE.<sup>17</sup>

In a cross-sectional analysis of 81 patients, 56 with PE and 25 healthy, it was noted that the ophthalmic artery resistance index (OARI) was lower in patients with the disease in both clinical forms of presentation: late or early onset.<sup>8</sup>

Another study<sup>18</sup> assessed 74 patients between 24 and 28 weeks of pregnancy with a high risk of development of PE. At these gestational ages, no significant difference was found in the OARI values between patients who subsequently developed and who did not develop PE. However, the same study found a higher mean PI of the uterine arteries and lower FMD among women who had PE. The authors suggest that chronologically, the CNS hy-

perflow is the latest change in the pathophysiology of PE, succeeding placental insufficiency and endothelial injury.

In this study, patients with subsequent development of PE presented OARI values lower than patients that remained normotensive ( $0.682 \pm 0.028$  X  $0.700 \pm 0.029$ ,  $p=0.044$ ). This fact has also been demonstrated by Oliveira et al.<sup>19</sup> when comparing 30 women with mild PE, 30 women with severe PE, 30 women with chronic hypertension and a control group of 289 normotensive pregnant women, with both groups between 20 and 40 weeks of pregnancy.

The ROC curve obtained with OARI values between 24 and 28 weeks of pregnancy did not present good results for sensitivity and specificity. Despite being significant, the difference between the two groups studied may not have been sufficient to discriminate a specific risk group. This fact can be explained by the heterogeneity of the etiology and manifestations of PE, or even the chronology of pathological events previously proposed.<sup>18</sup>

## CONCLUSION

The present study demonstrated that the Doppler flowmetry of ophthalmic artery was not a good method for predicting clinical manifestations of PE, supporting the hypothesis that the hyperflow of the CNS is also a late manifestation of the syndrome.

## RESUMO

Dopplerfluxometria de artérias oftálmicas para predição de pré-eclâmpsia.

**Introdução:** a hiperperfusão do sistema nervoso central (SNC) é um dos eventos que constitui substrato fisiopatológico para as manifestações clínicas e complicações da pré-eclâmpsia (PE). O fluxo aumentado no SNC, detectado por meio da dopplerfluxometria de artérias oftálmicas, poderia anteceder as manifestações clínicas da PE e, conseqüentemente, ser utilizado como marcador de subsequente desenvolvimento de PE.

**Objetivo:** avaliar os valores do índice de resistência das artérias oftálmicas (Irao) no segundo trimestre gestacional para a predição das manifestações clínicas da PE.

**Métodos:** 73 pacientes com fatores de risco para desenvolvimento de PE foram selecionadas no serviço de pré-natal do Hospital das Clínicas da Universidade Federal de Minas Gerais (HC-UFMG). Elas foram submetidas à dopplerfluxometria de artérias oftálmicas entre 24 e 28 semanas de gestação e acompanhadas até o final da gestação para averiguar a ocorrência de PE. Curvas ROC foram criadas para determinar as características preditivas do Irao.

**Resultados:** das pacientes selecionadas, 14 desenvolveram PE e 59 mantiveram-se normotensas até o puerpério. Pacientes com subsequente desenvolvimento de PE apresentaram valores de Irao menores do que pacientes que se mantiveram normotensas ( $0,682 \pm 0,028$  vs.  $0,700 \pm 0,029$ ,  $p=0,044$ ). Ao considerar o desenvolvimento de PE como desfecho, a área sobre a curva do Irao foi de 0,694 (IC 0,543-0,845), sem pontos com bons valores de sensibilidade ou especificidade. **Conclusão:** a dopplerfluxometria de artérias oftálmicas entre 24 e 28 semanas de gestação não se demonstrou um bom exame para a predição de PE.

**Palavras-chave:** endotélio vascular; pré-eclâmpsia; hipertensão; fluxometria por *laser*-Doppler.

## REFERENCES

1. World Health Organization. The World Health Report 2005 - make every mother and childcount. Geneva: World Health Organization; 2005.
2. Roberts JM, Gammill HS. Preeclampsia: recente insights. *Hypertension*. 2005;46:1243-9.
3. Cabral ACV, Cabral MA, Brandão A, et al. Aspectos atuais da fisiopatologia da pré-eclâmpsia com repercussões na conduta. *Femina*. 2009;37(2):305-8.
4. Plasencia W, Maiz N, L. Poon L, C. Yu C, Nicolaidis NH. Uterine artery Doppler at 11.0 to 13.6 weeks and 21.0 to 24.6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol*. 2008;32(2):138-46.
5. Barton JR, Sibai BM. Prediction and prevention of recurrent preeclampsia. *Obstet Gynecol*. 2008;112(2 part 1):359-72.
6. Huppertz B. Placental origins of preeclampsia: challenging the current hypothesis. *Hypertension*. 2008;51(4):970-5.
7. Davison JM, Homuth V, Jeyabalan A, et al. "New aspects in the pathophysiology of preeclampsia. *J Am Soc Nephrol*. 2004;15(9):2440-8.
8. Brandão AHF, Barbosa AS, Lopes APBM, Leite HV, Cabral ACV. Dopplerfluxometria de artérias oftálmicas e avaliação da função endotelial em gestantes normotensas. *Rev Med Minas Gerais*. 2011;09:09 PM-13.
9. Young BC, Levine RJ, Karumanchi SA. Pathogenesis of preeclampsia. *Annu Rev Pathol*. 2010;5:173-92.
10. Diniz AL, Moron AF, dos Santos MC, Sass N, Pires CR, Deb CL. Ophthalmic artery Doppler as a measure of severe preeclampsia. *Int J Gynaecol Obstet*. 2008;100(3):216-20.
11. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol*. 2000;183:S1-S22.
12. Sierra-Laguado J, García RG, López-Jaramillo P. Flow-mediated dilatation of the brachial artery in pregnancy. *Int J Gynaecol Obstet*. 2006;93(1):60-1.
13. Brandão AHF, Lopes APBM, Salomão CMN, et al. Dilatação fluxo-mediada da artéria braquial como método de avaliação da função endotelial na pré-eclâmpsia e em gestantes normotensas. *Rev Med Minas Gerais*. 2011;09:09 PM-13.
14. Takase B, Goto T, Hamabe A, et al. Flow-mediated dilation in brachial artery in the second half of pregnancy and prediction of pre-eclampsia. *J Hum Hypertens*. 2003;17:697-704.
15. Sawidou MD, Noori M, Anderson JM, et al. Maternal endothelial function and serum concentrations of placental growth factor and soluble endoglin in women with abnormal placentation. *Ultrasound Obstet Gynecol*. 2008;32:871-6.
16. Hamad RR, Eriksson MJ, Silveira A, et al. Decreased flow-mediated dilation is present 1 year after a pre-eclamptic pregnancy. *J Hypertens*. 2007;25:2301-7.
17. Barbosa AS, Pereira AK, Reis ZSN, et al. Ophthalmic artery-resistive index and evidence of overperfusion-related encephalopathy in severe preeclampsia. *Hypertension*. 2010;55:189-93.
18. Brandão AH, Cabral MA, Leite HV, Cabral AC. Endothelial function, uterine perfusion and central flow in pregnancies complicated by preeclampsia. *Arq Bras Cardiol*. 2012;99(4):931-5.
19. Oliveira CA, Sá RA, Valverde LG. Changes in ophthalmic artery Doppler indices in hypertensive disorders during pregnancy. 2013. American Institute of Ultrasound in Medicine. *J Ultrasound Med*. 2013;32:609-16.

# Profile and scientific production of the Brazilian Council for Scientific and Technological Development (CNPq) researchers in the field of Hematology/Oncology

MARIA CHRISTINA LOPES ARAUJO OLIVEIRA<sup>1\*</sup>, DANIELLA REIS MARTELLI<sup>2</sup>, ISABEL GOMES QUIRINO<sup>3</sup>, ENRICO ANTÔNIO COLOSIMO<sup>4</sup>,

ANA CRISTINA SIMÕES E SILVA<sup>5</sup>, HERCÍLIO MARTELLI JÚNIOR<sup>6</sup>, EDUARDO ARAUJO DE OLIVEIRA<sup>5\*</sup>

<sup>1</sup>Associate Professor, Faculty of Medicine of the Federal University of Minas Gerais (UFMG), Belo Horizonte, MG, Brazil

<sup>2</sup>Adjunct Professor, State University of Montes Claros, Montes Claros, MG, Brazil

<sup>3</sup>Professor, University of José do Rosário Vellano (Unifenas), Alfenas, MG, Brazil

<sup>4</sup>Full Professor, Statistics Department UFMG, Belo Horizonte, MG, Brazil

<sup>5</sup>Full Professor, Faculty of Medicine UFMG, Belo Horizonte, MG, Brazil

<sup>6</sup>Full Professor, Unimontes, Montes Claros, MG, Brazil

## SUMMARY

**Objective:** several studies have examined the academic production of the researchers at the CNPq, in several areas of knowledge. The aim of this study was to evaluate the scientific production of researchers in Hematology/Oncology who hold scientific productivity grants from the Brazilian Council for Scientific and Technological Development.

**Methods:** the Academic CVs of 28 researchers in Hematology/Oncology with active grants in the three-year period from 2006 to 2008 were included in the analysis. The variables of interest were: institution, researchers' time after doctorate, tutoring of undergraduate students, masters and PhD degree, scientific production and its impact.

**Results:** from a total of 411 researchers in Medicine, 28 (7%) were identified as being in the area of Hematology/Oncology. There was a slight predominance of males (53.6%) and grant holders in category 1. Three Brazilian states are responsible for approximately 90% of the researchers: São Paulo (21,75%), Rio de Janeiro (3,11%), and Minas Gerais (2, 7%). During their academic careers, the researchers published 2,655 articles, with a median of 87 articles per researcher (IQR = 52 to 122). 65 and 78% of this total were indexed on the Web of Science and Scopus databases, respectively. The researchers received 14,247 citations on the WoS database with a median of 385 citations per researcher. The average number of citations per article was 8.2.

**Conclusion:** in this investigation, it was noted that researchers in the field of Hematology/Oncology have a relevant scientific output from the point of view of quantity and quality compared to other medical specialties.

**Keywords:** scientific publication indicators, hematology, oncology, postgraduate programs in health, health sciences.

Study conducted by the Federal University of Minas Gerais and State University of Montes Claros, MG

Article received: 4/11/2014

Accepted for publication: 4/12/2014

\*Correspondence:

Address: Rua Engenheiro Amaro Lanari  
389 apt 501

Postal Code: 30310-580  
Belo Horizonte, MG  
eduoolive812@gmail.com

Financial Support: FAPEMIG

<http://dx.doi.org/10.1590/1806-9282.60.06.012>

Conflict of interest: none

## INTRODUCTION

In recent years a significant increase in Brazilian scientific production has been noted, demonstrated by the growing number of articles published in indexed periodicals concomitant with the formation of new researchers.<sup>1</sup> Scientific publications by Brazilian researchers in indexed periodicals jumped from 14,237 in 2003 to 30,415 in 2008, according to data from Thomson Reuters.<sup>2</sup> Recent

estimates have also shown that this production has been consistent and has improved from a qualitative point of view.<sup>3,4</sup> Data from January to October 2012 published by *Nature*, for example, show that Brazilian researchers have published 29,924 articles.<sup>5</sup> Furthermore, in 2012, 0.43% of the Brazilian scientific production was placed at the top of the most cited articles. Interestingly, the

country was ranked third in terms of growth in this criterion, with an 8.9% increase in articles placed among the top 1% most cited articles.<sup>5</sup>

In a recent analysis, we showed that among grant holders with scientific production at the CNPq in the area of medicine, the field of Hematology/Oncology corresponds to 7% of researchers.<sup>6</sup> In an extensive comparative analysis of scientific production in three major areas, Rodrigues et al.<sup>7</sup> showed that Oncology is a field with a growing trend to consolidate itself as an important area in science and technology in Brazil. However, systematic analyses by researchers in the area of Hematology/Oncology remain scarce.

Several studies have examined the academic production of the researchers at the CNPq, in several areas of knowledge.<sup>8-12</sup> This cross-sectional study has the objective of describing the demographic characteristics and academic production of researchers holding grants in Medicine from the CNPq, and whose main area of work is Hematology/Oncology.

## METHODS

### Participants

A database of 411 researchers registered as grant holders with scientific production at the CNPq was initially established, according to the list provided by this federal agency for research funding in February 2009.<sup>6</sup>

### Field of activity

The area specifically indicated by the researcher in his/her Academic (Lattes) CV was considered for this variable. Whenever this information was not given, the scientific production over the last five years was analyzed and an area was attributed according to the predominant topics published and/or directed. According to this methodology, we identified 28 researchers working in the field of Hematology/Oncology.

### Study design cross-sectional study

#### Data collection protocol

After identifying grant holders, the Academic CVs were systematically consulted, as published on the Lattes platform (CNPq). The Academic CVs were used to build a database with information relating to the distribution of grants by category (1A, 1B, 1C, 1D and category 2),<sup>13</sup> geographic and institution distribution, researchers' time after doctorate, scientific production (scientific articles) and guidance of human resources (supervision of undergraduates, masters and doctorates). To analyze scientific production, all publications and supervision during the researcher's career and the last five years of the period under study were included.

### Variables of interest

The following variables were analyzed: gender, the researcher's institution, researchers' time after doctorate, doctoral institution, grant category, supervision for undergraduate researchers (BIC), master's thesis and doctoral dissertation, and publications in journals. In relation to supervision and publications, the absolute values of the entire scientific career were evaluated, as well as the values relating to the period from 2004 to 2008. Furthermore, the supervision and publications adjusted by the researchers' time after doctorate were calculated. We also searched the Web of Science (WoS)- Institute for Scientific Information (apps.isiknowledge.com/) and Scopus (www.scopus.com/home.url) databases. Both were consulted via the CAPES website (novo.periodicos.capes.gov.br). These databases were used to search the scientific articles published by the researchers listed on the CNPq database. The scientific name of the researcher used in this investigation was that provided in their Academic CV, but there was an extensive search of possible variations in researcher names. The performance indicators of the researchers were also included in the analysis, such as the number of citations, the H-index and the M-index.<sup>14-18</sup>

### Statistical analysis

The development of a database and the statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) software, version 18.0 for Windows. For the statistical analysis, regarding the grant holder categories, researchers were stratified into three groups: levels 1A and 1B, levels 1C and 1D and level 2. The continuous data were reported using median and interquartile range (IQR). The non-parametric Mann-Whitney test was used for comparison between categories of researchers. Dichotomous variables or nominal variables were compared using the Chi-squared test. A significance level of 5% was used.

## RESULTS

From a total of 411 researchers in Medicine, 28 (7%) were identified as being in the area of Hematology/Oncology. The distribution of the 28 researchers by gender and grant category are summarized in Table 1. There was a slight predominance of males (53.6%) and grant holders in category 1 (53.6%). There was no significant difference in the distribution of categories between genders ( $p=0.24$ ). Three Brazilian states are responsible for approximately 90% of the researchers: São Paulo (21, 75%), Rio de Janeiro (3, 11%), and Minas Gerais (2, 7%). In relation to the institution of origin, the researchers are distributed among nine different institutions in the country. However, three institutions are responsible for approximately 70% of

the researchers: USP (8, 28.6%), Unicamp (8, 28.6%), and Unifesp (4, 14.3%). Three researchers (10.7%) reported pediatrics as their field of work.

The median doctoral time of the 28 researchers was 16 years (IQR, 13 - 24.5 years). In relation to the doctoral institution, 25 researchers obtained their title in Brazil and three at institutions abroad (England and Germany). Three institutions are responsible for training approximately 80% of the researchers: USP (9, 32%), Unifesp (6, 21%), and Unicamp (5, 18%), and UFRGS (3, 9%). Nineteen researchers (68%) have a post-doctorate, with institutions in the United States (7) and United Kingdom (4) predominating.

**TABLE 1** Distribution of grant-holding researchers in the field of Hematology/Oncology according to gender and CNPq categorization (n = 28)

Grant category	Male	Female	Total (%)
1A	3	2	5 (17.8)
1B	2	1	3 (10.7)
1C	4	0	4 (14.3)
1D	1	2	3 (10.7)
2	5	8	13 (46.4)
Total	15	13	28 (100)

#### Academic supervision

Overall in their academic careers, these Hematology/Oncology researchers supervised 213 undergraduate grant holders (BIC), with a median of 2 (IQR = 0.0 to 10.0) per researcher, with 293 master's theses (median 10, IQR = 5.0 - 16) and 188 doctoral dissertations (median 5, IQR = 3 - 10). The median supervision per year in relation to the values adjusted for doctoral time were 0.18 for BIC, 0.47 for master's degree students and 0.32 for doctoral students. Comparing the values adjusted by doctoral time there was no significant difference between the categories of grant holders in terms of student supervision for BIC students ( $p = 0.58$ ), master's students ( $p = 0.25$ ), and doctoral students ( $p = 0.24$ ).

#### Scientific production

During their academic careers, researchers published 2,655 articles in journals, with a median of 87 articles per researcher (IQR = 52 - 122), ranging from a minimum of 19 articles to a maximum of 220. In total, there were 1,719 articles indexed by the WoS database, approximately 65% of the total number of articles published (median of 50

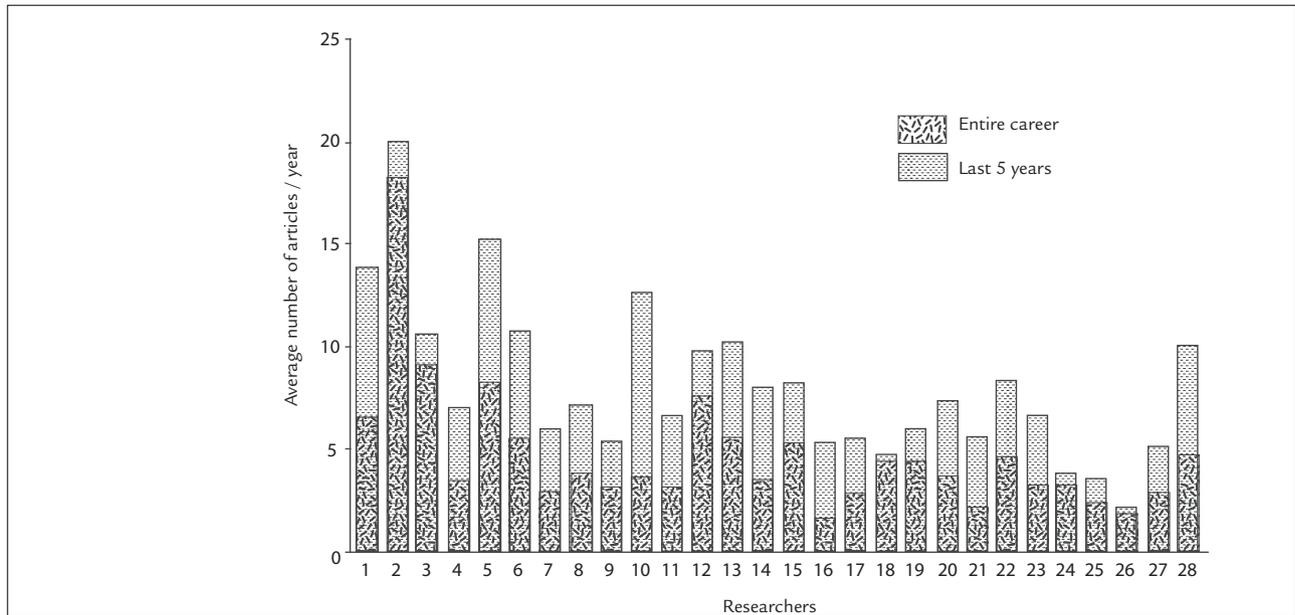
per researcher, IQR = 35 - 71). On the Scopus database there were 2,075 articles indexed (median of 69, IQR 41-62), equivalent to 78% of the academic production.

Considering the number of articles adjusted by time after doctorate, the median of publications was 4.4 articles/year (IQR = 3.6 to 5.7). The adjusted median for articles published on the WoS database was 2.7/year (IQR = 2.2 to 3.7) and 3.4/year (IQR = 2.5 to 4.6) on the Scopus database. Comparing the values adjusted by time after doctorate there was no significant difference between the categories of grant holders and the number of articles throughout their careers ( $p = 0.26$ ), articles indexed by the WoS ( $p = 0.13$ ) and articles indexed by Scopus database ( $p = 0.35$ ).

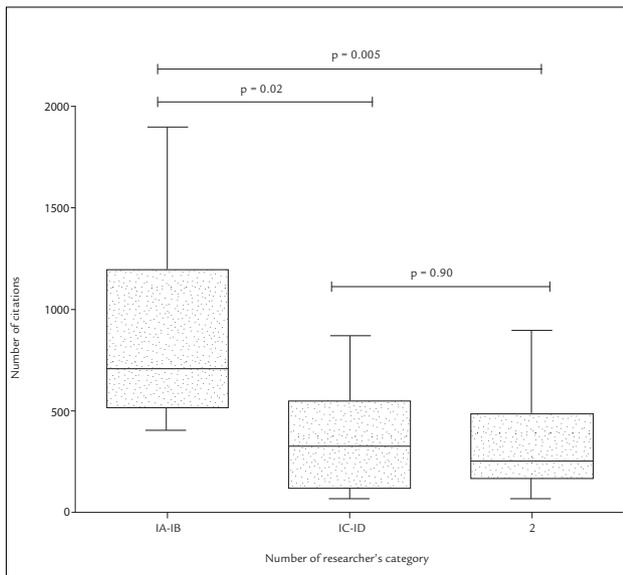
All 28 researchers increased scientific production over the last five years analyzed, considering the average number of articles published per year. This increase ranged from 8 to 243%, with a median increase of 85% (IQR 39 - 106%) in scientific production. The average number of articles published in the scientific career of the 28 researchers was 4.7 years (SD = 3.2) while over the last five years this average reached 7 per year (SD = 3.8). Figure 1 illustrates the annual average articles published in the entire scientific career of the 28 researchers, and their average over the past five years.

#### Impact of the scientific production

In their academic careers, researchers in Hematology/Oncology received a total of 14,247 citations in WoS database, with a median of 385 citations per researcher (IQR = 208 - 741, ranging 68 - 1897 citations). The average number of citations per article was 8.2 (SD = 3.6). There was a significant difference between the categories when comparing the absolute number of citations received by the researchers. The median citations for researchers in categories 1A/1B was 701 (IQR = 518 - 1195), while for categories 1C/1D this was 324 (IQR = 117 - 547) and 255 for category 2 (IQR = 166 - 483) ( $p = 0.011$ ). When assessing the groups, the difference occurred among 1A/1B groups compared to the 1C/1D and category 2 groups. However, there was no difference in the comparison between 1C/1D and category 2 groups (Figure 2). This significant difference persisted even after adjustment for the researchers' time after doctorate. The average for researchers in categories 1A and 1B were 39 citations/year (SD = 19.4), while for categories 1C-1D this was 19 citations year (SD = 11) and 24 citations/year (SD = 13.9) for category 2 ( $P = 0.04$ ).



**FIGURE 1** Articles published by CNPq researchers with expertise in the area of Hematology-Oncology, comparing all academic careers within the period of 2004-2008.



**FIGURE 2** Comparison of the number of citations received with the category of CNPq researchers operating in the area of Hematology-Oncology.

The median H-index on the WoS database was 11 (IQR 7.2 - 13) ranging from a minimum of 4 to a maximum of 20. There was a significant difference in the median of the H-index according to the researcher's grant category on the WoS database ( $P = 0.005$ ). The median H-index for

researchers in categories 1A and 1B was 14 (IQR = 12.2 to 16.8), while for categories 1C-1D this was 8 (IQR = 5-12) and 9 for category 2 (IQR = 6.5 to 11.5). The median M-index, i.e. the H-index corrected by the time of the researcher's academic career, was 0.55 on the WoS database (IQR = 0.39 to 0.72), ranging from a minimum of 0.29 up to a maximum of 1.3. However, there was no significant difference for the M-index between grant-holder categories on the WoS database ( $P = 0.38$ ). The median M-index for researchers in categories 1A and 1B was 0.58 (IQR = 0.44 to 0.99), while for categories 1C-1D this was 0.41 (IQR = 0.35 to 0.61) and 0.62 for category 2 (IQR = 0.42 to 0.62).

## DISCUSSION

Based on the criteria for granting funding for research productivity, including training of new researchers and publications in indexed journals, it can be inferred that this sample is representative of researchers from the academic elite in their respective fields of knowledge. Thus, this cross-sectional study, focusing on CNPq researchers in the field of Hematology/Oncology has shown that there are still few high productivity institutions dealing with research involving these areas of clinical knowledge. The results of this study show a high concentration of scientific production in a few states in the country, especially the states of São Paulo and Rio de Janeiro.

CNPq researchers in the field of Hematology/Oncology presented an average increase of approximately 85% in scientific production over the last five years compared to the entire academic career. This fact was also noted in other areas of Health Sciences, such as Dentistry, Public Health and Physiotherapy<sup>8,9,11,12</sup> as well as other fields of Clinical Medicine.<sup>19,20</sup> This increase relates to the current positive cycle of Brazilian scientific production and possibly reflects several factors, such as the increase in the federal budget for science and technology, and the various incentive mechanisms established by numerous development agencies in the country.<sup>4,21-23</sup> For example, the federal budget for science and technology, although still relatively low when compared to developed countries, rose from 1.26 to 1.43% of the Brazilian gross domestic product in 2008.<sup>4,23</sup>

The analysis of Hematology/Oncology researchers showed a significant number of articles published in indexed journals. During their academic careers, the median was 87 articles per researcher, identical to the median of 87 articles of the 411 researchers in the area of Medicine described in a previous study.<sup>6</sup> However, Hematology/Oncology researchers stand out in qualitative terms, as approximately 65 and 78% of all published articles were indexed by the WoS and Scopus databases, respectively. It should be noted that these qualitative data are far superior when compared to the general analysis in the scope of Medicine. In our previous analysis it was shown that only 51 and 68% of the total number of articles published by the 411 researchers were indexed by the WoS and Scopus, respectively.<sup>6</sup> The data related to researchers in the fields of Cardiology and Newborn's, for example, are also superior, with 55 and 58% of articles indexed by the WoS database, respectively.<sup>19,20</sup> This scenario certainly reflects a scientific production with international relevance, since the indexing of journals by these databases has been considered an important parameter for the quality of scientific production.

Despite the scathing criticism of the use of journal impact factor in the evaluation of institutions and researchers, unfortunately this index continues to be adopted by many research funding agencies, including the CNPq.<sup>15,17,24-29</sup> However, considering the current literature on scientific production rates, in our view, the individual assessment of the researchers' careers should be performed using proper indicators developed for this purpose. Among the various indicators for assessing the performance of researchers, the specialized literature has highlighted the H-index, proposed by Hirsch.<sup>16</sup> The H-index consists of a single number that seeks to summarize two dimensions of academic performance: productivity (number of publications) and visibility (citations for

those publications).<sup>18,30,31</sup> One point that has been emphasized about the H-index is that it counteracts both the excessive amount of publications with few citations as well as low productivity with many citations.<sup>32</sup> In our analysis, the median H-index for researchers in the field of Hematology/Oncology was 11, which was significantly higher for categories 1A and IB, with an H-index of 14. The median H-index for researchers in the field of Hematology/Oncology was similar to that previously observed in the areas of Cardiology and Nephrology, with respective medians of 11 and 10.<sup>19,20</sup>

One of the disadvantages of the H-index, however, is that it favors researchers with long careers and provides an incomplete picture of actual citations from a determined group of researchers.<sup>26</sup> Therefore, we understand that the H-index is most valuable if associated with the M-index, which takes into account the researchers' engagement time with their academic career. In this context, it should be noted that unlike the H-index, there was no significant difference for the M-index among the Hematology/Oncology grant holder categories, reinforcing the bias of this indicator proposed by Hirsch in 2005.<sup>16</sup> In our study, the median M-index in the WoS database was 0.55, ranging from a minimum of 0.29 to a maximum of 1.3. The median for the M-index was slightly lower than the median of 0.62 previously described for total of 411 researchers in Clinical Medicine.<sup>13</sup>

## CONCLUSION

In this study, it was noted that CNPq researchers in the field of Hematology/Oncology have a relevant scientific output from the point of view of quantity and quality, superior in several criteria compared to that presented by other medical specialties.

## ACKNOWLEDGMENTS

This study was partially funded by the FAPEMIG (Minas Gerais State Research Foundation) through the PPM-00345-11 and PPM-00273-13 projects. Eduardo A. Oliveira, Ana Cristina Simões and Silva are CNPq category 2 researchers in the area of Medicine. Hercílio Martelli-Júnior and Enrico A. Colosimo are CNPq category 2 researchers in the areas of Dentistry and Statistics, respectively.

## RESUMO

Perfil e produção científica dos pesquisadores do Conselho Nacional de Desenvolvimento Científico e Tecnológico na área de Hematologia-Oncologia.

**Objetivo:** vários estudos têm analisado a produção acadêmica dos pesquisadores do Conselho Nacional de De-

envolvimento Científico e Tecnológico (CNPq), em diversas áreas do conhecimento. O objetivo deste estudo foi avaliar a produção científica de pesquisadores de Hematologia-Oncologia, cadastrados como bolsistas de produtividade científica do CNPq.

**Métodos:** os currículos Lattes de 28 pesquisadores em Hematologia-Oncologia, com bolsas ativas no triênio 2006 a 2008, foram incluídos na análise. As variáveis de interesse foram: instituição, tempo de doutoramento, orientação de alunos de graduação, mestres e doutores, artigos publicados e seu impacto.

**Resultados:** de um total de 411 pesquisadores em Medicina, 28 (7%) foram identificados como da área da Hematologia-Oncologia. Houve uma discreta predominância do gênero masculino (53,6%) e de bolsistas na categoria 1 (53,6%). Três Estados da Federação são responsáveis por 90% dos pesquisadores: São Paulo (21; 75%), Rio de Janeiro (3; 11%) e Minas Gerais (2; 7%). No total da carreira acadêmica, os pesquisadores publicaram 2.655 artigos em periódicos, sendo a mediana de 87 artigos por pesquisador (intervalo interquartil [IQ] = 52-122). Desse total, 65% e 78% foram artigos indexados nas bases de dados Web of Science (WoS) e Scopus, respectivamente. Os pesquisadores receberam 14.247 citações na base de dados WoS, sendo a mediana por pesquisador de 385 citações. A média de citações por artigo foi de 8,2.

**Conclusão:** na presente investigação, observou-se que os pesquisadores na área de Hematologia-Oncologia apresentam uma produção científica relevante do ponto de vista qualitativo quando comparada a das demais especialidades médicas.

**Palavras-chave:** indicadores de produção científica; hematologia; oncologia; programas de pós-graduação em saúde; ciências da saúde.

## REFERENCES

- Zorzetto R, Razzouk D, Dubugras MT, Gerolin J, Schor N, Guimarães JA, et al. The scientific production in health and biological sciences of the top 20 Brazilian universities. *Braz J Med Biol Res.* 2006;39:1513-20.
- Petherick A. High hopes for Brazilian science. *Nature.* 2010;465:674-5.
- Regalado A. Science in Brazil. Talented but underfunded: Brazil's future scientists. *Science.* 2010;330:1311.
- Regalado A. Science in Brazil. Brazilian science: riding a gusher. *Science.* 2010;330:1306-12.
- Van Noorden R. 366 days: the year in science. *Nature.* 2013;492:324-7.
- Martelli-Junior H, Martelli DR, Quirino IG, Oliveira MC, Lima LS, Oliveira EA. [CNPq researchers in medicine: a comparative study of research areas]. *Rev Assoc Med Bras.* 2010;56:478-83.
- Rodrigues PS, Fonseca L, Chaimovich H. Mapping cancer, cardiovascular and malaria research in Brazil. *Braz J Med Biol Res.* 2000;33:853-67.
- Barata RB, Goldbaum M. [A profile of researchers in public health with productivity grants from the Brazilian National Research Council (CNPq)]. *Cad Saúde Pública.* 2003;19:1863-76.
- Cavalcante RA, Barbosa DR, Bonan PRF, Pires MBO, Martelli-Junior H. Perfil dos pesquisadores da área de odontologia no Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). *Rev Bras Epidemiol.* 2008;11:106-13.
- Mendes PHC, Martelli DR, Souza WP, Filho SQ, Martelli Junior H. Perfil dos pesquisadores bolsistas de produtividade científica na medicina no CNPq, Brasil. *Rev Bras Educ Med.* 2010;34:535-45.
- Santos NCF, Candido LFO, Kuppens CL. Produtividade em pesquisa do CNPq: análise do perfil dos pesquisadores da química. *Quim Nova.* 2010;33:489-95.
- Santos SMC, Lima LS, Martelli DR, Martelli Junior H. Perfil dos pesquisadores da Saúde Coletiva no Conselho Nacional de Desenvolvimento Científico e Tecnológico. *Physis.* 2009;19:761-75.
- Oliveira EA, Colosimo EA, Martelli DR, Quirino IG, Oliveira MCL, Lima LS, et al. Comparison of Brazilian researchers in clinical medicine: are criteria for ranking well-adjusted? *Scientometrics.* 2012;90:429-43.
- Bornmann L, Mutz R, Daniel H-D. Are there better indices for evaluation purposes than the h index? A comparison of nine different variants of the h index using data from biomedicine. *J Am Soc Inform Sci Technol.* 2008;59:830-7.
- Haefliger-Cavillon N, Graillot-Gak C. The use of bibliometric indicators to help peer-review assessment. *Arch Immunol Ther Exp (Warsz).* 2009;57:33-8.
- Hirsch JE. An index to quantify an individual's scientific research output. *Proc Natl Acad Sci USA.* 2005;102:16569-72.
- Lehmann S, Jackson AD, Lautrup BE. Measures for measures. *Nature.* 2006;444:1003-4.
- Panaretos J, Malesios C. Assessing scientific research performance and impact with single indices. *Scientometrics.* 2009;81:635-70.
- Oliveira EA, Pecoits-Filho R, Quirino IG, Oliveira MC, Martelli DR, Lima LS, et al. Perfil e produção científica dos pesquisadores do CNPq nas áreas de Nefrologia e Urologia. *J Bras Nefrol.* 2011;33:31-7.
- Oliveira EA, Ribeiro ALP, Quirino IG, Oliveira MCL, Martelli DR, Lima LS, et al. Perfil e produção científica dos pesquisadores do Conselho Nacional de Desenvolvimento Científico e Tecnológico na área de Cardiologia. *Arq Bras Cardiol.* 2011;97:186-93.
- Deheinzelin D, Caramelli B. [Scientific production, post-graduate education and Revista da Associação Médica Brasileira]. *Rev Assoc Med Bras.* 2007;53:471-2.
- Guimaraes R. Challenges of postgraduate human health programs in Brazil. *Rev Saúde Pública.* 2011;45:1-12, 1-3.
- Regalado A. Science in Brazil. Tapping a deep, pre-salt bounty. *Science.* 2010;330:1308-9.
- Bordons M, Fernandez MT, Gomes I. Advantages and limitations in the use of impact factor measures for the assessment of research performance in a peripheral country. *Scientometrics.* 2002;53:195-206.
- Brink AJ. Impact factor: use and abuse. *Cardiovasc J South Afr.* 2004;03:05 PM-7.
- Moed HF. New developments in the use of citation analysis in research evaluation. *Arch Immunol Ther Exp (Warsz).* 2009;57:13-8.
- Simons K. The misused impact factor. *Science.* 2008;322:165.
- Szklo M. Impact factor: good reasons for concern. *Epidemiology.* 2008;19:369.
- Wilcox AJ. Rise and fall of the Thomson impact factor. *Epidemiology.* 2008;19:373-4.
- Burrell QL. Hirsch index or Hirsch rate? Some thoughts arising from Liang's data. *Scientometrics.* 2007;73:19-28.
- Burrell QL. Hirsch's h-index: a stochastic model. *J Informetrics.* 2007;01:16 AM-25.
- Boell SK, Wilson CS. Journal Impact Factors for evaluating scientific performance: use of H-like indicators. *Scientometrics.* 2010;82:613-26.

# Single-site laparoscopy in gynecology: preliminary study of a series of 50 cases

ADMÁRIO SILVA SANTOS FILHO<sup>1</sup>, MAURÍCIO BECHARA NOVIELLO<sup>1</sup>, RACHEL CRUZ FRAGA DAMASCENO<sup>1</sup>, EVILANE DO CARMO PATRÍCIO<sup>1</sup>, LARA RODRIGUES FÉLIX<sup>2</sup>, PAOLA GASTON GIOSTRI<sup>1</sup>, AUGUSTO HENRIQUES F. BRANDÃO<sup>3\*</sup>

<sup>1</sup>Gynecologist, Hospital da Baleia – Benjamin Guimarães Foundation, Belo Horizonte, MG, Brazil

<sup>2</sup>PhD - Visiting Professor UFMG Women's Healthcare Post-Graduate Program, Gynecologist Hospital da Baleia – Benjamin Guimarães Foundation, Belo Horizonte, MG, Brazil

## SUMMARY

**Objective:** to describe the initial experience of a gynecology team, at a tertiary care center, when performing single-port laparoscopic surgery.

**Method:** this is a retrospective study reviewing the medical records of 50 patients treated at the outpatient gynecology clinic of our institution between June 2012 and July 2013 who underwent single-port laparoscopic surgery. This study was approved by the institution's Ethics in Research Committee.

**Result:** the mean age of patients is 37.8 years, ranging from 18 to 70 years, and the most frequent surgical indications were adnexal mass (72%) and chronic pelvic pain (24%). The mean operative time was 94.4 minutes with a mean hospital stay of 25.8 hours. There were no perioperative complications. We recorded two conversions to laparotomy due to technical difficulties during the procedure. All cases of conversion had pelvic adhesions. All operative complications were successfully treated and none were considered severe.

**Conclusion:** this is one of the largest case series in the literature regarding surgical treatment by single-port laparoscopy in gynecology and presents evidence on reduction of surgical morbidity and satisfactory cosmetic results. We conclude that single-port laparoscopy is a viable minimally invasive technique, and that it contributes to the construction of a new scenario in modern gynecological surgery.

**Keywords:** laparoscopy, endoscopy, gynecologic surgical procedures.

Hospital da Baleia – Benjamin Guimarães Foundation, Belo Horizonte, MG

Article received: 4/18/2014  
Accepted for publication: 5/22/2014

\*Correspondence:  
Rua Juramento, 1464, Saudade  
Postal Code: 30285-000  
Belo Horizonte – MG  
Phone: +55 31 3489-1500  
augustohfbrandao@hotmail.com

<http://dx.doi.org/10.1590/1806-9282.60.06.013>

Conflict of interest: none

## INTRODUCTION

Laparoscopy emerged as a promising surgical technique in the 1970s, as a less invasive method than a laparotomy in propedeutics and treatment of illnesses of the abdominal and pelvic cavities. It brought various benefits, such as better and quicker post-operative recovery, a lesser need for pain relievers, a shorter duration for the surgical procedure and early hospital discharge.<sup>1,2</sup>

With the evolution of surgical techniques, minimally invasive procedures such as single-port laparoscopy make headway in medical practices and emerge as a challenge to modern medicine. Both patients and healthcare professionals are constantly seeking better functional and esthetic results, with a focus on the quality of life in the post-operative period and in the long term, without compromising the efficiency of the surgical treatment.

Single-port laparoscopy consists in performing only one incision for access to the peritoneal cavity, commonly located on the umbilical scar, different from a conventional laparoscopy, in which two to four ports are created. The use of a single port would allow reducing operative morbidity in relation to conventional laparoscopy, since making each port brings with it the inherent risk of bleeding, injury to adjacent organs, the formation of hernias and compromised esthetic results.<sup>3</sup>

The dissemination of the single-port surgical technique, as well as the technological innovations to the surgical materials, has made it the new global trend in relation to the propedeutics and approach to benign gynecological illnesses, especially cases of adnexal tumors.

The concept of a single port is not new to gynecology, despite being only recently recognized and used in other areas, especially urologic and gastrointestinal procedures such as nephrectomies, appendectomies and cholecystectomies.<sup>4,5</sup> Some 150 years ago, Wheelless et al.<sup>6,7</sup> reported more than 4000 cases of women who had successful tubal ligations through “single-trocar laparoscopy.” In 1991, Pelosi performed the first single-port hysterectomy.<sup>8</sup>

Even after the successful introduction of the technique,<sup>6,7,8</sup> it did not become widespread as a standard procedure for reasons that range from lack of specific access systems (such as articulated instruments with rotational abilities), to the need for improvement of the optics used.<sup>9</sup>

Despite the strong focus on the topic these days, there are still only a few papers available about the use of a single port in gynecology, which comprise mainly case series and reports. Few are randomized studies and have a sufficient number of patients that encourage the dissemination of the technique.

The objective of the present work is to describe the initial experience of the Gynecology team from the Benjamim Guimarães Foundation – Hospital da Baleia, in Belo Horizonte, when performing single-port laparoscopy. We describe the technique used, highlighting the profile of the patients treated surgically, as well as the intra-operative events and the post-operative results in the short and mid term.

## MATERIALS AND METHODS

### Study design

This is a retrospective study, descriptive of a case series, which evaluated the data from medical records of 50 patients cared for in the outpatient gynecology clinic of the Benjamim Guimarães Foundation - Hospital da Baleia, in Belo Horizonte (Minas Gerais/Brazil), from June 2012 to July 2013.

All the patients whose pelvic illness was treated surgically through single-port laparoscopy were included in the study.

In the analysis of the medical records, we identified that the criteria for indication and application of the technique were: adnexal tumor with average diameter below 9 cm, a malignancy risk index<sup>10</sup> of less than 200, absence of prior umbilical hernioplasty with synthetic mesh. All the medical records consulted were considered eligible for the present study, since none of them presented a lack of any data that could be considered limiting.

The study was approved by the research ethics committee of the Benjamim Guimarães Foundation – Hospi-

tal da Baleia and is identified in the Brazil Platform with CAAE number 17036713.6.0000.5123.

### Statistical analysis

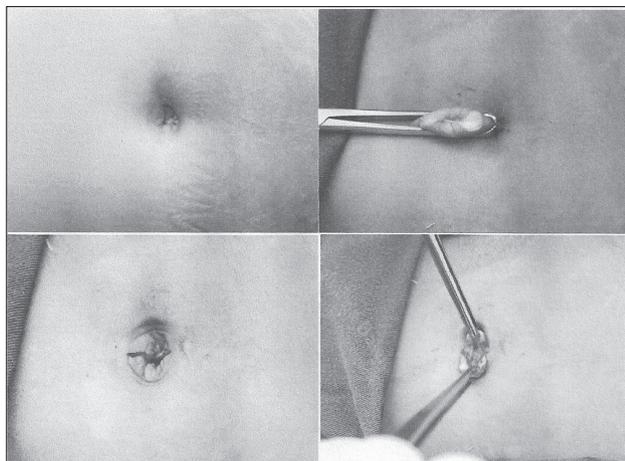
The data was collected and stored in a database created with the IBM SPSS software program, version 2.0, which was also used for calculating statistics and building the graphs and tables. The distribution frequency of the categorical and ordinary variables taken from the medical records was analyzed.

### Single-port laparoscopy

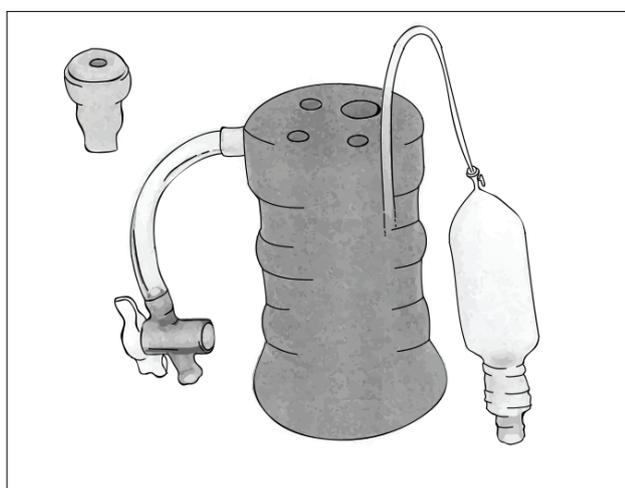
For the surgical procedure, all the patients underwent general anesthesia with tracheal intubation, indwelling bladder catheter and were placed in a decubitus dorsal position with their arms next to their body. Antisepsis was done with surface-active chlorhexidine solution. At the time anesthesia was induced, intravenous antibiotic prophylaxis with first-generation cephalosporin was established as routine.

The surgical technique was standardized as described below:

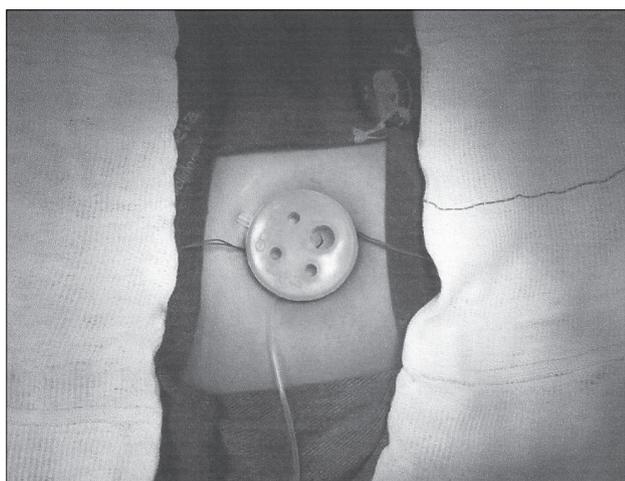
1. Periumbilical subcutaneous injection of 10mL of bupivacaine with a vasoconstrictor and, subsequently, a vertical or curved incision (in accordance with the anatomical characteristics of the patient) on the lower edge of the umbilical scar, with a length of around 2.5 to 3 cm. (Figure 1)
2. Dissection of the subcutaneous tissue and opening of the aponeurosis and parietal peritoneum under direct viewing.
3. Fixation of sutures at the angles of the aponeurosis, with a 1.0 Vicryl wire.
4. Introduction of the single access platform through the umbilical scar (Sitracc® - Edlo S/A Produtos Médicos). (Figures 2 and 3)
5. Insufflation into the abdominal cavity with carbon gas, reaching a maximum abdominal pressure of 15 mmHg. After the pneumoperitoneum is performed, a 10mm 0° optic is introduced into the orifice corresponding to the port.
6. Inventory of the entire abdominal and pelvic cavity is performed.
7. According to the characteristic of the pelvic disease and perioperative diagnosis, the forceps needed for the procedure were introduced through the other three 5mm access points of the port, with the availability of articulated 42cm Maryland forceps, 42cm flexible grasping forceps with a ring gear, 50cm



**FIGURE 1** Umbilical incision for insertion of the Sitracc®.



**FIGURE 2** Sitracc®.



**FIGURE 3** Sitracc® after insertion.

gallbladder grasping forceps with a curved ring gear and 42cm curved Metzenbaum-type scissors (Edlo S/A Produtos Médicos).

8. In the event of perioperative diagnosis of adnexal masses: grasping of the ovarian ligament by direct traction with the 42cm flexible grasping forceps through the 5mm orifice and ligation and sectioning of the pelvic infundibulum after identification of the ipsilateral ureter using a peritoneal x-ray. The resulting material from the excision, in all cases, was removed from the pelvic cavity through the umbilical orifice itself, used for the introduction of the port, where new incisions were not needed in the abdominal wall or at the bottom of the posterior fornix.
9. After excision, the pneumoperitoneum was undone and then the port was removed using direct traction.
10. Closure of the aponeurosis using continuous suture with a 1.0 Vicryl wire, hemostatis, skin suturing with a 4.0 Vicryl wire and localized bandage.

## RESULTS

The average age of the patients included in the study was 37.8 years, ranging from 18 to 70 years. The age groups were distributed in the following way: 22% of patients were under 30 years old, 40% of the patients were between 30 and 40 years old, 24% were between 40 and 50 years old and 14% were older than 50 years old.

The most frequent surgical indications were adnexal mass (72% of cases) and chronic pelvic pain (24% of cases). Hydrosalpinx and surgical sterilization each accounted for 2% of the cases.

Thirty percent of the patients had a history of abdominal surgery, among them, 12% reported only one prior procedure and 28% reported two or more procedures.

The patients presented, predominately, a favorable surgical profile, having their anesthetic risk determined according to the classification from the American Society of Anesthesiology (ASA).<sup>11</sup> Seventy five percent were healthy and, therefore, classified as ASA I. Patients presenting light or moderate systemic disease (ASA II) made up 38% of the sample and 2% had a serious systemic disease, which limited their activities (ASA III).

The average time for duration of the procedure was 94.4 minutes, ranging from 20 to 218 minutes. Thirty two percent of the procedures lasted up to 60 minutes, 48% between 60 and 120 minutes and 20% lasted over 120 minutes.

The patients remained hospitalized for an average of 25.8 hours, ranging from 19.9 to 68.8 hours. Eighty two percent of the patients remained in the hospital for up

to 24 hours, and only 18% for more than 24 hours. We recorded two conversions to laparotomy due to technical difficulties during the procedure. All the cases of conversion featured pelvic adhesions. Perioperative complications were not described.

The post-operative follow-up was done on at least two occasions, 15 and 45 days after the procedure. Two patients presented post-operative complications, which consisted of one case of infection at the surgical site and one case of an incisional hernia.

## DISCUSSION

According to a review article published in 2013, there are approximately 66 studies in the medical literature aimed at single-port laparoscopic surgery in gynecology, being 17 case reports, 32 descriptive studies, 13 retrospective studies and 4 randomized studies.<sup>12</sup>

Fagotti et al. published one of the largest series of cases, with 125 patients submitted to single-port surgery in gynecology over a 3-year period.<sup>13</sup>

Although limited, there are already papers that cite the use of a single port in patients with malignant diseases, both for staging, and tumor excision and lymphadenectomy. In 2009, Fader et al. published a pioneering study on the use of a single port on patients with a diagnosis of gynecological malignant neoplasms, showing favorable results.<sup>14</sup>

We emphasize, however, that even with the growing interest in minimally invasive procedures, there is still no consensus about which criteria should be used for patient selection, or studies that define what the determining factors for better post-operative prognoses would be.

Important aspects should be considered when employing the technique. As a positive point, we point out that the introduction of the single system (Sitracc®), through direct viewing, may minimize the risk of injury to adjacent organs. We also emphasize the reduced surgical time and the fact that the technique does not require a large learning curve for surgeons that are already qualified to perform conventional laparoscopy.

On the other hand, we observed less freedom of movement of the instrument inside and outside the abdominal cavity, somewhat requiring greater surgical ability. To dodge this limitation, the literature cites auxiliary methods, such as the associated use of an intrauterine handing device, and a combination of long and short instruments, which reduces the friction between them.<sup>15</sup>

The results found up until now are positive even for patients with an unfavorable surgical profile, such as those who have had previous abdominal surgeries or who

have a high body mass index, whose surgical morbidity may be significantly reduced by the technique.

In our series, the average time for hospitalization of the patients was 25.8 hours in the post-operative area, being discharged in good clinical conditions, with no complaints of pain, and being able to continue their day-to-day functions. Early discharge was possible especially due to the absence of serious and immediate post-operative complications.

Similar results were described by Escobar et al.,<sup>16</sup> and Kim et al.<sup>17</sup> The first, in a paper published in 2010, evaluated 9 patients that underwent single-port laparoscopy, and stated that hospital discharge occurred, in all the cases, with less than 24 hours of hospitalization.<sup>16</sup> Whereas the latter author prospectively followed 24 patients who had adnexal masses and underwent single-port laparoscopic surgery. In this study, there was no evidence of post-operative complications in any of the patients, and the average period of hospitalization was only one day (ranging from 1 to 3 days).<sup>17</sup>

When considering the post-operative outcomes of this study, we can see a reduction in the frequency of complaints of post-operative pain and a quicker return to daily activities. We point out, however, the fact that the evaluation was only done from information provided by the patients, without the use of objective parameters, such as visual pain scales. Nevertheless, our findings are compatible with the results from a recent study by Fagotti et al.<sup>15</sup> In their series of cases, the authors demonstrated that the technique is safe and effective, resulting in a significant reduction of post-operative pain, associated with better esthetic results.<sup>15</sup> The same author compared, in a randomized study, the rate of post-operative pain among patients who underwent single-port laparoscopy and multiple-port laparoscopy. This study included 60 patients with a sonographic diagnosis of benign adnexal mass and negative tumor markers, and found that the patients who underwent single-port surgery presented less pain, better recovery and lower hospitalization costs in relation to multiple-port surgeries.<sup>18</sup>

Cho et al.<sup>19</sup> published a randomized study comparing single-port surgery with multiple-port surgery, when performing a cystectomy with ovarian preservation. The variables evaluated included the time for return to work after surgery, the level of satisfaction with the wound and level of post-operative pain in 63 patients, and the majority of them, when asked, would recommend the minimally invasive procedure to a friend or family member.<sup>19</sup>

With respect to the duration of the surgical procedure, there are various results described, with times ranging

from 42<sup>1</sup> to 79.6 minutes.<sup>15</sup> The average surgical time observed in our study was 94.6 minutes, a value higher to that found in the literature. There are various factors that influence this data. Since this is a technique that has been recently implemented in the service, there was the need to train all the professionals involved, from the surgeons to the anesthesia and nursing teams. We highlight that the study was developed at a teaching institution in which there are medical residency training programs, and these knowingly have a higher learning curve compared to experienced surgeons. Furthermore, the procedures were done without the assistance of surgical technicians, professionals that can contribute to the optimization of the surgical time.

The low rate of conversion to laparotomy found in our work is consistent with the majority of the studies available. Even for diseases that may have a greater technical difficulty, single port surgery has been used successfully. We cite, as an example, a series of 20 cases of single-port salpingectomy due to ectopic pregnancy published by Yoon et al.,<sup>20</sup> in which there was no need for conversion to laparotomy in any of the patients.<sup>20</sup> Among the 13 cases of hysterectomies, with or without lymphadenectomy due to malignant gynecological disease described by Fader et al., there was also no description of surgical conversions.<sup>14</sup>

Another parameter commonly used as an operative morbidity indicator is the estimation of blood loss during the procedure. Lee et al. evaluated the blood loss of 24 patients that underwent a video-assisted, vaginal, single-port hysterectomy, and found an average value of 400 milliliters (mL).<sup>21</sup> Whereas Yoon et al., in a study that included 7 cases of subtotal hysterectomies done using morcellators, showed an average blood loss of 200 mL.<sup>22</sup> The values are exciting; however, in a single randomized study that evaluated this parameter, Cho et al. reported that the drop in hemoglobin levels was statistically higher in patients that underwent single-port surgery (2.0 0.7g/dL) compared to those who underwent multiple-port video-laparoscopy (1.7 0.6g/dL). The authors believe that this difference may be reduced with an increase in the surgeons' experience performing the less invasive procedure.<sup>19</sup>

In our series of cases, an objective evaluation of blood loss was not done, but none of the patients needed a post-operative blood transfusion, since neither acute anemia symptoms nor hemodynamic instability symptoms were identified.

The purpose of this study was not to compare the aesthetic results of single-port laparoscopy with those of

conventional surgery, just as with any other type of comparison between two techniques. Nonetheless, during the post-operative follow-up interviews, we noted that this was a positive impact factor in the patients' satisfaction with the surgical procedure.

Some works, such as the one by Song et al., published in 2013, have already confirmed better aesthetic results and, consequently, higher levels of post-operative satisfaction with the single-port surgery as compared to the multiple-port laparoscopy.<sup>23</sup> In a recent, randomized study published by Yoo and Shim, 73 patients were evaluated for pain and satisfaction associated with surgical scarring 1 month, 6 months and 1 year after the single-port surgery and compared with pain and satisfaction associated with multiple-port surgery. There was no difference found between the 1-month post-operative groups. However, for all the other time points evaluated, the patients that underwent single-port surgery showed better results.<sup>24</sup>

Although relevant, all the randomized studies previously cited involve a small number of patients and there are some conflicting results, which have led to questioning by several researchers. The largest study about single-port laparoscopy in gynecology was then published by Muriji et al.<sup>25</sup> in April 2013, consisting of a meta-analysis that included 15 observational studies and 6 randomized studies, 10 of which on adnexal mass and 11 on hysterectomies, totaling 2,085 patients. The initial objective was to compare post-operative complications, classifying them as "major" and "minor." The secondary outcomes evaluated were surgical time, post-operative pain, objective blood loss (drop in hemoglobin levels), hospitalization time and aesthetic satisfaction with the scar. There were no statistically significant differences found concerning complications in the two groups. We observed a difference in surgical time of 6.97 minutes more for the single-port in adnexal mass surgeries in the randomized studies. In the studies involving hysterectomies, there was no difference in surgical time.

Among the secondary outcomes, post-operative pain could not be adequately evaluated due to various analysis criteria adopted by the different studies. Nevertheless, after a systematic review, the majority of the studies did not find a difference in the rate of pain after 24 hours of surgery.

No differences were found in hospitalization time between the two surgical approaches, however, this is a variable that is highly dependent on factors that are extrinsic to the surgical act itself, such as geographical and cultural factors, socio-economic conditions and conditions imposed by the public or private healthcare systems.

The other secondary outcomes were biased due to the scarcity of data, not being, however, considered significant to the publication.

In an article published in October 2013, Song et al.<sup>26</sup> prepared a meta-analysis from 6 randomized studies, comparing multiple and single-port surgeries in gynecology, being 3 on hysterectomies and 3 on adnexal masses. There were no statistically significant differences in relation to the rate of perioperative complications, conversion to laparotomy, drop in hemoglobin levels, time for elimination of flatus, surgical time and hospitalization time. It was concluded that single-port laparoscopy is comparable, in efficacy and safety, to conventional laparoscopy, but there were no proven advantages in terms of reduced post-operative pain and satisfaction with the surgical scar.<sup>26</sup>

Through the present analysis, we can see that single-port laparoscopy in gynecology is a viable technique and shows good results in the short and medium term. Currently, minimally invasive laparoscopic techniques represent an evolution of the standard laparoscopy with respect to the needs of patients regarding the post-operative aesthetic and functional results. It also shows advantages for healthcare managers, through a reduced rate of complications and costs for hospitalization.

Its biggest contribution is related to the treatment of patients with adnexal disease and those with suspected endometriosis, but there are still many possibilities to be explored with the evolution of the technique and better training of the surgeons involved.

## CONCLUSION

This is one of the biggest series of cases in the literature regarding single-port laparoscopy surgical treatment in gynecology. The data available up until now, including this series of cases, reaffirm the hypotheses that the technique offers an important contribution to reduced surgical aggression and better post-operative results, reinforcing the fact that difficulties found in the learning phase do not justify the low adherence of gynecologists to the procedure's regular use.

The data observed in this study is in line with the data available in the scientific literature, especially when we note the short hospitalization time, reduced morbidity and the small number of post-operative complications, highlighting the absence of complications considered serious, as well as the aesthetic results.

All the characteristics observed contribute to the increased quality of life of the patients, reducing unpleasant experiences, which is closely related to the overall sensation of well-being.

The findings accumulated up until now do not present any prominent advantage of the single-port over the multiple-port technique. However, single-port laparoscopy has already been shown to be a safe and viable option.

Even with these findings, new prospective and randomized studies are still needed to define the scope of the impact of this technique in the refinement of the aesthetic result, in the reduction of surgical morbidity and in the improvement of the patients' quality of life.

## RESUMO

Laparoscopia por portal único em ginecologia: estudo preliminar de uma série de 50 casos.

**Objetivo:** descrever a experiência inicial da equipe de ginecologia, em um centro de referência, na realização de cirurgia laparoscópica por portal único.

**Métodos:** trata-se de estudo retrospectivo, com a revisão dos prontuários de 50 pacientes atendidas no ambulatório de ginecologia do Hospital da Baleia – Fundação Benjamin Guimarães, entre junho de 2012 e julho de 2013, e que foram submetidas a tratamento cirúrgico laparoscópico por portal único. Este trabalho foi aprovado pelo Comitê de Ética em Pesquisa da instituição.

**Resultados:** a idade média das pacientes incluídas no estudo é de 37,8 anos, variando entre 18 e 70 anos, e as indicações cirúrgicas mais frequentes foram massa anexial (72%) e dor pélvica crônica (24%). O tempo médio cirúrgico foi de 94,4 minutos, com tempo de internação médio de 25,8 horas. Em nenhum caso ocorreu qualquer tipo de complicação perioperatória. Registraram-se duas conversões para laparotomia por dificuldade técnica durante o procedimento. Todos os casos de conversão apresentavam aderências pélvicas. Todas as complicações operatórias foram tratadas com sucesso e nenhuma delas foi considerada grave.

**Conclusão:** esta é uma das maiores séries de casos da literatura em relação ao tratamento cirúrgico por laparoscopia de portal único em ginecologia e apresenta resultados que sugerem a redução da morbidade cirúrgica e resultados estéticos satisfatórios. Concluímos que a laparoscopia por portal único é uma técnica minimamente invasiva viável e que traz importante contribuição à construção de um novo cenário na cirurgia ginecológica moderna.

**Palavras-chave:** laparoscopia; endoscopia; procedimentos cirúrgicos em ginecologia.

## REFERENCES

- Sorensen CH, Vistad I, Ballard K. Is single-port laparoscopy for benign adnexal disease less painful than conventional laparoscopy? A single-center randomized controlled Trial. *Fertil Steril.* 2012;98(4):973-9.
- Nieboer TE, Johnson N, Lethaby A, Tavender E, Curr E, Garry R, et al. Surgical approach to hysterectomy for benign gynaecological disease. *Cochrane Database Syst Rev.* 2009; Issue 3. Art n CD 003677.
- Kommu SS, Kaouk JH, Rané A. Laparo-endoscopic single-site surgery: preliminary advances in renal surgery. *BJU Int.* 2009;103(8):1034-7.
- Rané A, Rao P. Single-port access nephrectomy and other laparoscopic urologic procedures using a novel laparoscopic port (R-port). *Urology.* 2008;72(2):260-3.
- Gumbs AA, Milone L, Sinha P, Bessler M. Totally transumbilical laparoscopic cholecystectomy. *J Gastrointest Surg.* 2009;13(3):533-4.
- Wheless CR. A rapid, inexpensive and effective method of surgical sterilization by laparoscopy. *J Reprod Med.* 1969;3(1):65-9.
- Wheless CR Jr, Thompsom BH. Laparoscopic sterilization. Review of 3600 cases. *Obstet Gynecol.* 1973;42(5):751-8.
- Pelosi MA, Pelosi 3<sup>rd</sup> MA. Laparoscopic hysterectomy with bilateral salpingo-oophorectomy using a single umbilical puncture. *N J Med.* 1991;88(10):721-6.
- Escobar PF, Starks D, Fader AN, Catenacci M, Falcone T. Laparoendoscopic single-site and natural orifice surgery in gynecology. *Fertil Steril.* 2010;94(7):2497-502.
- Jacobs I, Oram D, Faerbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol.* 1990;97(10):922-9.
- ASA Physical Status Classification. Available from: <http://www.asahq.org/>.
- Mencaglia L, Mereu L, Carri G, Arena I, Khalifa H, Tateo S, Angioni S. Single port entry- are there any advantages? *Best Pract Clin Obstet Gynaecol.* 2013;27(3):441-55.
- Fagotti A, Bottoni C, Vizzielli G, Rossitto C, Tortorella L, Monterossi G, Fanfani F, Scambia G. Laparoendoscopic Single-Site Surgery (LESS) for treatment of benign adnexal disease: single-center experience over 3-years. *J Minim Invasive Gynecol.* 2012;19(6):695-700.
- Fader NA, Escobar PF. Laparoendoscopic single-site surgery (LESS) in gynecologic oncology: technique and initial report. *Gynecol Oncol.* 2009;114(2):157-61.
- Fagotti A, Fanfani F, Marocco F, Rossitto C, Gallotta V, Scambia G. Laparoendoscopic single-site surgery (LESS) for ovarian cyst enucleation: report of first 3 cases. *Fertil Steril.* 2009;92(1):1168 e 13-6.
- Escobar PF, Bedaiwy MA, Fader AN, Falcone T. Laparoendoscopic single-site (LESS) surgery in patients with benign adnexal disease. *Fertil Steril.* 2010;93(6):2074.e7-10.
- Kim TJ, Lee YY, Kim MJ, Kim CJ, Kang H, Choi CH, et al. Single port access laparoscopic adnexal surgery. *J Minim Invasive Gynecol.* 2009;16(5):612-5.
- Fagotti A, Bottoni C, Vizzielli G, Alletti SG, Scambia G, Marana E, et al. Postoperative pain after conventional laparoscopy and laparoendoscopic single site surgery (LESS) for benign adnexal disease: a randomized trial. *Fertil Steril.* 2011;96(1):255-9.e2.
- Cho YJ, Kim ML, Lee SY, Lee HS, Kim JM, Joo KY. Laparoendoscopic single-site surgery (LESS) *versus* conventional laparoscopic surgery for adnexal preservation: a randomized controlled study. *Int J Womens Health.* 2012;4:85-91.
- Yoon BS, Park H, Seong SJ, Park CT, Park SW, Lee KJ. Single-port laparoscopic salpingectomy for the surgical treatment of ectopic pregnancy. *J Minim Invasive Gynecol.* 2010;17(1):26-9.
- Lee YY, Kim TJ, Kim CJ, Kang H, Choi CH, Lee JW, et al. Single-port access laparoscopic-assisted vaginal hysterectomy: a novel method with a wound retractor and a glove. *J Minim Invasive Gynecol.* 2009;16(4):450-3.
- Yoon G, Kim TJ, Lee YY, Kim CJ, Choi CH, Lee JW, et al. Single-port access subtotal hysterectomy with transcervical morcellation: a pilot study. *J Minim Invasive Gynecol.* 2010;17(1):78-81.
- Song T, Kim MK, Kim ML, Yoon BS, Seong SJ. Would fewer port numbers in laparoscopy produce better cosmesis? Prospective Study. *J Minim Invasive Gynecol.* 2014;21(1):68-73.
- Yoo EH, Shim E. Single-port access compared with three-port laparoscopic adnexal surgery in a randomized controlled trial. *J Int Med Res.* 2013;41(3):673-80.
- Muriji A, Patel VI, Leyland N, Choi M. Single-incision laparoscopy in gynecologic surgery: a systematic review and meta-analysis. *Obstet Gynecol.* 2013;121(4):819-28.
- Song T, Kim ML, Jung YW, Yoon BS, Joo WD, Seong SJ. Laparoendoscopic single-site *versus* conventional laparoscopic gynecologic surgery: a metaanalysis of randomized controlled trials. *Am J Obstet Gynecol.* 2013;209(4):317.e1-9.

# Intake of antioxidants in patients with rheumatoid arthritis

BRUNA NOLASCO SIQUEIRA SILVA<sup>1\*</sup>, ÍSIS LUCÍLIA SANTOS BORGES DE ARAÚJO<sup>1</sup>, PEDRITA MIRELLA ALBUQUERQUE QUEIROZ<sup>2</sup>, ANGELA LUZIA BRANCO PINTO DUARTE<sup>3</sup>, MARIA GORETTI PESSOA DE ARAÚJO BURGOS<sup>4</sup>

<sup>1</sup>Master's degree student on the Postgraduate Program in Child and Adolescent Health – Federal University of Pernambuco (UFPE), Recife, PE, Brazil

<sup>2</sup>Master's degree student on the Postgraduate Program in Nutrition - UFPE, Recife, PE, Brazil

<sup>3</sup>Full Professor, Doctor and Head of the Rheumatology Service at the Hospital das Clínicas UFPE, Recife, PE, Brazil

<sup>4</sup>Professor and Doctor of Clinical Nutrition at the UFPE Department of Nutrition, Recife, PE, Brazil

## SUMMARY

**Objective:** to investigate dietary intake of antioxidants in patients with rheumatoid arthritis.

**Methods:** this is a cross-sectional case series study with 53 women accompanied at the Rheumatology Outpatient Clinic, Hospital das Clínicas/UFPE, from January to October 2012. Demographic and anthropometric parameters (weight, height, body mass index, weight change) were collected by means of a form. The assessment of food consumption was conducted using a semi-quantitative food frequency survey, analyzed according to a food composition table. Database construction and statistical analysis were performed using Excel and SPSS version 18.0, using chi-squared test, Anova, and Student's *t*-test, at a confidence level of 5%.

**Results:** the sample was composed of 53 women with a mean age of  $54.51 \pm 4.24$  years and BMI of  $25.97 \pm 5.94$  kg/m<sup>2</sup>. In the sociodemographic variables, statistically significant differences in origin, occupation, and income were observed. Daily consumption showed significance for vitamins A, C, and zinc. In adults, vitamins A and C were in accordance with recommendations, while in the elderly a low intake of vitamin E and selenium was observed. The relation between vitamin E and origin was significant.

**Conclusion:** patients demonstrated low consumption of vitamins A, C, and zinc. Therefore, there is a need for increased consumption of foods rich in antioxidants in order to contribute to the prevention of joint injury and loss of rheumatic function, thus, improving quality of life of patients.

**Keywords:** arthritis, rheumatoid, antioxidants, micronutrients.

Study conducted at the Hospital das Clínicas, Federal University of Recife, PE

Article received: 5/2/2014

Accepted for publication: 5/29/2014

\*Correspondence:

Address: Av. Prof. Moraes Rego, 1235 -

Cidade Universitária

Postal Code: 50670-901

Recife - PE

Phone: +55 81 2126-8000

brunanolascosiqueira@gmail.com

<http://dx.doi.org/10.1590/1806-9282.60.06.014>

Conflict of interest: none

## INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease that affects the synovial membrane of peripheral joints. Prevalence is estimated at 0.5 to 1% of the population, predominantly in women, with a greater incidence in the age group of 30-50 years.<sup>1</sup> In Brazil, a multicenter study verified the prevalence of adult RA as ranging from 0.2 to 1%.<sup>2</sup>

It is characterized by local and systemic inflammation with high plasma concentrations of proinflammatory cytokines, such as interleukin-6, interleukin 1 $\beta$ , tumor necrosis factor- $\alpha$  and acute phase proteins, characterizing a condition of oxidative stress. The disease could be related to genetic susceptibility, manifesting itself in response to

an environmental stimulus. However, the exact cause or causes of the disease are unknown.<sup>3</sup>

The term oxidative stress is defined as a pro-oxidant disorder leading to cellular damage. Various cells can tolerate mild oxidative stress, as they have the ability of antioxidant defense and a repair system, which recognize and remove molecules damaged by oxidation<sup>4</sup> including antioxidant enzymes, which constitute the first defense for neutralization of endogenous reactive oxygen species (EROS) as well as antioxidant nutrients.

Antioxidant nutrients are substances that at low concentrations delay or minimize the oxidation of oxidizable substrates.<sup>5</sup> Among non-enzymatic antioxidants responsi-

ble for lower molecular and cellular oxidative stress, vitamin A, C and E, zinc and selenium deserve special attention.<sup>6</sup>

Progress in clinical research has demonstrated an association between antioxidant nutrients intake and lower formation of free radicals, as well as aspects related to the pathogenesis of the disease,<sup>7</sup> showing that these antioxidants effectively suppress the release of inflammatory cytokines, reducing EROS<sup>8</sup> and presenting a protective effect on the development of RA.<sup>9</sup>

The purpose of this study was to evaluate the dietary intake of antioxidant micronutrients, associating this with sociodemographic variables, nutritional status, age range and weight change after use of antirheumatic drugs.

## METHODS

This was a cross-sectional case series study lasting for 10 months (2012), in which 53 women with RA were assessed at the Rheumatology Outpatient Service of Hospital das Clínicas, Federal University of Pernambuco (HC/UFPE), Recife/state of Pernambuco. Patients aged  $\geq 20$  years from urban and rural areas of Pernambuco were included.

Patients who did not know their precise feed consumption were excluded, as well as amputees, pregnant women, nursing mothers and those in advanced stages of the disease.

Sociodemographic and anthropometric parameters (age, gender, origin, marital status, occupation, family income, education level) were evaluated, as well as measurements of weight (kg), height (m) and Body Mass Index (BMI) ( $\text{kg}/\text{m}^2$ ), classified according to the World Health Organization (2002)<sup>10</sup> for adults, and Lipschitz<sup>11</sup> for seniors.

Furthermore, patients were classified according to the presence of weight changes.<sup>12</sup> They first reported their usual weight before the rheumatic disease, in order to observe weight gains, maintenance or loss related to current weight, with or without the use of antirheumatic drugs.

Food consumption was assessed at a daily frequency using a dietary frequency semi-quantitative questionnaire (QFASQ), adapted by Rohenkohl,<sup>13</sup> structured into five distinct groups of micronutrients: vitamin A, vitamin C, vitamin E, Zinc and Selenium. This was done using Brazilian food sources with reasonable amounts of these micronutrients and frequently consumed by the Brazilian population, and based on the food composition table by Philippi.<sup>14</sup> An illustrative album with usual cooking measures was used for appropriate portioning and the table

of food composition by Philippi<sup>14</sup> was used to analyze the frequency of food consumption.

The study was approved by the Ethics Committee for research involving human subjects at the Health Sciences Center/UFPE under number 0510.0.172.000-11.

## STATISTICAL ANALYSIS

The construction of the database and the statistical analysis were performed using Excel and the Statistical Package for Social Sciences (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA), respectively.

The continuous variables were tested for normality using the Kolmogorov-Smirnov test, when necessary. Variables with normal distribution were described in the form of means and their respective standard deviations.

While verifying the occurrence of statistical associations, chi-squared, Anova and Student's *t*-test were used to compare means, presenting their respective p-value for determination of statistical significance. The prevalence ratio was used as a measure of effect, considering food intake of the main antioxidants in patients as the dependent variable. A confidence level of 5% was adopted for rejection of the null hypothesis.

## RESULTS

The study consisted of 53 women with a mean age of  $54.51 \pm 4.24$  years (70% adults and 30% seniors), with a mean BMI of  $25.97 \pm 5.94 \text{ kg}/\text{m}^2$ . There was no association between weight change and the use of antirheumatic drugs.

Table 1 presents sociodemographic and clinical characteristics of the sample. Being from urban areas, employed and with an income of 1-3 minimum wages were significant characteristics in the group. It is noteworthy that no differences were detected in other parameters, although there was a trend toward a greater number of literate and overweight individuals.

In relation to daily consumption of antioxidant micronutrients between age groups (Table 2), we observed a significantly higher intake in of vitamin A, C and zinc in seniors. Adequacy of consumption using the DRIs was greater than 100% for vitamin A and C in adults, with inadequate intake of vitamin E and selenium in seniors.

Table 3 shows the comparison between sociodemographic factors and inadequate intake of micronutrients (vitamin E, selenium and zinc).

**TABLE 1** Association of sociodemographic, anthropometric and clinical characteristics of the sample (n = 53)

Variables	N (%)	Mean	Standard deviation	p Value
<b>Origin</b>				
Urban area	29 (54.7%)	57.55	11.76	0.040*
Rural area	24 (45.3%)	50.83	11.27	
<b>Marital status</b>				
Single/widowed/divorced	28 (52.8%)	56.50	12.56	0.201
Married/common-law partner	25 (47.2%)	52.28	10.98	
<b>Occupation</b>				
Employed	41 (77.4%)	56.68	10.94	0.013*
Unemployed	12 (22.6%)	47.08	12.59	
<b>Income</b>				
No income	6 (11.3%)	48.00	13.71	
<1 minimum salary	8 (15.1%)	46.38	12.43	0.021**
1-3 minimum salaries	39 (73.6%)	57.18	10.64	
<b>Education</b>				
Illiterate	5 (9.4%)	55.40	4.56	0.863
Literate	48 (90.6%)	54.42	12.46	
<b>Nutritional status</b>				
Low weight	4 (7.7%)	56.75	14.84	
Normal weight	18 (34.6%)	52.56	13.12	0.856
Overweight	19 (36.5%)	55.58	12.69	
Obese	11 (21.2%)	55.27	8.81	
<b>Antirheumatic drugs</b>				
One drug	27 (50.9%)	51.93	9.57	0.108
Two or more drugs	26 (49.1%)	57.19	13.62	

\*T-test; \*\*ANOVA.

## DISCUSSION

A mean of  $54.51 \pm 4.24$  years was observed in this study, with a predominance of women, confirming the findings of most authors<sup>13,15</sup> who assessed the intake of antioxidants.

In relation to BMI, our results are in agreement with Avelar, Melo and Souza<sup>16</sup> in a study of a group similar to this one, where a BMI of  $26.39 \pm 3.80$  kg/m<sup>2</sup> was found. On the other hand, Fernandes et al.<sup>17</sup> found a higher percentage of obesity in their sample, where 68.3% had some degree of obesity.

The data in the literature is scarce when relating the intake of antioxidants and/or rheumatic diseases with patient origin and *per capita* income. According to some authors,<sup>18,19</sup> rheumatic patients are a group with prevalent inactivity (around 30%), which is also seen in this study. Corbacho and Dapuetto,<sup>20</sup> with an equal number of individuals and pathology as this study, observed similar results in terms of education, although different in relation to antirheumatic drug therapy, with only 24.5% using combined treatment.

Evidence suggests a high intake of vitamin C and low of vitamin E when assessing the dietary intake of women with RA,<sup>15</sup> a result similar to this group. Edmonds et al.<sup>21</sup> have shown that vitamin E supplementation (600 mg/day) improves the clinical symptoms of the disease, through a possible mechanism of reduced formation of prostaglandins, molecules produced during inflammatory processes.

When evaluating selenium intake, Salvador et al.<sup>15</sup> detected that 90% of the sample had a higher consumption than the recommendations, a fact confirmed by Hagfors et al.<sup>22</sup> and not verified by this study, which found inadequacy greater than 40% of the DRIs. Current data confirms the importance of selenium in RA, since deficiency is associated with increased incidence of the disease.<sup>23</sup>

**TABLE 2** Adequacy of dietary intake of antioxidants and comparison between age groups (n=53)

Nutrients	Average intake	Reference value (DRIs)	Adults	Adequacy %	Elderly	Adequacy %	p Value
Vitamin A (µg)	953.81	700	838.17	119.74	1221.23	174.46	0.037*
Vitamin C (mg)	147.15	75	117.72	156.96	215.19	286.92	0.036*
Vitamin E (mg)	8.51	15	8.83	58.87	7.77	51.80	0.505
Selenium (µg)	24.48	55	22.09	40.16	30.01	54.56	0.283
Zinc (mg)	5.77	8	4.73	59.12	8.17	102.12	0.038*

\* Student's t-test; Dietary Reference Intake (DRIs) 2000: vitamins E, C, selenium and 2001: vitamin A, zinc.

**TABLE 3** Relationship between sociodemographic characteristics and food consumption (n=53)

Variables	Vitamin E			Selenium			Zinc		
	Mean	Standard deviation	p Value	Mean	Standard deviation	p Value	Mean	Standard deviation	p Value
<b>Origin</b>									
Urban	6.97	4.46	0.017*	28.31	25.84	0.213*	6.24	5.17	0.507*
Rural	10.38	5.64		19.86	22.23		5.20	6.11	
<b>Marital status</b>									
Single/widowed/divorced	9.33	4.79	0.234*	29.65	26.34	0.103*	6.96	5.96	0.102*
Married/common-law partner	7.60	5.71		18.69	21.09		4.44	4.91	
<b>Occupation</b>									
Employed	8.43	5.23	0.843*	27.07	25.67	0.155*	6.51	5.55	0.076*
Unemployed	8.78	5.62		15.64	17.64		3.26	5.16	
<b>Income</b>									
No income	7.99	6.86		19.52	18.21		4.47	6.61	
<1 minimum salary	8.52	4.60	0.968**	12.08	15.79	0.223**	2.49	3.53	0.132**
1-3 minimum salaries	8.59	5.27		27.79	26.05		6.64	5.59	
<b>Education</b>									
Illiterate	10.76	6.13	0.320*	18.19	26.83	0.550*	4.16	5.82	0.503*
Literate	8.23	5.18		25.14	24.36		5.94	5.59	

\* T-test; \*\* Anova

Regarding the consumption of vitamin A, Bae et al.<sup>24</sup> observed that daily intake was significantly lower in RA patients than in the control group, which was not demonstrated by this study.

The current literature is sparse in relation to the association between antioxidant intake and nutritional status in rheumatic diseases. In healthy obese individuals, Marreiro et al.<sup>25</sup> found a reduction in plasma concentrations of zinc, demonstrating that supplementation reduces insulin resistance. These findings demonstrate the influence of this antioxidant on changes in nutritional status, which was observed in our results.

Few studies have compared the intake of micronutrients and sociodemographic factors. A study<sup>26</sup> conducted in Brazil suggests that vitamin E intake is inadequate, regardless of gender, age, race, income, social class and nutritional status, corroborating the results of this group. On the other side, 13.4% inadequate intake of selenium was also shown, contrary to the results in this study (55%). In relation to zinc, 52.1% inadequacy was found the entire sample, similar to this study on adults (40%). However, in this Brazilian case series, micronutrient intakes were not associated with sociodemographic factors.

In relation to the use of the RA medication, anti-inflammatory and immunomodulatory drugs are important in the treatment of patients with RA, although this may occasionally be a cause of troubling metabolic effects (obe-

sity, glucose intolerance, weight and appetite changes).<sup>27</sup> However, the patient may occasionally present persistent anorexia, decreased absorption and/or abnormal utilization of nutrients, promoting hypercatabolism, malnutrition and changes in the bodily composition,<sup>28</sup> confirming the findings of this study, which detected a greater tendency to weight loss in the group as a whole and within the different age ranges.

## CONCLUSION

This research has shown that patients with RA had a low consumption of antioxidant micronutrients: vitamins A, C and zinc. Therefore, we can emphasize the importance of dietary guidance based on major sources of antioxidant micronutrients, especially fruits, raw vegetables, fish and oilseeds in order to contribute to the prevention of joint damage and loss of rheumatic function.

## RESUMO

Consumo de antioxidantes em portadores de artrite reumatoide.

**Objetivo:** investigar o consumo alimentar de antioxidantes em pacientes portadores de artrite reumatoide.

**Métodos:** estudo transversal do tipo série de casos com 53 mulheres acompanhadas no Ambulatório de Reumatolo-

gia do Hospital das Clínicas da Universidade Federal de Pernambuco (HC-UFPE), de janeiro a outubro de 2012. Por meio de formulário, foram coletados parâmetros sociodemográficos e antropométricos (peso, estatura, índice de massa corpórea [IMC], alteração ponderal). A avaliação do consumo alimentar foi realizada por questionário de frequência alimentar semiquantitativo, analisado por tabela de composição de alimentos. A construção do banco de dados e a análise estatística foram realizadas por Excel e SPSS versão 18.0, com aplicação de testes Qui-quadrado, Anova e t-Student, com nível de confiança de 5%.

**Resultados:** amostra composta por 53 mulheres, idade de 54,51±4,24 anos e IMC de 25,97±5,94 kg/m<sup>2</sup>. Nas variáveis sociodemográficas, observou-se diferença estatística em procedência, ocupação e renda. O consumo diário apresentou significância para as vitaminas A, C e zinco. Nos adultos, as vitaminas A e C estavam de acordo com as recomendações; nos idosos, houve baixo consumo de vitamina E e selênio. Foi significativo ao relacionar a vitamina E com a variável procedência.

**Conclusão:** demonstrou-se que os pacientes apresentaram baixo consumo de vitaminas A, C e zinco. Portanto, ressalta-se a importância de maior consumo de alimentos fontes em antioxidantes, a fim de contribuir para a prevenção da lesão articular e a perda da função reumática, melhorando a qualidade de vida do paciente.

**Palavras-chave:** artrite reumatoide; antioxidantes; consumo alimentar.

## REFERENCES

- Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin Arthritis Rheum.* 2006;36(3):182-8.
- Marques Neto JF, Gonçalves ET, Barros EFO, Cunha MFL, Radominsk S, Oliveira SM, et al. Estudo multicêntrico da prevalência da artrite reumatoide do adulto em amostras da população brasileira. *Rev Bras Reumatol.* 1993;33(5):169-73.
- Rennie KL, Hughes J, Lang R, Jebb SA. Nutritional management of rheumatoid arthritis: a review of the evidence. *The British Dietetic Association. J Hum Nutr Diet.* 2003;16(2):97-109.
- Zadák Z, Hyspler R, Tichá A, Hronek M, Fikrová P, Rathouská J, et al. Antioxidants and vitamins in clinical conditions. *Physiol Res.* 2009;58(1):13-7.
- Halliwell B, Aeschbach R, Löliger J, Aruoma OI. The characterization of antioxidants. *Food Chem Toxicol.* 1995;33(7):601-17.
- Berger MM. Can oxidative damage be treated nutritionally? *Clin Nutr.* 2005;24(2):172-83.
- Riccioni G, Bucciarelli T, Mancini B, Corradi F, Di Ilio C, Mattei PA, et al. Antioxidant vitamin supplementation in cardiovascular diseases. *Ann Clin Lab Sci.* 2007;37(1):89-95.
- Surh YJ, Kundu JK, Na HK, Lee JS. Redox-sensitive transcription factors as prime targets for chemoprevention with anti-inflammatory and antioxidative phytochemicals. *J Nutr.* 2005; 135(12):2993-3001.
- Pattison DJ, Harrison RA, Symmons DPM. The role of diet in susceptibility to rheumatoid arthritis: a systematic review. *J Rheumatol* 2004;31(7):1310-9.
- World Health Organization: the world report 2002: reducing risks, promoting healthy life. Geneva: World Health Organization; 2002.
- Lipschitz DA. Screening for nutritional status in the elderly. *Prim Care.* 1994;21(1):55-67.
- Blackburn GL, Bristian BR. Nutritional and metabolic assessment of the hospitalized patient. *JPEN J Parenter Enteral Nutr.* 1977;1(1):11-22.
- Rohenkohl CC, Carniel AP, Colpo E. Consumo de antioxidantes durante tratamento quimioterápico. *ABCD Arq Bras Cir Dig.* 2011;24(2):107-12.
- Philippi ST. Tabela de composição de alimentos: suporte para decisão nutricional. 2a ed. São Paulo: Editora Coronário; 2002.
- Salvador MB, Sarkis KS, Silva RG, Zerbini CAF, Martini LA. Avaliação da ingestão de ácidos graxos, antioxidantes e da composição corporal em mulheres com artrite reumatoide. *Rev Soc Bras Alim Nutr.* 2008;33(3):17-30.
- Avelar AB, Melo AKG, Souza BDB. Avaliação prospectiva do perfil lipídico na artrite reumatoide. *Rev Bras Reumatol.* 2008;48(4):213-7.
- Fernandes M, Paes C, Nogueira C, Souza G, Aquino L, Borges F et al. Perfil de consumo de nutrientes antioxidantes em pacientes com síndrome metabólica. *Rev Ciênc Méd.* 2007;16(4-6):209-19.
- Abreu MM, Kowalski SC, Ciconelli RM, Ferraz MB. Avaliação do perfil sociodemográfico, clínico-laboratorial e terapêutico dos pacientes com artrite reumatoide que participaram de projetos de pesquisa na Escola Paulista de Medicina, nos últimos 25 anos. *Rev Bras Reumatol.* 2006;46(2):103-9.
- Louzana-Junior P, Souza BDB, Toledo RA, Ciconelli RM. Análise descritiva das características demográficas e clínicas de pacientes com artrite reumatoide no Estado de São Paulo, Brasil. *Rev Bras Reumatol* 2007;47(2):84-90.
- Corbacho MI, Dapuetto JJ. Avaliação da capacidade funcional e da qualidade de vida de pacientes com artrite reumatoide. *Rev Bras Reumatol.* 2010;50(1):31-43.
- Edmonds SE, Winyard PG, Guo R, Kidd B, Merry P, Lnaqrish-Smith A, et al. Putative analgesic activity of repeated oral doses of vitamin E in the treatment of rheumatoid arthritis. Results of a prospective placebo controlled double blind trial. *Ann Rheum Dis.* 1997;56(11):649-55.
- Hagfors L, Leanderson P, Sköldstam L, Andersson J, Johansson G. Antioxidant intake, plasma antioxidants and oxidative stress in a randomized, controlled, parallel, Mediterranean dietary intervention study on patients with rheumatoid arthritis. *Nutr J.* 2003;2(1):1-11.
- Cerhan JR, Saag KG, Merlino LA, Mikuls TR, Criswell LA. Antioxidant micronutrients and risk of rheumatoid arthritis in a cohort of older women. *Am J Epidemiol.* 2003;157(4):345-54.
- Bae S, Jung W, Lee E, Yu R, Sung M. Effects of antioxidant supplements intervention on the level of plasma inflammatory molecules and disease severity of rheumatoid arthritis patients. *J Am Coll Nutr.* 2009;28(1):56-62.
- Marreiro DN, Fisberg M, Cozzolino SM. Zinc nutritional status and its relationships with hyperinsulinemia in obese children and adolescents. *Biol Trace Elem Res.* 2004;100(2):137-49.
- Pinheiro MM, Ciconelli RM, Chaves GV, Aquino L, Juzwiak CR, Genaro PS, et al. Antioxidant intake among Brazilian adults - The Brazilian Osteoporosis Study (BRAZOS): a cross-sectional study. *Nutr J.* 2011;10(39):1-8.
- Castro TDM, Obana FK, Martins MFM, Andrade CAF. Efeitos adversos metabólicos dos glicocorticóides no tratamento da artrite idiopática juvenil: uma revisão sistemática. *Rev Saúde.* 2010;1(2)31-42.
- Chaud DMA, Hilário MOE, Yanaguibashi G, Amancio OMS. Avaliações dietética e antropométrica em pacientes com artrite reumatoide juvenil. *Rev Assoc Med Bras.* 2003;49(2):181-4.

# Endometriosis is an important cause of pelvic pain in adolescence

MARINA DE PAULA ANDRES<sup>1\*</sup>, SERGIO PODGAEC<sup>2</sup>, KARINA BELICKAS CARREIRO<sup>3</sup>, EDMUND CHADA BARACAT<sup>4</sup>

<sup>1</sup>Collaborating Physician at Hospital das Clínicas, Faculty of Medicine, University of São Paulo (HC-FMUSP), Brazil

<sup>2</sup>Post-doctoral Professor at the Division of Gynecology at the Faculty of Medicine, University of São Paulo, Head of the endometriosis clinic at HC-FMUSP, Brazil

<sup>3</sup>Resident Physician at the Gynecology Division at HC-FMUSP, Brazil

<sup>4</sup>Full Professor of Gynecology, FMUSP, Brazil

## SUMMARY

**Objective:** despite endometriosis being a common disease, where early detection is key to preventing its progression, it is a condition often overlooked in adolescents. The aim of this study was to report the clinical characteristics of adolescent patients with endometriosis monitored in a tertiary hospital.

**Methods:** a retrospective study of 394 patients undergoing surgery with a histological diagnosis of endometriosis at the Endometriosis Division of the Gynecology Department at the Hospital das Clínicas of the University of São Paulo Medical School from 2008 to 2013. 21 adolescents were included (aged under 21 years).

**Results:** the age ranged from  $17.95 \pm 1.48$  years, the average time for diagnostic confirmation was  $2.96 \pm 2.93$  years, and the age at the onset of symptoms was  $15.28 \pm 3.03$  years on average. The sites affected were ovarian (38%), peritoneal (47.6%) and retrocervical (23.8%). Dysmenorrhea was found in 80.9 % of adolescents (severe in 33.3% of cases) and chronic pelvic pain in 66.6%.

**Conclusion:** endometriosis in adolescents is an important differential diagnosis from pelvic pain and ovarian cysts, mainly among those with no response to conventional treatment. The main forms of involvement are peritoneal and ovarian. Despite the onset of symptoms in adolescence and advances in imaging methods, the diagnosis of this disease is still delayed.

**Keywords:** endometriosis, adolescent, dysmenorrhea, ovarian cysts.

Study conducted at the Hospital das Clínicas, Faculty of Medicine, University of São Paulo (FMUSP), São Paulo, SP

Article received: 7/2/2014

Accepted for publication: 7/23/2014

\*Correspondence:

Address: Av. Dr. Enéas de Carvalho Aguiar,  
255, Cerqueira César  
São Paulo – SP  
marina.dpandres@gmail.com

<http://dx.doi.org/10.1590/1806-9282.60.06.015>

Conflict of interest: none

## INTRODUCTION

Endometriosis is a gynecological disease defined by the presence of glands and/or endometrial stroma outside the uterine cavity.<sup>1</sup> The sites of disease involvement are the ovaries and retrocervical region, most often beyond the pelvic peritoneum, vagina, rectum, sigmoid, appendix, ureter and bladder, among others.<sup>2</sup> One of the most common gynecological diseases, it may be present in 10-15% of women of childbearing age and up to 70% of women with a diagnosis of chronic pelvic pain.<sup>1,3</sup> Its etiopathogenesis is still controversial and several theories have been proposed to justify the presence of the disease.<sup>1,4,5</sup> It can be classified as superficial, ovarian and deep, the latter being characterized by the infiltration of endometrial implants above a depth.<sup>6,7</sup>

Endometriosis presents diverse clinical presentations. The main complaint of patients with endometriosis is chronic pelvic pain (non-cyclical) and dysmenorrhea, with an incidence of up to 75%. Other complaints include in-

fertility, deep dyspareunia and cyclic urinary and intestinal disorders associated with the menstrual period.<sup>5</sup> The prevalence of endometriosis can reach 40-60% in patients complaining of dysmenorrhea and 30-40% in women complaining of infertility.<sup>6,8-11</sup>

This clinical condition can affect women during the reproductive period, including adolescence, defined as transition from childhood to adulthood, occurring between 10 to 19 years according to the World Health Organization (WHO).<sup>12</sup> The main gynecological complaint by adolescents is dysmenorrhea, which affects between 60 and 93% of these patients. In most cases, this is primary or functional dysmenorrhea related to more frequent ovulatory cycles after 2 to 3 years of menarche. The pathophysiology of primary dysmenorrhea is still controversial and involves the release of leukotrienes and prostaglandins which cause systemic symptoms such as nausea and headache, and local pelvic symptoms, secon-

dary to potent vasoconstriction and myometrial contraction, leading to ischemia and pain.<sup>13</sup> Despite the high prevalence of dysmenorrhea in adolescents, many girls do not seek professional help or treatment.<sup>14</sup> In a 2006 study, Houston et al.<sup>15</sup> reported that 98% of teens use non-pharmacological therapies such as rest and warm compresses (with success rates of 40% or less) and 30-70% self-treatment with simple analgesics, with 57% using doses below those recommended.<sup>15</sup>

Secondary dysmenorrhea is that related to pelvic abnormalities and can be found in up to 10% of adolescents with endometriosis as the primary cause.<sup>13</sup> As the incidence of gynecological diseases increases with age, secondary dysmenorrhea is more prevalent in young adults than adolescents.<sup>13</sup>

The treatment of endometriosis in adolescents presents particularities owing to the age of the patients. The use of hormonal contraceptives and anti-inflammatory drugs does not have any restriction, however, the use of GnRH analogues should be analyzed because of its side effects.<sup>16</sup>

## OBJECTIVE

Although endometriosis is a common disease, where early detection is key to preventing its progression, it is a condition often overlooked in patients during puberty. The aim of this study was to report the clinical characteristics of adolescent patients with endometriosis monitored in a tertiary hospital.

## METHODS

The study was conducted retrospectively by surveying medical records, thereby exempt from the approval of the Research Ethics Committee.

A retrospective analysis of the database belonging to the Endometriosis Sector at the Gynecology Clinic Division at the University of São Paulo Medical School's Hospital das Clínicas, (HC-USP) was conducted in the period from 2008 to 2013. The inclusion criterion was patients up to 20 years of age with a histologically confirmed diagnosis of endometriosis.

After anamnesis and clinical examination, all patients with clinically suspected endometriosis underwent a specialized image evaluation for this purpose, with transvaginal ultrasound and pelvic examination with bowel preparation prior to the exam or magnetic resonance imaging

of the pelvis (if the patient had not started sexual activity). Clinical data related to the different pains reported by patients are measured by a visual analog scale, ranging from zero to 10, where 10 is the worst pain.

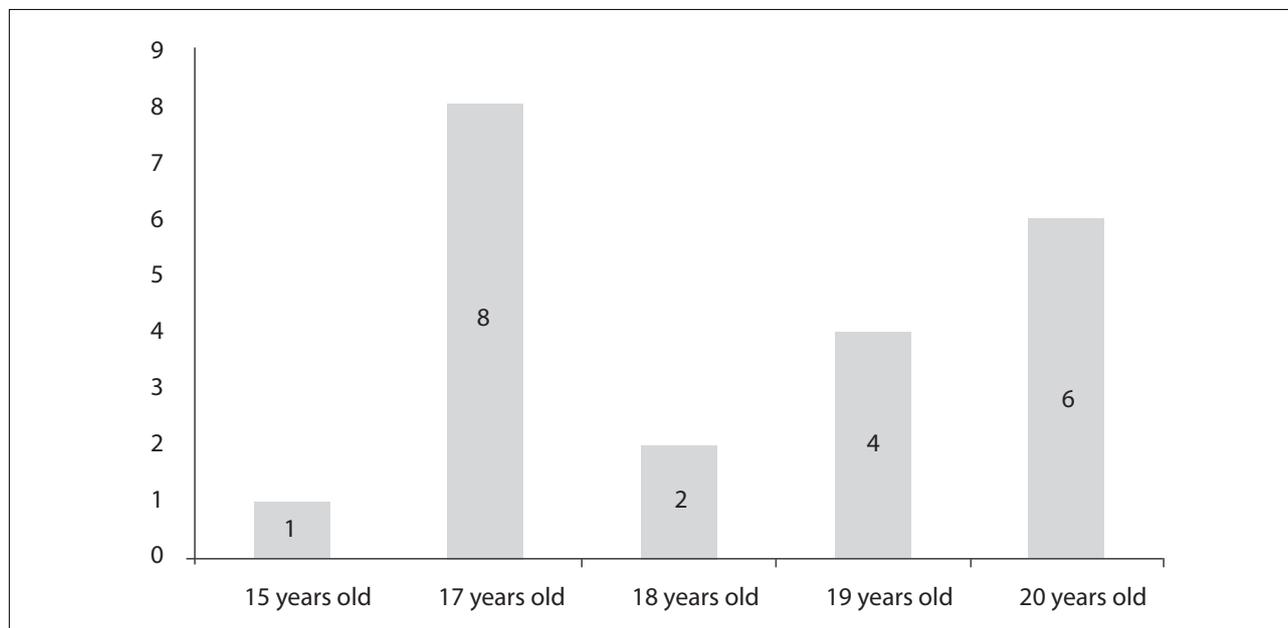
Clinical hormonal treatment with combined contraceptives or continuous progestogens is indicated for patients who do not present evidence of lesions in this assessment (as it may be superficial endometriosis), or in cases of ovarian endometriomas less than 3 cm or when there is deep endometriosis, provided this does not affect the ureter, appendix, terminal ileum and or rectosigmoid in conditions of sub-occlusion. Periodically, at average intervals of 6 months, patients are clinically reassessed and undergo imaging exams, where appropriate. Medication treatment failure is considered if there is no improvement in symptoms (measured with the aid of the visual pain scale) and/or an increase in lesions, even during the course of steroid hormone use. When there are no lesions visualized in the imaging exam, then diagnostic laparoscopy is recommended and, in the case of deep endometriosis and/or ovarian endometrioma surgical treatment of the diseases is recommended.

Using this protocol, from the 394 patients undergoing surgery with a diagnosis of endometriosis in this period, 21 adolescents were selected from this group. In addition to the data above, all patients were assessed for symptoms, age at diagnosis, duration of clinical history, level of education, site of onset of the disease, and family history. They were also assessed in relation to the presence of outbreaks of disease in the peritoneum, ovaries and/or deep infiltrative locations.

## RESULTS

The mean age of patients was  $17.95 \pm 1.48$  years, ranging from 13-20 years. The race of patients was predominantly white ( $n = 15$ ), corresponding to 68% of cases. The level of education was high in affected patients, corresponding to 72.7% ( $n = 16$ ) with a high school diploma or still studying at this level. Only two patients presented a family history of endometriosis (Figure 1).

The average time elapsed between onset of symptoms and the diagnostic confirmation was  $2.96 \pm 2.93$  years, ranging from six months to four years, and the age of onset of symptoms was  $15.28 \pm 3.03$  years on average (Table 1). The sites affected by the disease are described in Table 2.



**FIGURE 1** Number of adolescents with endometriosis by age. Hospital das Clínicas. 2008-2013.

**TABLE 1** Clinical condition of adolescents with endometriosis

Symptoms	% (n)
Dysmenorrhea	80.9 (17)
Light (VAS 1 to 4)	28.5 (6)
Moderate (VAS 5 to 7)	19 (4)
Incapacitating (VAS 8 to 10)	33.3 (7)
Chronic pelvic pain	66.6 (14)
Infertility	4.7 (1)
Deep dyspareunia	33.3 (7)
Cyclic bowel symptoms	14.2 (3)

VAS: visual analogue scale for pain (zero to 10).

**TABLE 2** Clinical characteristics of adolescents with endometriosis

Clinical characteristics	% (n)
Family history of endometriosis	9.4(2)
<b>Race</b>	
White	71.4 (15)
Black	23.8 (5)
Mixed	7 (1)
<b>Site affected by the disease</b>	
Ovaries	38 (8)
Superficial peritoneal	47.6 (10)
Retrocervical	23.8 (5)
Retrocervical and ovaries	9.4 (2)

After surgery, 19 patients received adjuvant clinical treatment: combined oral contraceptives (42.8%), GnRH analogue (33.3%), oral progestogen (19%), levonorgestrel-releasing intrauterine system (4.7%) and Danazol (4.7%).

## DISCUSSION

It is estimated that the prevalence of endometriosis in adolescents is 45-70% in those undergoing laparoscopy for chronic pelvic pain.<sup>13,16</sup> In the present study, among adolescent patients with a confirmed endometriosis diagnosis, the mean age was  $18.24 \pm 1.48$  years, ranging from 13-20 years. The median age is 17 years, in accordance with other studies in the literature where the average age of diagnosis was 18.6 years.<sup>16</sup>

As presented in other studies, the incidence of endometriosis is higher in white patients. In this study, the incidence was 68% of patients. Templeman reported a higher incidence of school absenteeism among white patients with endometriosis than in black patients, which may represent a higher proportion of disease in this group of adolescents.<sup>17</sup> The importance of endometriosis in patients with a higher educational level was also noted in this study, as 72.7% of patients had been attending high school, which has also been observed by other authors.<sup>17-19</sup>

We noted that the average time elapsed between onset of symptoms of pain and the diagnostic confirmation was  $2.96 \pm 2.93$  years, varying from six months to four years, and the age of onset of symptoms was 15.28

$\pm 3.03$  years on average. Part of these complaints reported by the adolescents should be considered as relating to common psychosocial disorders during this period of life, which ultimately cause delays in the diagnosis of chronic diseases. According to the American Association of Endometriosis, 66% of adult women describe the onset of complaints of pelvic pain before reaching 20 years of age, and even those that seek help from specialists need at least four professionals to reach the correct diagnosis. Patients with symptoms of endometriosis before 19 years of age took an average of 12.1 years for the diagnosis of endometriosis, while women over 30 took 3.3 years.<sup>2, 8, 13, 20</sup>

Arruda et al.<sup>21</sup> applied questionnaires to 200 patients, on average, 26 months after histological diagnosis of endometriosis. Among the patients analyzed, 2.5% were aged less than 20 years, 50% were between 30 and 39 years, and 20.5% were older than 40 years. The main complaint was dysmenorrhea, present in 67% of patients, and chronic pelvic pain was found in 12.5%, infertility in 10%, dyspareunia in 5.5%, and more than one symptom in 88%. The mean interval between onset of symptoms and diagnosis of endometriosis was seven years, taking nine years when the symptoms began in adolescence, and only three years when started after 30 years of age. Patients with complaints of pelvic pain took on average six months to see a doctor, while patients complaining of infertility took on average 1.7 years. Although 44% of patients develop symptoms before 20 years of age, only 3.5% received a definitive diagnosis in this age group.<sup>21</sup>

Another study published in 2010 was based on data from 12 centers in Italy, which study patients with endometriosis. 39 patients aged between 10 and 21 years were evaluated, regarding complaints presented and laparoscopic findings with histological confirmation. The average age at diagnosis was 18.6 years, with three cases diagnosed before 15 years of age. Genital malformations that could justify the precocity of the diseases were not observed. The main complaint triggering the start of the investigation was chronic pelvic pain with non-cyclic presentation or acute pelvic pain. In three patients, the investigation was based on adnexal masses.<sup>16</sup>

A study conducted in New Zealand assessed 163 patients with histological diagnosis of endometriosis in the period from 2003 to 2009. 20 of these patients were adolescents. Among adolescent patients, the main complaint was dysmenorrhea in 80% *versus* 55% among adults, and the use of more than one analgesic for pain control was 95% *versus* 59%, respectively.<sup>22</sup>

In over half the cases evaluated in our study, the adolescents had moderate or disabling intensity dysmenorrhea (VAS over 5), with 16 of them being part of their initial complaint. Chronic pelvic pain was also noted in the majority of patients (66.6%). This data is corroborated by the literature, in which the symptom leading to diagnosis of the disease was chronic or acute pelvic pain in 79% of patients, and pelvic mass in 21%.<sup>14-16, 17, 23</sup>

The majority of disease involvement was peritoneal (47.6%) and ovarian (38%). Deep endometriosis was diagnosed in 33.3% of adolescents, with retrocervical involvement in all of them, with no correlation with an exuberant clinical picture. The main symptom presented by this group was non-cyclic pelvic pain. In the literature, the early stages are less frequent in adolescents and ovarian endometriosis is common, suggesting that despite pain being the main symptom leading to gynecological examination, surgery is most appropriate when there are ultrasound findings of ovarian cysts.<sup>16, 24</sup>

Postoperative treatment was mostly with combined oral contraceptives (42.8%). The levonorgestrel-releasing intrauterine system was only used in one patient and the GnRH analogue was used in 33.3% of them. It should be highlighted that GnRH should not be used in patients younger than 17 years and its use should be for short periods due to the effects of hypoestrogenism, mainly hot flushes and osteopenia.<sup>16</sup>

## CONCLUSION

Endometriosis in adolescents is a disease to be considered as an important differential diagnosis in pelvic pain and adnexal cysts, especially among those with pain resistant to the use of commonly used medication. The main forms of involvement are peritoneal and ovarian, and despite advances in imaging methods, there is still a delay in diagnosis of this disease, which often has symptoms starting in adolescence, bringing physical and emotional damage, with a major impact on quality of life in such girls. The gynecologist should be aware of the signs and symptoms to make an early diagnosis, thereby preventing progression of the disease and providing the most appropriate treatment for each patient.

## RESUMO

Endometriose é causa importante de dor pélvica na adolescência.

**Objetivo:** embora a endometriose seja uma doença prevalente, cujo diagnóstico precoce é fundamental para a

prevenção de sua progressão, é uma condição frequentemente negligenciada em adolescentes. O objetivo deste estudo é levantar as características clínicas das pacientes adolescentes com endometriose acompanhadas em um hospital terciário.

**Métodos:** levantamento retrospectivo de 394 pacientes submetidas à cirurgia com diagnóstico histológico de endometriose no Setor de Endometriose da Divisão de Clínica de Ginecologia do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, de 2008 a 2013. Foram incluídas 21 adolescentes (idade menor de 21 anos).

**Resultados:** a idade média foi de  $17,95 \pm 1,48$  anos, a média de tempo para a confirmação diagnóstica foi de  $2,96 \pm 2,93$  anos e a idade do início dos sintomas foi em média de  $15,28 \pm 3,03$  anos. Os locais de acometimento foram ovariano (38%), peritoneal (47,6%) e retrocervical (23,8%). Dismenorreia esteve presente em 80,9% das adolescentes (sendo severa em 33,3% dos casos) e dor pélvica crônica em 66,6%.

**Conclusão:** endometriose em adolescentes é um importante diagnóstico diferencial de dor pélvica e cistos anexiais, principalmente entre aquelas sem resposta ao tratamento convencional. As principais formas de acometimento são peritoneais e ovarianas. Apesar do início dos sintomas na adolescência e dos avanços nos métodos de imagem, ainda se observa demora no diagnóstico dessa doença.

**Palavras-chave:** endometriose; adolescente; dismenorreia; cistos ovarianos.

## REFERENCES

1. Signorile PG, Baldi A. Endometriosis: new concepts in the pathogenesis. *Int J Biochem Cell Biol.* 2010;42(6):778-80.
2. Harel Z. Dysmenorrhea in adolescents. *Ann N Y Acad Sci.* 2008;1135:185-95. Review.
3. Practice committee of American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis. *Fertil Steril.* 2008;90(5):s260-9. Review.
4. Podgaec S, Rizzo LV, Fernandes LF, Baracat EC, Abrao MS. CD4(+) CD25(high) Foxp3(+) cells increased in the peritoneal fluid of patients with endometriosis. *Am J Reprod Immunol.* 2012;68(4):301-8.
5. Bulun SE. Endometriosis. *N Engl J Med.* 2009;360(3):268-79. Review.
6. Hails G, Machsner S, Ebert AD. The diagnosis and treatment of deep infiltrating endometriosis. *Dtsch Arztebl Int.* 2010;107(25):446-56;quiz 456.
7. Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. *Fertil Steril.* 1997;68(4):585-96.
8. Farquhar CM. Extracts from the "clinical evidence". *Endometriosis. BMJ.* 2000;320(7247):1449-52. Review.
9. Bellelis PK, Dias JÁ Jr, Podgaec S, Gonzales M, Baracat EC, Abrão MS. Aspectos epidemiológicos e clínicos da endometriose pélvica - uma série de casos. *Rev Assoc Med Bras.* 2010;56(4):467-71.
10. Abrão MS, Gonçalves MO, Dias JA Jr, Podgaec S, Chamie LP, Blasbalg R. Comparison between clinical examination, transvaginal sonography and magnetic resonance imaging for the diagnosis of deep endometriosis. *Hum Reprod.* 2007;22(12):3092-97.
11. Gonçalves MO, Podgaec S, Dias JA Jr, Gonzalez M, Abrão MS. Transvaginal ultrasonography with bowel preparation is able to predict the number of lesions and rectosigmoid layers affected in cases of deep endometriosis, defining surgical strategy. *Hum Reprod.* 2010;25(3):665-71.
12. Rossi P, Ribeiro RM, Baracat EC. *Manual de ginecologia de consultório.* São Paulo: Atheneu; 2007. p.115-9.
13. Parker MA, Sneddon AE, Arbon P. The menstrual disorder of teenagers (MDOT) study: determining typical menstrual patterns and menstrual disturbance in a large population based study of Australian teenagers. *BJOG.* 2009;117(2):185-92.
14. Campbell MA, McGrath PJ. Non-pharmacologic strategies used by adolescents for the management of menstrual discomfort. *Clin J Pain.* 1999;15(4):313-20.
15. Houston AM, Abraham A, Huang Z, D'Angelo LJ. Knowledge, attitudes, and consequences of menstrual health in urban adolescent females. *J Pediatr Adolesc Gynecol.* 2006;19(4):271-5.
16. Vicino M, Parazzini F, Cipriani S, Frontino G. Endometriosis in young women: the experience of GISE. *J Pediatr Adolesc Gynecol.* 2010;23(4):223-5.
17. Templeman C. Adolescent endometriosis. *Obst Gynecol Clin North Am.* 2009;36(1):177-85.
18. Treloar SA, Bell TA, Nagle CN, Purdie DM, Green AC. Early menstrual characteristics associated with subsequent diagnosis of endometriosis. *Am J Obstet Gynecol.* 2010;202(6):534.e1-6.
19. Chapron C, Lafay-Pillet MC, Monceau E, Borghese B, Ngô C, Souza C, et al. Questioning patients about their adolescent history can identify markers associated with deep infiltrating endometriosis. *Fertil Steril.* 2011;95(3):877-81.
20. Dmowski WP, Gebel HN, Braun DP. The role of cell-mediated immunity in pathogenesis of endometriosis. *Acta Obstet Gynecol Scand.* 1994;159(1):7-14.
21. Arruda MS, Petta CA, Abrão MS, Benetti-Pinto CL. Time elapsed from onset of symptoms to diagnosis of endometriosis in a cohort study of Brazilian women. *Hum Reprod.* 2003;18(4):756-9.
22. Roman JD. Adolescent endometriosis in the waikato region of New Zealand - a comparative cohort study with a mean follow-up time of 2.6 years. *Aust N Z J Obstet Gynecol.* 2010;50(2):179-83.
23. Bai SW, Cho HJ, Kim JY, Jeong KA, Kim SK, Cho DJ, et al. Endometriosis in an adolescent population: the severance hospital in Korean experience. *Yonsei Med J.* 2002;43(1):48-52.
24. Wright KN, Laufer MR. Endometrioma in adolescents. *Fertil Steril.* 2010;94(4):1529.e7-9.

# Space-time description of dengue outbreaks in Cruzeiro, São Paulo, in 2006 and 2011

RENATA MARZZANO DE CARVALHO<sup>1</sup>, LUIZ FERNANDO COSTA NASCIMENTO<sup>2\*</sup>

<sup>1</sup>Doctor of Health Sciences. Department of Mechanical Engineering, Faculty of Engineering of Guaratinguetá. São Paulo State University (Unesp), São José do Rio Preto, SP, Brazil.

<sup>2</sup>Doctor of Public Health. Department of Medicine. University of Taubaté, Taubaté, SP, Brazil

## SUMMARY

**Objective:** to identify patterns in the spatial and temporal distribution of cases of dengue fever occurring in the city of Cruzeiro, state of São Paulo (SP).

**Methods:** an ecological and exploratory study was undertaken using spatial analysis tools and data from dengue cases obtained on the SinanNet. The analysis was carried out by area, using the IBGE census sector as a unit. The months of March to June 2006 and 2011 were assessed, revealing progress of the disease. TerraView 3.3.1 was used to calculate the Global Moran's I, month to month, and the Kernel estimator.

**Results:** in the year 2006, 691 cases of dengue fever (rate of 864.2 cases/100,000 inhabitants) were georeferenced; and the Moran's I and p-values were significant in the months of April and May ( $I_M = 0.28$ ;  $p = 0.01$ ;  $I_M = 0.20$ ;  $p = 0.01$ ) with higher densities in the central, north, northeast and south regions. In the year 2011, 654 cases of dengue fever (rate of 886.8 cases/100,000 inhabitants) were georeferenced; and the Moran's I and p-values were significant in the months of April and May ( $I_M = 0.28$ ;  $p = 0.01$ ;  $I_M = 0.16$ ;  $p = 0.05$ ) with densities in the same regions as 2006. The Global Moran's I is a global measure of spatial autocorrelation, which indicates the degree of spatial association in the set of information from the product in relation to the average. The I varies between -1 and +1 and can be attributed to a level of significance (p-value). The positive value points to a positive or direct spatial autocorrelation.

**Conclusion:** we were able to identify patterns in the spatial and temporal distribution of dengue cases occurring in the city of Cruzeiro, SP, and locate the census sectors where the outbreak began and how it evolved.

**Keywords:** dengue, geographic information systems, epidemiological surveillance, ecological study, spatial distribution of the population.

Study conducted at the University of Taubaté, Taubaté, SP

Article received: 7/3/2013  
Accepted for publication: 2/3/2014

\*Correspondence:

Address: Rua Durval Rocha, 500  
Vila Paraíba  
Postal Code: 12515-710  
Guaratinguetá – SP  
Phone: +55 12 3125-1103  
Fax: +55 12 3621-8796  
luiz.nascimento@unitau.com.br

<http://dx.doi.org/10.1590/1806-9282.60.06.016>

Conflict of interest: none

## INTRODUCTION

In the 1980's, new cases of dengue were reported in Brazil<sup>1</sup> and in the state of São Paulo, and in 1986 dengue was defined as a disease requiring compulsory notification.<sup>2</sup> The Vale do Paraíba suffered a dengue outbreak in 2002, on the state's northern coast, municipality of São Sebastião, with 972 indigenous contaminations.<sup>3,4</sup>

A study conducted in the city of São José do Rio Preto between September 2001 and August 2006 using a spatial approach enabled the identification of areas at higher risk for the occurrence of dengue fever, concentrated in the north part of the city. The geocoding process was obtained through equalization of the addresses of dengue cases with the segment map supplied by the city hall.<sup>5</sup>

Georeferencing and spatial analysis techniques have been increasingly used to assess the distribution of vectors and diseases transmitted by them, contributing to improved surveillance and control activities. Its greatest use is to outline strategies dependent upon the different realities of which the city is composed. Thus, the use of these tools enables the identification of risk areas that deserve intensification and/or prioritization of control measures. Souza-Santos & Carvalho<sup>6</sup> demonstrated that the analysis of spatial data is an important tool in the surveillance and control not only of *Aedes aegypti*, but other insect vectors.

In the same manner, we can cite articles by Barbosa and Lourenço<sup>7</sup> which verified that the incorporation of

geoprocessing and spatial analysis techniques in the program, provided that these are used immediately after conducting the activities, can contribute to control actions, indicating the spatial clusters with greater incidence. Carvalho and Nascimento,<sup>8</sup> who conducted the first study in São Paulo's Vale do Paraíba, using geoprocessing techniques to study the spatial and temporal distribution of dengue fever, were able to identify a pattern of the outbreak occurring in the city of Cruzeiro in 2006.

This article has the objective of identifying patterns in the spatial and temporal distribution of dengue cases occurring in the city of Cruzeiro in the months of March, April, May and June 2006, compared with the same months in 2011. The two years chosen can be justified by the occurrence of outbreaks, and the months listed correspond to the period with the greatest incidence of cases.

## METHODS

The area under study refers to the city of Cruzeiro located at the far eastern end of the state of São Paulo, in the region known as Vale do Paraíba; latitude 22° 33' South and longitude 44° 60' West, at an altitude of 514 meters, occupying 331 km<sup>2</sup>, 36 km<sup>2</sup> of which constitutes urban area, and 295 km<sup>2</sup> rural area (Figure 1).<sup>9</sup>



**FIGURE 1** Location of the city of Cruzeiro with territorial boundaries and highlighting the Presidente Dutra Highway.<sup>10</sup>

The climate is tropical (hot and humid), with temperatures varying between 20 and 27°C. The hottest months are from November to April, and the coldest between May and October. Rain is most present between December and March, with January being the wettest month. The driest period is covered between the months of June and September.

The cases of dengue fever occurring in the city are notified to the Municipal Epidemiological Surveillance sector and confirmed by laboratory or clinical-epidemiological criteria in accordance with guidelines from the Ministry of Health.<sup>11</sup>

The ecological and exploratory study consisted in listing the cases of dengue fever reported and confirmed, identifying the address and the date of onset of the first symptoms, and distributing the data on the city map in accordance with the 96 census sectors for the year 2000 provided by the Brazilian Institute of Geography and Statistics (available at: [downloads.ibge.gov.br/downloads\\_geociencias.htm](http://downloads.ibge.gov.br/downloads_geociencias.htm)).

The following approach were used to verify the association between the incidence of dengue, and mapping of cases in the years 2006 and 2011 for the months of March, April, May and June; spatial statistical analyses were used to check for autocorrelation using the Local and Global Moran's I and the Kernel estimator.

To identify the presence of spatial autocorrelation, the Global Moran's I was used ( $I_M$ ), which analyzed if there were any sector clusters with high rates, and clusters with low rates. The  $I_M$  varies between -1 and +1 and may be attributed a significance level (p-value), considering the rates of each census sector in relation to the rates of neighboring sectors, and the average of this rate.

Once calculated, it is important to establish its statistical validity, estimating its significance. If this value corresponds to an extreme simulation of a distribution, it is a value with statistical significance. The closer to 1 (one), the greater the similarity between neighbors. The value 0 (zero) indicates that there is no correlation, and negative values indicate dissimilarity. The public domain application TerraView developed by the Image Processing Division (DPI) of the National Institute of Spatial Research was used (available at: [www.dpi.inpe.br/terraview/index.php](http://www.dpi.inpe.br/terraview/index.php)).

The Kernel estimator, as stated, evaluates the events using analysis units. Taking into account that the population data is grouped and the official minimum grouping unit is the census sector, when attributing the known population data to the centroid of the region, there is the possibility of estimating the intensity of this process (population) using a Kernel function. The darker areas (hot spots) correspond to the higher density of cases.

## RESULTS

691 cases of dengue fever were georeferenced in the year 2006 (rate of 864.2 cases/100,000 inhabitants). The first cases were identified in the central region, and the latter cases in the north, northeast and central region. In the month of March, 35 cases were registered, varying from 0 to 7 per census sector, while in April 358 cases were recorded, varying from 0 to 20, 271 cases in May, varying from 0 to 15, and 23 cases in June, varying from 0 to 3 cases per census sector. It was not possible to identify the address of four confirmed cases as this was not completed in the notification form.

Thematic maps with the distribution of cases (Figure 2), according to the months of the year in 2006, show that the first cases occurred in March, in the central and eastern region, on the banks of the Paraíba do Sul river and its effluent stream, called Córrego da Barrinha, also following the route of the railroad that cuts the central region of the city and highway linking Cruzeiro to Lavrinhas. In the month of April, cases appear in practically all census sectors, heading to the south, southeast, central region and northeast. In May, 76 (79%) census sectors had at least 1 case of dengue fever, with the highest number of cases in the central, south, southeast and east regions, following the course of the Paraíba do Sul river and Córrego da Barrinha stream. In June, only two sectors presented 3 cases, located in the north/northeast and central/south regions.

The Global Moran's I and respective p-values for March, April, May and June are shown in Table 1. It can be seen that the Global Moran's I was significant in the months of April and May, with a positive autocorrelation.

In 2011, 654 cases of dengue fever were georeferenced (rate of 886.8 cases/100,000 inhabitants). The first cases also occurred in March, in the north, northeast, central, south and southeast regions, with latter cases occurring in the north region. In the month of March, 70 cases were registered, varying from 0 to 14 per census sector, while in April, 292 cases were recorded, varying from 0 to 24, 279 cases in May, varying from 0 to 26, and 13 cases in June, varying from 0 to 2 cases per census sector. It was not possible to identify the address of 55 confirmed cases. The impossibility of geocoding these cases was due, above all, to the absence or insufficiency of data contained in the Sinan database and failure to complete the Notification Form.

**TABLE 1** Moran's I and p-values of the spatial distribution of dengue cases, Cruzeiro 2006 and 2011

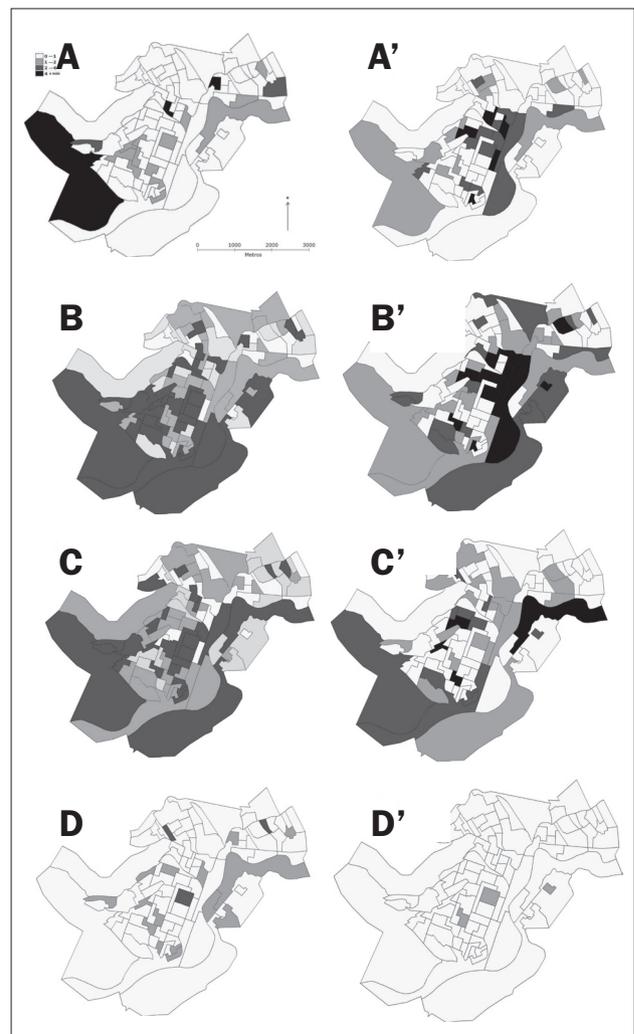
Months	Moran 2006	p-value	Moran 2011	p-value
March	0.08	0.09	0.23	0.01
April	0.28	0.01	0.16	0.05
May	0.20	0.01	0.05	0.24
June	0.01	0.46	0.08	0.09

The thematic maps with distribution of cases (Figure 2), according to the months from the first half of 2011, show that the first cases occurred in March, near to the banks of the Paraíba do Sul River, and the Cruzeiro-Passa Quatro and Cruzeiro-Lavrinhas highways. In the month of April, the cases are located in the Central, South, North, Northwest and Northeast regions, taking over the entire urban extent of the city. In May, 80 (83%) of the census

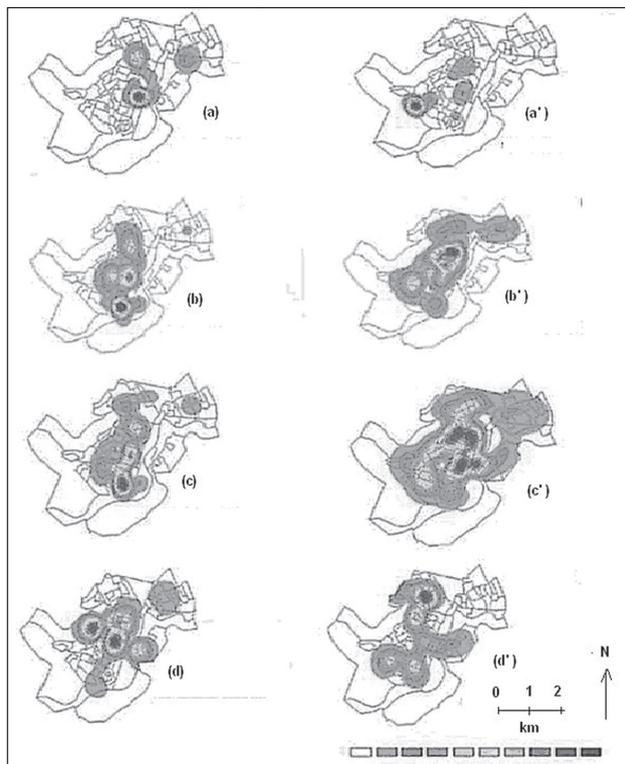
sectors had at least 1 case of dengue. In the month of June, only one sector presented more than one case of dengue fever, situated in the north region.

The Global Moran's I and respective p-values for March, April, May and June 2011 are shown in Table 1. Note that the Global Moran's I was significant in the months of March and April, with a positive autocorrelation and significance.

In March 2006, the highest density of cases occurred in the Central and North regions, as demonstrated by the Kernel estimator. In the months of April and May the highest density occurred in the North, Central and South regions. In June, the hot spot manifested in the Central, North, Northeast, Northwest and Southeast regions (Figure 3).



**FIGURE 2** Distribution of cases of dengue according to census sectors occurring in the months of March (a), April (b), May (c), and June (d) 2006, and in the months of March (a'), April (b'), May (c') and June (d') 2011, Cruzeiro, 2006 and 2011.



**FIGURE 3** Comparative thematic maps with the Kernel estimator of the distribution of cases of dengue notified and confirmed in the months of March (A), April (B), May (C), and June (D) 2006, and in the months of March (A'), April (B'), May (C') and June (D') 2011, Cruzeiro, 2006 and 2011.

The month of March 2011 presented the highest density in the west region. In April, the hot spot was concentrated near to the Central region, facing north. In May, the highest density occurred in the Central region, spreading a little to the East, North, Northeast and Nest. In the month of June, the hot spot moved to the north-south region (Figure 3).

## DISCUSSION

In this study, conducted at two different times using geoprocessing techniques, it was possible to identify a spatiotemporal pattern of dengue outbreaks occurring in Cruzeiro in 2006 and 2011.

The introduction of the dengue virus in Cruzeiro produced two large scale waves of outbreaks in the classic form of the disease. The risk of occurrence of these outbreaks was foreseeable owing to the intense circulation of the virus in the region, as well as the incidence of the disease in neighboring cities.

The infestation of the mosquito that transmits the dengue virus, population density and the lack of

group immunity against this agent can be identified as possible factors that led to the occurrence of the outbreaks, not only in the first wave, which occurred explosively, but also in the second, which had the highest incidence rate (864.2 and 886.8 cases per 100,000 inhabitants).

At both times, the outbreak began in one region, spreading to almost all regions of the urban area, following the banks of the Paraíba do Sul river, highways and railways cutting across the city and responsible for the large circulation of people, products and vehicles. This trend was also noted in a study conducted in the city of Tupã, state of São Paulo.<sup>7</sup>

In the month of April there was a sharp increase in the notification and confirmation of cases, possibly as a consequence of the presence of breeding sites in urban areas, susceptible population, high temperatures and heavy rainfall.

The quarterly coverage of the “House to House” program in the city was reached by disease control agents in almost the entire city. Even so, there were dengue fever outbreaks in the years 2006 and 2007.<sup>12</sup>

In the Cruzeiro outbreaks, an explanation for the occurrence of cases concentrated in different regions of the city could perhaps be due to the decrease in susceptibility in the region where a larger number of cases occurred, thereby shifting the concentration of the outbreak to another area.

In this study, fewer new cases were registered from the month of June onward, with milder temperatures and lower humidity levels recorded. This strongly suggests that the adverse climate conditions for proliferation of the vector have an important role in the transmission of the disease in the city.<sup>13</sup>

Three factors should be considered in the decrease in the number of cases in the outbreak: depletion of susceptible individuals; vector control interventions and unfavorable natural conditions, such as lower temperature and humidity, thereby reducing the vector population; and good sanitation conditions. Poorer areas that have good basic sanitation conditions may have the same levels of infestation as more affluent areas. On the other hand, areas with high coverage of water supply services and higher agglomeration of people in the same residence present higher concentrations of the vector.<sup>14</sup> In relation to susceptible individuals, it has been suggested that in 2006 only one type of virus circulated in the region, serotype DEN-3, and therefore people became immune after contact with the virus, a similar situation to that found in the city of Tupã.<sup>7</sup>

In 2011, the circulating serotype was DEN-1, which arose in the city for the first time and was found in the entire susceptible population, including those already sensitive to DEN-3, resulting in another outbreak.

The Global Moran's I applied to the cases of dengue fever occurring in the months of March, April and May of 2006 and 2011 presented positive values, indicating a positive spatial autocorrelation. The values tend to be similar to neighboring sectors, indicating that the occurrence of cases of dengue fever in the city are connected, with a strong relationship between sectors, which is even stronger between nearby neighboring sectors. We must call attention to the fact that the Global Moran's I presented a positive spatial correlation for the months of April and May 2006 and March and April 2011. Only the month of June 2011 presented a negative Global Moran's I, which leads us to believe that there are sectors with high indices of dengue cases surrounded by sectors with low indices, though this did not present statistical significance.

Comparing the maps with the Kernel estimators for the years 2006 and 2011 (Figure 3), it can be noted that the hot spot did not behave in the same manner during the two outbreaks. In 2006, the hot spot began in the central region and moved North-south and East-west, while in 2011, it began in the Center-west region and moved to the Central region and then finally the North-south and East-west regions.

In the months of April and May there was a sharp increase in the notification and confirmation of cases, possibly as a consequence of the presence of breeding sites in urban areas, susceptible population, high temperatures and heavy rainfall. The risk for dengue fever has also been identified in areas with the highest concentration of individuals, high economic diversity, strong population density, high household density, and high density of vacant lots (wasteland) in more remote districts of the central region.<sup>15</sup>

Dengue control measures have been based exclusively on chemical control of the vector to the detriment of important factors modulating the disease transmission dynamics, especially those related to social determinants, such as spatial occupation and living conditions. Therefore, with each introduction of a new serotype there is a new outbreak.<sup>15</sup>

The rapid growth of the urban population provides a major source of susceptible and infected individuals, concentrated in restricted areas. This fact, associated with poor sanitation, housing and cultural factors specific to large urban centers provides the ecological conditions favorable to the transmission of the dengue virus.<sup>16</sup>

Therefore, it is understandable that locations with a higher proportion of urban population may have higher incidences of dengue.<sup>17</sup> The spatial relationship between the transmission of dengue and other variables, such as the level of immunity of the population, effectiveness of the control measures, degree of infestation by the vector, the habits and attitudes of the population, etc, must be assessed. It is important to reiterate that the studies using spatial location approaches and use of GIS, although recent in the scope of health sciences, have gradually become indispensable for the analysis of disease determination.<sup>15</sup>

Despite epidemiological surveillance guidelines for dengue fever, when investigating the probable locations of infection considering residence, workplace and travel, in the investigation form standardized by the Ministry of Health, only data referring to the residential address are structured to allow precise localization of the case. Thus, analyses considering the patient's address as the risk factor exposure site assume that individuals are immobile and ignore any possibility of exposure at other places, for example, work or leisure environments.<sup>18</sup>

With the use of information originating from public health services only, it is possible for some of the cases not to be computed, in addition to the occurrence of cases whose clinical manifestation are discreet, leading to underreporting. Other sources of errors can be considered, such as disappearance of exam results, undetermined diagnoses and failure to locate addresses.

Difficulties encountered in the georeferencing of reported cases of the disease, due to address problems, prevented the location of cases in census sectors.<sup>1,5</sup> We cannot say where the focus of infection is exactly, since people can either have contracted the disease in their own homes, or at work, while in transit or anywhere else in the city. Even with the difficulties described above, the prompt location of cases or the aggregation of information in small areas, such as census sectors, can be quite enlightening.<sup>18</sup>

The evaluation of different exposures to the factors involved in transmission allows us to identify geographic areas with a higher risk of infection, and this is fundamental to the development of programs for the prevention and control of dengue fever.<sup>19</sup>

## CONCLUSION

It can be concluded that by using the geoprocessing technique, it was possible to map the address of people's homes affected by dengue outbreaks occurring in Cruzeiro in 2006 and 2011, as well as to show how the disease

spread through the city on these two occasions, bearing in mind the presence of two different viral serotypes and the susceptibilities of the individuals.

## RESUMO

Descrição espaço-temporal das epidemias de dengue em Cruzeiro, SP, em 2006 e 2011.

**Objetivo:** identificar padrões na distribuição espaço-temporal dos casos de dengue ocorridos no município de Cruzeiro, SP.

**Métodos:** foi desenvolvido um estudo ecológico e exploratório utilizando ferramentas de análise espacial e com dados de casos de dengue obtidos do SinanNet. Foi feita uma análise por área, tomando-se como unidade o setor censitário do Instituto Brasileiro de Geografia e Estatística (IBGE). Foram analisados os meses de março a junho de 2006 e 2011, que mostraram o avanço da doença. Utilizou-se o programa TerraView 3.3.1; foram calculados os índices de Moran global, mês a mês, e o estimador de Kernel.

**Resultados:** no ano de 2006, foram georreferenciados 691 casos de dengue (taxa de 864,2 casos/100 mil hab.); os índices de Moran e p-valores foram significativos nos meses de abril e maio ( $I_M = 0,28$ ,  $p=0,01$ ;  $I_M = 0,20$ ,  $p=0,01$ ) com densidades maiores nas regiões central, norte, nordeste e sul. Em 2011, foram geocodificados 654 casos (886,8 casos/100 mil hab.); os índices de Moran e p-valores foram significativos nos meses de março e abril ( $I_M = 0,28$ ,  $p=0,01$ ;  $I_M = 0,16$ ,  $p=0,05$ ) com densidades nas mesmas regiões de 2006. O índice de Moran global ( $I_M$ ) é uma medida global de autocorrelação espacial, que indica o grau de associação espacial no conjunto de informações a partir do produto em relação à média. O  $I_M$  varia entre -1 e +1, e a ele pode ser atribuído um nível de significância (p-valor). O valor positivo aponta para uma autocorrelação espacial positiva ou direta.

**Conclusão:** foi possível identificar padrões na distribuição espaço-temporal dos casos de dengue ocorridos no município de Cruzeiro, SP, e localizar os setores censitários onde a epidemia teve início e como evoluiu.

**Palavras-chave:** dengue; sistemas de informação geográfica; vigilância epidemiológica; estudo ecológico; distribuição espacial da população.

## REFERENCES

1. Pontes RJS, Ruffino-Netto A. Dengue em localidade urbana da região sudeste do Brasil: aspectos epidemiológicos. Rev Saúde Pública. 1994;28(3): 218-27.
2. Costa AIP. Identificação de unidades ambientais urbanas como condicionantes da ocorrência de *Aedes aegypti* (Diptera Culicidae) e de dengue na cidade de São José do Rio Preto, S.P., em 1995. [Dissertação]. São Paulo: Faculdade de Saúde Pública, Universidade de São Paulo; 1995.
3. Serpa LLN, Costa KVRM, Voltolini JC, Kakitani I. Variação sazonal de *Aedes aegypti* e *Aedes albopictus* no município de Potim, São Paulo. Rev Saúde Pública. 2006;40(6):1101-5.
4. São Paulo. (Estado). Secretaria da Saúde. Centro de Vigilância Epidemiológica. Dengue. São Paulo, 2011. [citado 1 fev 2011]. Disponível em: [http://www.cve.saude.sp.gov.br/hm/zoo/if\\_sem\\_den02.htm](http://www.cve.saude.sp.gov.br/hm/zoo/if_sem_den02.htm).
5. Galli B, Chiaravalloti Neto F. Modelo de risco tempo-espacial para identificação de áreas de risco para ocorrência de dengue. Rev Saúde Pública. 2008;42(4):656-63.
6. Souza-Santos R, Carvalho MS. Análise da distribuição espacial de larvas de *Aedes aegypti* na Ilha do Governador, Rio de Janeiro, Brasil. Cad Saúde Pública. 2000;16(1):31-42.
7. Barbosa GL, Lourenço RW. Análise da distribuição espaço-temporal de dengue e da infestação larvária no município de Tupã, Estado de São Paulo. Rev Soc Bras Med Trop. 2010;43(2):145-51.
8. Carvalho RM, Nascimento LFC. Spatial distribution of dengue in the city of Cruzeiro, São Paulo State, Brazil: use of geoprocessing tools. Rev Inst Med Trop São Paulo. 2012;54(5):261-6.
9. Cruzeiro. Prefeitura Municipal. Plano Municipal de Saúde 2010-2013. 49p.
10. Nascimento LFC, Batista GT, Dias NW, Catelani CS, Becker D, Rodrigues L. Análise espacial de neonatal no Vale do Paraíba, 1999 - 2001. Rev Saúde Pública. 2007;41(1):94-100.
11. Brasil. Departamento de Operações, Fundação Nacional de Saúde, Ministério da Saúde. Manual de dengue: vigilância epidemiológica e atenção ao doente. Brasília (DF): Departamento de Operações, Fundação Nacional de Saúde, Ministério da Saúde; 1995.
12. Chiaravalloti-Neto F, Costa AIP, Moura MSA, Soares MRD, Pereira FC, Battigaglia M, et al. Avaliação de ações municipais de combate a vetores da dengue na região de São José do Rio Preto, São Paulo, 1989 a 1995. Rev Soc Bras Med Trop. 1999;32(4):357-62.
13. Gubler DJ, Clark GG. Dengue/dengue hemorrhagic fever: the emergence of a global health problem. Emerg Infect Dis. 1995;2(1):55-7.
14. Mondini A, Chiaravalloti-Neto F. Variáveis socioeconômicas e a transmissão de dengue. Rev Saúde Pública. 2007;41(6): 923-30.
15. Flauzino RF, Santos RS, Oliveira RM. Dengue, geoprocessamento e indicadores socioeconômicos e ambientais: um estudo de revisão. Rev Panam Salud Publica. 2009;25(3):456-61.
16. Costa AIP, Natal D. Distribuição espacial da dengue e determinantes socioeconômicos em localidade urbana no Sudeste do Brasil. Rev Saúde Pública. 1998;32(3):232-6.
17. Teixeira MG, Costa MCN, Barreto ML, Mota E. Dengue and dengue hemorrhagic fever epidemics in Brazil: what research is needed based on trends, surveillance, and control experiences? Cad Saúde Pública. 2005;21(5):1307-15.
18. Almeida MCM, Assunção RM, Proietti FA, Caiaffa WT. Dinâmica intra-urbana das epidemias de dengue em Belo Horizonte, Minas Gerais, Brasil, 1996-2002. Cad Saúde Pública. 2008;24(10): 2385-95.
19. Almeida AS, Medronho RA, Valencia LIO. Análise espacial da dengue e o contexto socioeconômico no município do Rio de Janeiro, RJ. Rev Saúde Pública. 2009;43(4):666-73.

# Surgical treatment of clinically early-stage endometrial carcinoma without systematic lymphadenectomy

ARTUR LÍCIO ROCHA BEZERRA<sup>1</sup>, THALES PAULO BATISTA<sup>1,2\*</sup>, MÁRIO RINO MARTINS<sup>2</sup>, VANDRÉ CABRAL GOMES CARNEIRO<sup>1,2</sup>

<sup>1</sup>Faculdade Pernambucana de Saúde, Instituto de Medicina Integral Professor Fernando Figueira (FIS/IMIP), Recife, PE, Brazil

<sup>2</sup>Hospital do Câncer de Pernambuco, Recife, PE, Brazil

## SUMMARY

**Objective:** the main aim of this study was to describe the authors' experience with the surgical treatment of endometrial cancer without systematic lymphadenectomy.

**Methods:** a retrospective cohort study was carried out on a subset of patients suffering of clinically early-stage endometrial carcinoma who underwent hysterectomy and salpingo-oophorectomy without systematic (radical) lymph nodes dissection at our centers from June, 2002, to November, 2011. Descriptive statistics were explored as medians (interquartile range) or frequencies (percentages), as appropriated, and the Kaplan-Meier method was applied for survival estimation.

**Results:** eighty-three patients who underwent surgical treatment with no lymph node dissection (n = 20; 24.1%) or with only a sampling procedure (n=63; 75.98%) were selected for analysis. Among these patients, 27 (32.53%) underwent surgery alone and 56 (67.46%) received some adjuvant treatment. Postoperative complications occurred in five patients (6.02%). Over a median follow-up of 27.4 months ( $Q_{25} = 13.7 - Q_{75} = 46.5$ ), 15 (18.07%) patients suffered from relapses and 11 deaths occurred as result of disease recurrence. Cumulative 1, 2 and 3-year disease-free survivals were 97.32, 91.18 and 78.02%, respectively.

**Conclusion:** on a case-by-case basis, the surgical treatment of clinically early-stage endometrial carcinoma without systematic lymphadenectomy did not seem to decrease survival outcomes and presented low rates of surgical morbidity in our experience, but was also related to a high rate use of adjuvant therapy.

**Keywords:** endometrial neoplasms, survival analysis, lymph node dissection.

Article received: 12/3/13  
Accepted for publication: 3/19/14

\*Correspondence:  
Address: Av. Boa Viagem, 5212  
apto. 1515  
Postal Code: 51030-000  
Recife - PE  
Phone: (81) 8886-1203  
t.paulo@bol.com.br

<http://dx.doi.org/10.1590/1806-9282.60.06.017>

Conflict of interest: none

## INTRODUCTION

Endometrial cancer is the most frequent malignancy of the female genital tract in developed countries and stands as second most common in developing countries, accounting for approximately 319,498 newly diagnosed cases of cancer worldwide.<sup>1</sup> An estimated 5,900 new cases of endometrial cancer are expected to be diagnosed in 2014/2015 in Brazil, with a cumulative risk estimated in 5,79/100,000 women in this country.<sup>2</sup> Fortunately, since vaginal bleeding is commonly associated with the presence of disease, the majority of patients with endometrial cancer are diagnosed at an early-stage, resulting in over-

rall favorable prognosis with high cancer-specific survival rates.<sup>3,4</sup>

Although simple hysterectomy plus bilateral salpingo-oophorectomy remains a cornerstone for the management of endometrial cancer, whether patients suffering of this malignancy would benefit from systematic lymph node dissection is a matter of great debate.<sup>5-10</sup> The pelvic lymph nodes represent the most common site of extra-uterine disease in patients with clinical early-stage disease and thus, pelvic lymph node dissection is incorporated as an integral part of the standard surgical procedures recommen-

ded to treat early-stage endometrial carcinomas;<sup>3</sup> however more conservative surgical approaches without lymphadenectomy might reduce treatment-related morbidity in these settings.

Since evidences from two large randomized European trials reporting that lymphadenectomy had no effect on survival for women with apparent early-stage endometrial cancer,<sup>5,6</sup> this current study aimed to describe our experience with the management of early-stage endometrial carcinoma in a subset of our patients who underwent surgical treatment without systematic lymphadenectomy.

## METHODS

### Study design

A retrospective cohort study was carried out on patients who underwent surgical treatment for early-stage endometrial carcinoma at the Hospital de Cancer de Pernambuco (HCP) and at the Instituto de Medicina Integral (IMIP) from June, 2002, to November, 2011. Using our own database, we included for analysis patients who underwent hysterectomy and salpingo-oophorectomy without systematic lymph nodes dissection or with only a sampling dissection. We also limited our study to adults ( $\geq 18$  years) with complete data in their medical records and excluded patients with  $\geq 10$  nodes dissected in the sampling procedure or who had gross and unresectable extra-uterine disease at laparotomy, and those patients with non-epithelial/mixed histology (i.e.: carcinosarcomas). This study protocol was reviewed by our Ethics Research Committee (CAAE: 09894712.9.0000.5201).

### Variables, outcomes and analytical approach

The baseline characteristics were reviewed as some clinical/pathologic prognostic factors, such as age, histological type and grade, lymph node metastasis, depth of myometrial invasion, cervical involvement, evidence of extra-uterine disease, and pathological FIGO stage. We summarized the descriptive statistics as medians (interquartile range) or frequencies (percentages), as appropriated.

Disease-free survival was explored as a function of time after surgical treatment until the date of disease recurrence or the end of the study. Data on those patients with no recurrence at the time of analysis were 'censored' for survival estimation. Patients were usually followed up with clinical general/pelvic exams, lab tests and imaging exams every 3-6 months in the first two years, every 6-12

months up to 5-year, and annually thereafter. The Statistica Data Analysis Software System, Version 8.0 (Statsoft, Inc., Tulsa, OK, USA) was used to disease-free survival estimation applying the Kaplan–Meier method.

### Sample characteristics

A subset of 104 patients suffering from clinically early-stage endometrial carcinoma was treated surgically without systematic lymphadenectomy at our centers from June, 2002, to November, 2011. All of them had biopsy-proven endometrial carcinoma reported after pre-operative hysteroscopy ( $n = 67$ , 63.8%), uterine curettage ( $n = 29$ , 27.61%) or other procedures ( $n = 8$ , 7.61%). This sample included patients with endometrioid ( $n = 92$ , 88.46%), clear cell ( $n = 8$ , 7.69%) and other tumors ( $n = 4$ , 3.84%). Most of the patients did not smoke (85.84%) and lived at the metropolitan area from the capital city of Pernambuco State (68.67%). Their median age and number of pregnancies were 63 ( $Q_{25} = 56 - Q_{75} = 70$ ) and 4 ( $Q_{25} = 2 - Q_{75} = 5$ ), respectively. Amongst these eligible patients, 21 were excluded from our final analysis mainly due to nodal counts  $\geq 10$  nodes ( $n = 12$ ), gross extra-uterine disease ( $n = 2$ ), loss on follow-up ( $n = 6$ ) and carcinosarcoma histology ( $n = 1$ ).

The same surgical team performed all procedures using standard techniques (i.e.: hysterectomy and bilateral salpingo-oophorectomy) without systematic lymphadenectomy ( $n = 24$ , 23.07%) or with only a sampling procedure alone ( $n = 80$ , 76.92%). A single dose of cefazolin (2g) was applied as antibiotic prophylaxis and transurethral catheterization used for postoperative bladder drainage, being removed on the first postoperative day. Adjuvant radiotherapy usually included external pelvic radiotherapy (total dose ranging from 45 to 50 Gy; 180 cGy/day) and/or vaginal HDR brachytherapy fractioned in 4 daily doses (total dose of 15 Gy). This treatment was offered based on the pathological FIGO staging and evidence of high-intermediate risk factors. When applied, chemoradiation included concurrent cisplatin-based chemotherapy (40 mg/m<sup>2</sup>). Radiation, platinum or taxane-based chemotherapy, and best support care were offered after disease recurrence, as appropriated.

### Results

Our analysis involved 83 patients who underwent surgical treatment with only a sampling procedure ( $n = 63$ ; 75.98%) or no lymph node dissection ( $n = 20$ ; 24.1%). Five patients suffered from postoperative complications (6.02%), such as

wound infection (n = 1) and wound dehiscence (n = 4). Among all patients, 56 (67.46%) received some adjuvant treatment, including radiotherapy (n = 44, 53.01%), chemotherapy (n = 3, 3.61%) or chemoradiation (n = 9, 10.84%). The usage rate of adjuvant therapy was 61.9 and 85% for the sampling and no lymph node dissection groups, respectively. The post-operative pathological exam involved 270 pelvic lymph nodes dissected (median = 3;  $Q_{25} = 1 - Q_{75} = 5$ ) from patients who underwent sampling lymph node dissection. Most of them had no metastatic nodes (n = 58; 92.06%). Pelvic washing was collected from 75 (90.36%) patients and none had positive free-cancer cells. Baseline characteristics regarding some clinical and pathological prognostic factors are summarized in Table 1.

At a median follow-up of 27.4 months ( $Q_{25} = 13.7 - Q_{75} = 46.5$ ), 15 (18.07%) patients suffered from disease recurrence. These relapses were recorded as pelvic (n = 1), peritoneal/retro-peritoneal (n = 4) vaginal (n = 2), distant metastasis to lung (n = 1) and bone (n = 1), mixed pelvic and retroperitoneal (n = 1), and others/not reported (n = 5). Eleven deaths occurred as a result of disease recurrence. Three patients were alive with disease at the time of this analysis, receiving palliative chemotherapy (n = 2) or best support care (n = 1). One patient presented vaginal recurrence and received salvage radiotherapy. Overall, our cumulative 1, 2 and 3-year disease-free survivals were 97.32, 91.18 and 78.02%, respectively (Figure 1).

## DISCUSSION

Lymph node dissection is performed by skeletonizing vessels and removing lymph node bearing fat tissue, whereas a comprehensive systematic lymphadenectomy usually includes the pelvic and para-aortic nodes. Nevertheless, although lymph node dissection is important to nodal staging of patients with endometrial cancer, its therapeutic value for patients with early-stage disease has been questioned.<sup>5,6</sup> Thus, following the publication of two large randomized European trials suggesting no survival benefit for routine pelvic lymphadenectomy in endometrial cancer,<sup>5,6</sup> we considered important to present our experience with the surgical management of clinically early-stage endometrial without radical lymphadenectomy using our data from Northeast Brazil.

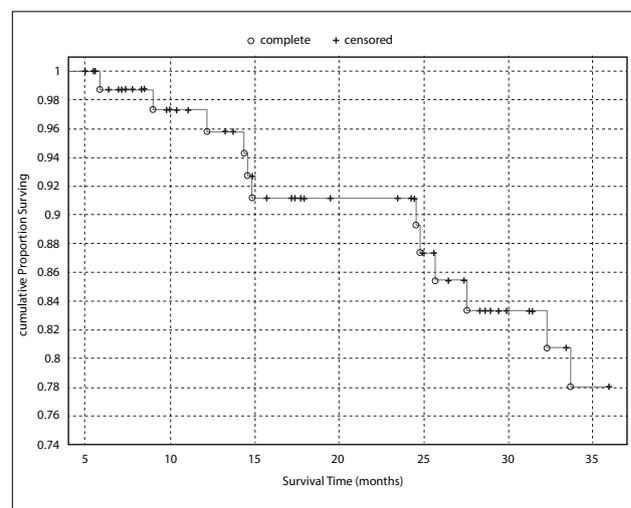
The choice of treatment without systematic lymphadenectomy was made on a case-by-case basis, taking into account clinical/pathologic features, surgical findings

**TABLE 1** Baseline characteristics

Prognostic factors	n (%)
<b>Age (years)</b>	
≤50	9 (10.8)
51 - 70	59 (71.1)
>70	15 (18.1)
<b>Histological type</b>	
Endometrioid	74 (89.1)
Others	9 (10.8)
<b>Histological grade</b>	
G1 <sup>1</sup>	55 (66.3)
G2/3 <sup>2</sup>	28 (33.7)
<b>Myometrial invasion</b>	
<50%	45 (54.3)
≥50%	38 (45.8)
<b>Cervical involvement</b>	
Present	24 (28.9)
Absent	59 (71.1)
<b>Lymph node metastasis</b>	
Present	5 (6)
Absent	78 (94)
<b>Extra-uterine disease</b>	
Present	5 (6)
Absent	78 (94)
<b>FIGO Stage (pathological)</b>	
I	56 (67.5)
II	18 (21.7)
III	9 (10.8)

<sup>1</sup>G1: well differentiated.

<sup>2</sup>G2: moderately differentiated; G3: poorly or undifferentiated.



**FIGURE 1** Kaplan-Meier disease-free survival. The correspondent 1, 2 and 3-year disease-free survival were 97.32, 91.18 and 78.02%, respectively.

and patient's characteristics. However, while a radical lymphadenectomy was not performed, the majority of our patients underwent some pelvic lymph node dissection as a sampling procedure in order to improve their nodal staging. In our experience, replacing the systematic lymphadenectomy with a sampling procedure, or no procedure at all, did not impair disease-free survival and also presented low rates of surgical morbidity. Interestingly, albeit similar rates of lymph node metastasis (if nodes harvested), most of our patients (67.46%) received some adjuvant treatment compared to the report by Benedetti Panici et al.<sup>6</sup> and the Astec trial<sup>5</sup> – about 33% in both European trials. Similar results were also previously described by Chan et al.,<sup>11</sup> who explored the Surveillance, Epidemiology and End Results (SEER) program conducted by the United States National Cancer Institute from 1988 to 2001, including a population database of 39,396 women with endometrioid *corpus* cancer who underwent hysterectomy and bilateral salpingo-oophorectomy with or without lymph node resection. According to these authors, women who did not undergo a systematic lymphadenectomy had a significantly increased use of adjuvant radiotherapy, with a usage rate of adjuvant radiotherapy two times higher (32.8% *vs.* 16.4%,  $p < 0.001$ ) – as we also observed comparing our sample to the report by Benedetti Panici et al.<sup>6</sup> and the Astec trial.<sup>5</sup> In our experience, the increased use of adjuvant treatments was probably related to the inaccuracies of our preoperative staging and the lack of some standardized prognostic information from the pathological exams (i.e.: lymphovascular invasion) in many of the first years of the period analyzed.

Even though the report by Benedetti Panici et al.<sup>6</sup> and the Astec trial<sup>5</sup> have both suggested that lymphadenectomy had no effect on survival for women with apparent early-stage endometrial cancer, some of their limitations are open to criticism as the inclusion of low-risk patients, and the lack of systematic para-aortic lymphadenectomy or lack of standardization of postoperative treatment.<sup>7,8</sup> In view of these limitations, Todo et al.<sup>9</sup> compared two cohorts of patients receiving either pelvic lymphadenectomy or combined pelvic and para-aortic lymphadenectomy for endometrial cancer. Applying multivariate analysis, these authors observed that pelvic and para-aortic lymphadenectomy reduced the risk of death compared with pelvic lymphadenectomy alone in patients with intermediate or high risk of recurrence (0.44, 0.30–0.64;  $p < 0.0001$ ), suggesting that combined pelvic and para-aor-

tic lymphadenectomy should be recommended as treatment for these patients, whereas the pelvic lymphadenectomy alone might be an insufficient surgical procedure for endometrial cancer in patients at risk of lymph node metastasis.<sup>9</sup> Accordingly, pelvic and para-aortic lymphadenectomy currently have been our preferred approach for patients with intermediate or high risk of recurrence, while conservative surgical approaches with no lymph node dissection or with a sampling dissection alone have been applied in order to reduce treatment-related morbidity only for low-risk patients and old or very obese patients. Unfortunately, laparoscopic approach to endometrial cancer<sup>12</sup> has not been easily available for our patients from the public health system at present.

Considering the available evidences supporting the surgical treatment of endometrial cancer without lymphadenectomy for low-risk patients,<sup>5,6,9,11</sup> the identification of patients at low-risk of recurrence before surgery is a cornerstone for the management of this malignancy.<sup>13–17</sup> Nevertheless, how accurately these patients may be identified preoperatively remains unclear.<sup>13</sup> Exploring this important issue, Kang et al.<sup>14</sup> developed a low-risk criteria for lymph node metastasis based on *serum* CA-125 levels and magnetic resonance imaging data (i.e.: depth of myometrial invasion, lymph node enlargement, and extension beyond uterine *corpus*) that can be obtained before surgery. According to these authors, this preoperative risk prediction model resulted in the accurate identification of a low-risk group for lymph node metastasis among patients with endometrial cancer (AUC = 0.89), with a false negative rate lower than 2%. However, in light of others findings, an accurate evaluation of tumor diameter<sup>15</sup> and lymphovascular space involvement,<sup>16,17</sup> both pre or intra-operatively, should also be incorporated as a tool to predict lymph node metastasis and to guide operations with or without radical lymphadenectomy. Whether a selective approach based on predictive models using *serum* CA-125 and magnetic resonance imaging as criteria or based on intra-operative assessment of pathological prognostic factors is more cost-effective than routine lymphadenectomy in patients with endometrial cancer, especially for developing countries, requires further and careful evaluation.<sup>18</sup>

Finally, it is important to highlight that most of the overall cancer recurrences occur early in the firsts 2-3 years after treatment, which justifies the use of disease-free survival as a primary end-point, especially because the 3-year disease-free survival is an excellent predictor of later overall survival. Further, more than a third of deaths are

usually not related to endometrial cancer itself,<sup>4,5</sup> probably due to a combination of increased life expectancy and an epidemic of obesity that predisposes to this disease,<sup>3</sup> which strongly suggest that disease-free survival can be used as a better primary end-point in such studies. In these settings, we expect to have detected almost all recurrences at the time of this analysis. Additionally, by using a data from Northeast Brazil, this descriptive study made it possible to estimate how reproducible conclusions from European trials can be when applied to heterogeneous populations in Brazil.

## CONCLUSION

On a case-by-case basis, the surgical treatment of clinically early-stage endometrial carcinoma without systematic lymphadenectomy did not seem to decrease survival outcomes and presented low rates of surgical morbidity in our experience. However, this conservative approach was also related to high rate use of adjuvant therapy.

## RESUMO

Tratamento cirúrgico do câncer de endométrio em estágio clínico precoce sem linfadenectomia radical.

**Objetivo:** descrever a experiência dos autores com o tratamento cirúrgico do câncer de endométrio em estágio precoce sem linfadenectomia radical.

**Métodos:** realizou-se estudo de coorte retrospectivo envolvendo um subgrupo de pacientes com câncer de endométrio em estágio clínico precoce tratadas com histerectomia e salpingo-ooforectomia sem linfadenectomia radical, em dois centros pernambucanos, de junho de 2002 a novembro de 2011. As variáveis foram descritas como mediana (intervalo interquartil) ou frequências (percentuais), utilizando-se o método de Kaplan-Meier para a estimativa das taxas de sobrevivência.

**Resultados:** oitenta e três pacientes submetidas a tratamento cirúrgico sem dissecação linfonodal (n = 20, 24,1%) ou com dissecação apenas por amostragem (n = 63; 75,98%) foram selecionadas para análise. Entre essas pacientes, 27 (32,53%) foram tratadas somente com cirurgia e 56 (67,46%) receberam tratamento adjuvante. Cinco pacientes apresentaram complicações pós-operatórias (6,02%). Durante o acompanhamento mediano de 27,4 meses (Q<sub>25</sub> = 13,7 - Q<sub>75</sub> = 46,5), 15 (18,07%) pacientes apresentaram recorrência, dentre as quais 11 faleceram em decorrência da recidiva neoplásica. Observou-se sobrevivência cumulativa proporcional livre de

doença em um, dois e três anos de 97,32, 91,18 e 78,02%, respectivamente.

**Conclusão:** em um contexto de indicação caso-a-caso, o tratamento cirúrgico do câncer de endométrio em estágio precoce sem linfadenectomia radical parece não ter prejudicado a sobrevivência e apresentou baixas taxas de morbidade cirúrgica em nossa experiência, mas também foi acompanhado de elevada utilização de terapia adjuvante.

**Palavras-chave:** neoplasias do endométrio, análise de sobrevivência, excisão de linfonodo.

## REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0: Cancer Incidence and Mortality Worldwide: IARC CancerBase N° 11 Lyon: International Agency for Research on Cancer; 2013. [cited 2014 mar 10]. Available from: [globocan.iarc.fr](http://globocan.iarc.fr).
2. Brazilian Ministry of Health. Estimation 2014: Cancer incidence in Brazil. Rio de Janeiro: National Cancer Institute (INCA); 2014. [cited 2014 mar 10]. Available from: <http://www.inca.gov.br/estimativa/2014/>.
3. Benedetti JL, Bender H, Jones H 3<sup>rd</sup>, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. *Int J Gynaecol Obstet.* 2000;70(2):209-62.
4. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Surgery and postoperative radiotherapy *versus* surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. *Post Operative Radiation Therapy in Endometrial Carcinoma.* *Lancet.* 2000;355(9213):1404-11.
5. ASTEC study group, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet.* 2009;373(9658):125-36.
6. Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, et al. Systematic pelvic lymphadenectomy *vs.* no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst.* 2008;100(23):1707-16.
7. Uccella S, Podratz KC, Aletti GD, Mariani A. Re: Systematic pelvic lymphadenectomy *vs.* no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J Natl Cancer Inst.* 2009;101(12):897-8; author reply 898-9.
8. Creasman WT, Mutch DE, Herzog TJ. ASTEC lymphadenectomy and radiation therapy studies: are conclusions valid? *Gynecol Oncol.* 2010;116(3):293-4.
9. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. *Lancet.* 2010;375(9721):1165-72.
10. Dowdy SC, Mariani A. Lymphadenectomy in endometrial cancer: when, not if. *Lancet.* 2010;375(9721):1138-40.
11. Chan JK, Wu H, Cheung MK, Shin JY, Osann K, Kapp DS. The outcomes of 27,063 women with unstaged endometrioid uterine cancer. *Gynecol Oncol.* 2007;106(2):282-8.
12. Barbosa CP, Moscovitz T, Martins NV, Souza AMB, Soubhia IT, Aldrighi APS. [Laparoscopic approach to endometrial cancer]. *Rev Bras Ginecol Obstet.* 1999;21(1):41-5.
13. Kang S, Lee JM, Lee JK, Kim JW, Cho CH, Kim SM, et al. How low is low enough? Evaluation of various risk-assessment models for lymph node metastasis in endometrial cancer: a Korean multicenter study. *J Gynecol Oncol.* 2012;23(4):251-6.
14. Kang S, Kang WD, Chung HH, Jeong DH, Seo SS, Lee JM, et al. Preoperative identification of a low-risk group for lymph node metastasis in endometrial cancer: a Korean gynecologic oncology group study. *J Clin Oncol.* 2012;30(12):1329-34.

15. Alhilli MM, Podratz KC, Dowdy SC, Bakkum-Gamez JN, Weaver AL, McGree ME, et al. Risk-scoring system for the individualized prediction of lymphatic dissemination in patients with endometrioid endometrial cancer. *Gynecol Oncol.* 2013;13(1):103-8.
16. Vaizoglu F, Yuce K, Salman MC, Basaran D, Calis P, Ozgul N, et al. Lymphovascular space involvement is the sole independent predictor of lymph node metastasis in clinical early stage endometrial cancer. *Arch Gynecol Obstet.* 2013;288(6):1391-7.
17. Zhang C, Wang C, Feng W. Clinicopathological risk factors for pelvic lymph node metastasis in clinical early-stage endometrioid endometrial adenocarcinoma. *Int J Gynecol Cancer.* 2012;22(8):1373-7.
18. Clements AE, Tierney BJ, Cohn DE, Straughn JM Jr. Is selective lymphadenectomy more cost-effective than routine lymphadenectomy in patients with endometrial cancer? *Gynecol Oncol.* 2013;128(2):166-70.

# Psychogenic non-epileptic seizures and psychoanalytical treatment: results

NIRALDO DE OLIVEIRA SANTOS<sup>1\*</sup>, GLÁUCIA ROSANA GUERRA BENUTE<sup>1</sup>, ALESSANDRA SANTIAGO<sup>1</sup>, PAULO EURÍPEDES MARCHIORI<sup>2</sup>, MARA CRISTINA SOUZA DE LUCIA<sup>1</sup>

<sup>1</sup>Psychology Division of the Central Institute at the University of São Paulo (USP) Medical School's Hospital das Clínicas, São Paulo, SP Brazil

<sup>2</sup>Neurology Department at the USP Medical School, São Paulo, SP Brazil

## SUMMARY

**Background:** the occurrence of psychogenic non-epileptic seizures (PNES) is estimated to be between 2 to 33 cases in every 100,000 inhabitants. The number of patients with PNES reaches 19% of those treated as epileptics. Patients with PNES are treated as if they had intractable epilepsy, with unsatisfactory results even after medication treatment is used to its maximum. The aim of this study is to present the effects of individual psychoanalytical treatment in patients with PNES, assessing its impact in the evolution of the clinical picture and its association with sex, time of disease, social, psychological and professional harm, as well as going through with treatment.

**Methods:** The case base was composed of 37 patients with PNES. The diagnosis was reached with video-EEG monitoring. Psychoanalytical treatment was carried out through 12 months of weekly sessions timed for around 50-minutes each, in a total of 48 individual sessions.

**Results:** This study found a high rate of success in the treatment of PNES patients. 29.7% (n=11) of patients had cessation or cure of symptoms and 51.4% (n=19) had a decrease in the number of episodes. There is an association between cessation or decrease in the number of episodes and sex ( $p<0.01$ ), religion ( $p<0.01$ ) and concluding treatment ( $p<0.01$ ).

**Conclusion:** Individual psychoanalytical treatment applied to patients with PNES is considered effective and can be an essential form of assistance for the reduction or cessation of episodes.

**Keywords:** psychogenic non-epileptic seizures, conversion disorder, psychoanalysis, treatment.

Study conducted at the Psychology Division of the Central Institute at the FMUSP Hospital das Clínicas, São Paulo, SP

Article received: 11/14/2013

Accepted for publication: 3/17/2014

\*Correspondence:

Address: Av. Dr. Enéas de Carvalho Aguiar, 155

Prédio dos Ambulatórios. Andar Térreo. São Paulo, SP

Postal Code: 05403-000

Phone: +55 11 2661-6459

niraldo@usp.br

niraldosp@uol.com.br

<http://dx.doi.org/10.1590/1806-9282.60.06.018>

Conflict of interest: none

## INTRODUCTION

Psychogenic symptoms are common in medicine. Conservative estimates consider that around 10% of patients in medical services have psychogenic symptoms. In the neurological clinic they represent 9% of patients admitted to hospital, and probably a higher percentage of patients seeking outpatient services. Symptoms such as paralysis, mutism, visual and sensory disorders, movement and balance problems, as well as pain represent a challenge in establishing a diagnosis and treatment. The exception is psychogenic non-epileptic seizures (PNES): the

diagnosis is clearly of psychogenic symptoms and treatment must be psychological.

Recognized as a public health problem,<sup>1</sup> PNES may be defined as episodes of changes in movements, sensations or experiences similar to epilepsy caused by psychological process not associated with cerebral electrical discharge.<sup>2</sup> Its prevalence in the general population is difficult to calculate given that it is underreported and an accurate diagnosis is difficult to perform. Thus, there is great variation in the presentation of these rates, between 2 and

33 per 100,000 inhabitants. PNES rates correspond to approximately 5% of patients with an epilepsy diagnosis.<sup>3</sup>

It is estimated that between 10 and 58% of patients seeking care at epilepsy centers in tertiary hospitals do not present epilepsy.<sup>3</sup> One in every 4 or 5 patients referred for video-EEG monitoring diagnosed with intractable epilepsy will not have this diagnosis confirmed, and the majority will present PNES.<sup>4</sup>

The difficulty in the diagnosis results from the similarity with epileptic seizures, the diversity in the manifestation of these seizures, and the changes found in the electroencephalogram.<sup>5,6</sup> Patients with PNES before the correct diagnosis - which can take decades - are treated as having refractory epilepsy, using maximum doses of anticonvulsant drugs with risk of iatrogenic complications; and will pass through 6 emergency units on average in the six months prior to the correct diagnosis<sup>7</sup> as well as admission to ICUs, resulting in redundancy in diagnostic imaging and laboratory tests. These factors result in significant economic losses for the patient, the family and health services. As a result, the quality of life of patients with PNES and the unemployment index (22-23%) are worse than those encountered for patients with epilepsy.<sup>8,9</sup> These conditions experienced over the years of treatment and without therapeutic results lead the patient to seek out government programs for financial assistance, such as disability benefit and even disability retirement. Thus, the economic impact of PNES is immeasurable. It derives from direct costs of diagnostic assessment, interventions, laboratory tests, ineffective use of anticonvulsants and hospital admissions, and indirect costs related to loss of employment by the patient and family/caregivers.<sup>10</sup>

The "gold standard" diagnosis should be performed with simultaneous recording of clinical manifestations (video) and electroencephalogram,<sup>11</sup> and is indicated for all patients with frequent seizures despite the use of prescription drugs.<sup>12</sup> In possession of the results of the recording, together with a good neurological and psychiatric history, the diagnostic uncertainty (epilepsy *versus* PNES) is usually answered, with the PNES diagnosis holding a high level of reliability.<sup>13</sup> However, video-EEG monitoring is only available in large healthcare centers.<sup>14,15</sup>

Various treatments for PNES patients have been reported in the literature: biofeedback,<sup>16</sup> hypnosis,<sup>17</sup> acupuncture,<sup>18</sup> transcranial magnetic stimulation<sup>19</sup> and psychotherapy.<sup>2,5,20,21,22,23,24</sup> Nevertheless, the amount of studies encountered with a focus on psychological treatment is limited.<sup>20</sup>

A study<sup>25</sup> conducted with the purpose of verifying the method considered most effective in the treatment of PNES by health professionals showed that 91% of these professionals would prefer psychotherapy. Prigatano et al.<sup>21</sup> assessed the effectiveness of a psychotherapeutic intervention and verified the importance of individual therapeutic work.

Psychoanalyst Kalogjera-Sackellares,<sup>26</sup> defines post-traumatic PNES as a response to a traumatic experience or experiences, which the patient was unable to elaborate owing to the inability of their psychological resources. In developmental PNES, seizures are not considered as a result of a single trauma or even a chronically traumatic life, but rather a difficulty in dealing with large and complex vital tasks for psychosocial development, such as the passage from adolescence to life as an adult.

Specifically in cases of patients who have conversive symptoms, the search for the unconscious factors related to the symptom is the route used to allow the conflict to be made conscious and find another route to its symbolic manifestation, mainly through words, making violent release through aggressiveness to the body unnecessary.

This study is justified given that patients with PNES are treated as having refractory epilepsy, reaching the maximum level of drug treatment (use of anticonvulsants and psychotropic drugs) without obtaining satisfactory results in the reduction of seizures and improving quality of life, resulting in burdensome hospital costs and causing immeasurable losses in the personal, family and social life of such patients.

Therefore, the objective of this study is to report on the effects of individual psychoanalytical treatment in PNES patients in order to evaluate the clinical development of PNES and verify its association with gender, seizure time, social, emotional and professional losses, as well as the end of treatment. The reduction or cessation of convulsive seizures was used as the criteria for effectiveness in the presentation of quantitative data from the results obtained.

## METHODS

This is a prospective longitudinal study, with design and Informed Consent form approved by the institution's research ethics committee (CapPesq n° 383/04).

### Patients

The selection of cases consisted of all patients referred for outpatient psychoanalytic treatment, consecutively,

in the period from 2004 to 2007, by the Epilepsy Group at the tertiary university hospital.

All patients referred had a PNES diagnosis conducted via video-EEG monitoring. The professionals conducting the video-EEG communicated the diagnosis to the patient and recommended the cessation of anticonvulsants, except in cases where the patients had concomitant epilepsy and PNES. The patients included reported that they were not undertaking concomitant psychiatric treatment. No patient presented structural alterations in the neuroimaging exam. The patients diagnosed with concomitant epilepsy and PNES had idiopathic epilepsy syndromes. All of the patients participating in the study, including those who were diagnosed with PNES through EEG-video monitoring, had been treated as though they had refractory epilepsy prior to the exam.

11 of the 48 patients referred (2 males and 9 females) did not accept the PNES diagnosis and psychoanalytical treatment and were excluded from the study. Therefore, the data presented relates to 37 patients, with 27% (n=10) having a diagnosis of concomitant epilepsy and CNEP.

Table 1 shows the demographic characteristics of the 37 patients that participated in the study.

**TABLE 1** Demographic data of the 37 patients included in the study, collected before the start of treatment

Number of patients	n=37
<b>Age, years</b>	
Median (Q1 - Q3)	32 (22 - 43)
Minimum - Maximum	11-59
<b>Years of seizures</b>	
Median (Q1 - Q3)	8 (2 - 17)
Minimum - Maximum	0.4 - 45
<b>Marital status</b>	
Married	15 (40.6%)
Single/separated	22 (59.4%)
<b>Religion</b>	
Buddhist	2 (5.4%)
Catholic	13 (35.2%)
Spiritists	8 (21.6%)
Evangelical	7 (18.9%)
Not informed	7 (18.9%)

The following instruments were used to analyze the material present in the psychoanalysis sessions:

- a. Initial interview script, aiming to collect information such as: age; marital status; education; occupation; religion; personal income and family income; seizure frequency; time of onset of seizures; what the patient thought caused the seizures; losses resulting from seizures; reaction to referral for psychoanalytic treatment; and expectations regarding treatment.
- b. Script for elaboration of the psychoanalytic diagnosis: ways the patient reacts in relation to situations that cause anxiety; defensive strategies; symbolic resources; the symptom as "compromise formation" between conscious and unconscious forces.
- c. Diagnostic interview sessions: between 3 and 4 preliminary interviews were conducted to elaborate the psychoanalytic diagnosis.
- d. Psychoanalytic treatment sessions: individual clinical care consultations with a weekly frequency, lasting about 50 minutes, face to face, and with a total duration of 48 sessions over 12 months.
- e. Finalization interview script: applied at the end of treatment with the objective of investigating: ease and difficulty in following treatment; what changed after treatment; frequency and intensity of seizures compared to the start of treatment.

The clinical data from the services were collected according to the psychoanalytical framework, through clinical reports on sessions. The sessions were not recorded so as not to interfere in the result. The transcription of the sessions was performed from memory. This data was systematically discussed at clinical meetings with the professional responsible for the project, with the objective of systematizing the organization of the material collected and enabling greater accuracy in the identification and classification of the characteristics of the participants, as well as achievement of the proposed objectives.

#### Statistical analysis

Clinical cases were taken on with their particularities and treated individually. However, for quantitative presentation of the results, indicators were created for pre- and post-psychoanalytic treatment evaluation.

The results encountered are presented in the form of means, medians, standard deviations, absolute and relative frequencies. For the 2x2 tables, the Fisher exact test and the nonparametric Mann-Whitney test were used. To compare results in more than two groups, we used the nonparametric Kruskal-Wallis test. A significance level of 0.05 (al-

pha = 5%) was adopted. As such, descriptive levels (p) lower than this value were considered as significant (p<0.05).

## RESULTS

This study found a high rate of success in the treatment of patients with PNES: 29.7% (n=11) cessation/cure of symptoms and 51.4% (n=19) reduction in convulsive seizures.

Patients (n = 11, 100%) who refused psychoanalytic treatment attended the scheduling service in person and said

they did not believe in the PNES diagnosis and would seek other medical services to continue treatment for "epilepsy".

When associating the results obtained after treatment, there was statistical significance between the variables: end of treatment (p<0.01); gender (p<0.01) and religion (p<0.01). Table 2 presents the results.

There was no statistical significance (p = 0.06) in the association between end of treatment and seizure time, according to the data presented in Table 3.

**TABLE 2** Data distribution according to the association between development of PNES and end of treatment, gender, diagnosis, social losses, emotional losses, professional losses, welfare assistance, religion and age of the 37 patients included in the study

Variables analyzed	Evolution of the PNES clinical profile				P
	Stopped n=11	Reduced n=19	Not reduced n=7	Total n=37	
<b>End of treatment</b>					
No	2 (10.5%)	10 (52.6%)	7(36.8%)	19 (100%)	<0,01 <sup>#</sup>
Yes	9 (50%)	9 (50%)	0	18 (100%)	
<b>Gender</b>					
Female	5 (17.2%)	18 (62.1%)	6 (20.7%)	29 (100%)	<0.01 <sup>#</sup>
Male	6 (75%)	1 (12.5%)	1 (12.5%)	8 (100%)	
<b>Diagnosis</b>					>0.99 <sup>#</sup>
PNES	14 (51.9%)	8 (29.6%)	5 (18.5%)	27 (100%)	
PNES + epilepsy	3 (30.0%)	5 (50.0%)	2 (20.0%)	10 (100%)	
<b>Social losses</b>					0.41 <sup>#</sup>
No	3 (20.0%)	8 (53.3%)	4 (26.7%)	15 (100%)	
Yes	8 (36.4%)	11 (50.0%)	3 (13.6%)	22 (100%)	
<b>Emotional losses</b>					0.45 <sup>#</sup>
No	7 (41.2%)	7 (41.2%)	3 (17.6%)	17 (100%)	
Yes	4 (20.0%)	12 (60.0%)	4 (20.0%)	20 (100%)	
<b>Professional losses</b>					0.29 <sup>#</sup>
No	5 (22.7%)	11 (50.0%)	6 (27.3%)	22 (100%)	
Yes	6 (20.0%)	8 (53.3%)	1 (6.7%)	15 (100%)	
<b>Receiving welfare assistance (INSS*)</b>					0.90 <sup>#</sup>
No	7 (29.2%)	13 (54.2%)	4 (16.7%)	24 (100%)	
Yes	4 (30.8%)	6 (46.2%)	3 (23.1%)	13 (100%)	
<b>Religion</b>					<0.01 <sup>#</sup>
Informed	11 (36.7%)	16 (53.3%)	3 (10.0%)	30 (100%)	
Not informed	-	3 (42.9%)	4 (57.1%)	7 (100%)	
<b>Age (years)</b>					0.93 <sup>##</sup>
Median (Q1-Q3)	32 (14 - 47)	28 (21-43)	36 (24-43)		
Min - Max	Nov/59	13 - 58	18-45		

#Generalization of the Fisher Exact Test

## Kruskal-Wallis Test

\*Brazilian Social Security System

**TABLE 3** Distribution of the 37 patients according to seizure time and end of treatment

Seizure time	End of treatment			p
	No	Yes	Total	
< 2 years	4 (50%)	4 (50%)	8 (100%)	0.06#
2 to 15 years	12 (70.6%)	5 (29.4%)	17 (100%)	
> 15 years	3 (25%)	9 (75%)	12 (100%)	
Total	19 (51.4%)	18 (48.6%)	37 (100%)	

\*Generalization of the Fisher Exact Test

## DISCUSSION

The high rates of successful treatment of patients with PNES through the psychoanalytic method – leading to recovery from symptoms in 29.7% (n=11) and a decrease in 51.4% (n=19) – initially lead us to reflect on the association between PNES, ‘major conversions’ and psychoanalysis. Yes, PNES may be recognized as hysteria or a conversive syndrome; however, the common sense connotation of the term hysteria has become pejorative, with a change observed in the international diagnostic classification manuals.

Decreased sexual repression, detected as responsible for the onset of hysteria, led to a belief in the eradication of this condition. However, according to Hermann,<sup>27</sup> psychopathological items rarely disappear without a trace. The pathoplasty and frequency may change, but the symptoms do not disappear.<sup>27</sup> Thus, this does not mean proving the effectiveness of the psychoanalytic method, demonstrated by Freud within the academic scope more than a century ago. This means presenting the results obtained by means of the psychoanalytic method, consolidating that effective treatment begins with accurate diagnosis by the neurologist and correct referral to psychological treatment.

The analysis of the relationship among conversive crisis *versus* environmental function *versus* the function of the physician serves as the basis for analyzing the difficulties and resistances to psychoanalytic treatment presented by 22.9% (n=9) of the patients. These resistances need to be understood within the context to which these subjects are exposed: years of diagnosis of “epilepsy”, drug treatment and intense seizures, and then a sudden diagnosis of PNES. Thus, that which appeared to be the responsibility of the neurologist, i.e. the cure, becomes the patient’s responsibility, and is subjective, psychologi-

cal. Is it possible to believe that after years of drug treatment and suffering the cure of the symptom could be the responsibility of the individual suffering from it? How can you tell the family, which also suffers, that this is not an organic dysfunction, but the production of a psychological symptom? Is the subject now lying about, faking or inventing convulsions? Moreover, could they be “crazy”? Embarrassed and failing to understand what may be happening, the patient denies the offer of treatment, not necessarily because it is psychoanalytic or psychological, but for being included in a diffuse field, which seems inconsistent with so much suffering. Thus, diagnosis alone is not sufficient. It is also necessary to authorize the search for adequate treatment.

Therefore, the therapeutic connection between neurologist and patient contributes to the patient accepting the PNES diagnosis or not<sup>28</sup> and understanding that the possibility of help, or indeed a cure, results from the assistance of another professional. At this time, the understanding of what psychogenic means and the implied consequences of the reaction of family members, the differentiation between what is unconscious and what is voluntary, may lead the individual to accept the diagnosis and undergo treatment with the psychoanalyst. When the diagnosis is not well received, an iatrogenic process begins and the search for other services that mistakenly reproduce the epilepsy diagnosis. Howell et al.<sup>29</sup> indicated that 50% of patients with a diagnosis of epilepsy admitted to the emergency service in England not having the disease. These patients have a high risk of iatrogenic comorbidity given that when presenting seizures and being taken to the emergency services, despite having PNES, they will again be mistakenly diagnosed as having epilepsy.<sup>4</sup>

Thus, the first step in PNES is to facilitate the understanding and acceptance of the patient upon diagnosis.<sup>4</sup> Therefore, the diagnosis of PNES should be given in an environment of trust, recognizing the seizures and the suffering caused by them, with correct referrals while providing support and long-term outpatient monitoring, and also avoiding the resumption of the use of anti-epileptic drugs that may be inadvertently reintroduced in emergency rooms.

Scientific studies have shown that the latency period between the manifestation of symptoms and correct diagnosis of PNES is 7.2 years.<sup>30</sup> Furthermore,  $\frac{3}{4}$  of patients with PNES are treated with anticonvulsants.<sup>2</sup> This study was conducted in a tertiary hospital and, possibly, the

fact that the average time for correct diagnosis was lower in this case compared to that found in the literature relates to care being delivered in a center of excellence.

Among the studies described about the efficiency of psychological treatment, Prigatano et al.<sup>21</sup> reported a 66.6% (n=5) reduction in seizures for patients concluding the psychological treatment (n=9) and indicated an increase in seizure frequency of 11.1% (n=1). In a study<sup>31</sup> conducted for an average of 12 weeks and which included 16 patients, the authors found cessation of seizures in 9 (56.2%) patients. King et al.<sup>32</sup> treated 14 patients and reported effectiveness in the cessation and improvement of seizures at 79%. The educational approach has also been indicated<sup>33</sup> as a form of support and assistance for patients, aimed at accepting the psychological nature of their symptoms and the need for psychological monitoring.

When comparing the results of the studies described above with the results presented in this work (81.1% reduction or cure of the symptom, with 29.7% cured and 51.4% with a decrease in seizures), the effectiveness of treatment becomes apparent. Thus, despite the costs involved in psychoanalytic/psychological treatments being considered high, in the treatment of patients with PNES this becomes minimal considering years of misdiagnosis, assistance at neurological clinics, visits to the emergency room and the high cost of the medication used. Furthermore, there are the social, professional and personal costs resulting from the symptom. In this light, the costs of psychoanalytic treatment and the time of 48 sessions are negligible, objective and assertive.

The patients in this sample were considered as having a poor prognosis given the chronicity of the disease, were placed on welfare (INSS) and had a concomitant diagnosis of PNES and epilepsy. Despite this, the results obtained with the psychoanalytic method in relation to decrease and cessation of seizures were higher than those presented in the scientific literature,<sup>21,34</sup> given that these studies only presented a decline in the frequency of seizures and not cessation of symptoms.

The patients that concluded psychoanalytic treatment (considered as 48 sessions here) obtained a better evolution of PNES symptoms. The highest rates of treatment effectiveness can be observed in longer treatments, a product of the encounter between individuals who suffer and need to talk about themselves with a professional trained to assist them in the task of finding other means for the manifestation of their subjectivity and to

elucidate the unconscious conflict.<sup>35</sup> Schmutz<sup>35</sup> highlights that, when analyzing the fact that psychoanalytic treatment does not prove effective for all patients, one should take into account that the abandonment of the treatment can be interpreted as a choice, conscious or unconscious, for maintaining the condition of invalid, due to the secondary gains present in this condition.

Upon analyzing the data that the cessation of seizures was more common in males, whereas in females there was a greater reduction in seizures, we may question whether this result can be attributed to a greater difficulty in women of completely abandoning the PNES. If so, we would be facing a condition where the difficulty in losing the identity of "invalid" or "epileptic" would imply an unconscious satisfaction whose repetition points to the paradox present in the dissociative crisis itself - the moment of disconnection, beyond the disease, as well as the unconscious search for an intra-psychic comfort zone. The cathartic effect of the seizure is in itself an attempt at a "cure", so it can be difficult to give up in some cases.

With respect to religion, it can be imagined that this factor allows subjects some form of dialectic response to the symptom, since it is possible to establish a symbolic relationship between the sufferer, and their belief that something may modify their condition beyond the purely organic interventions. When there is a firm belief in the organic nature of the seizures, inviting the subjects to question their involvement in the formation of symptoms during analysis seems to be a much harder task. In this case, the degree of acceptance of the diagnosis and proposed treatment may be factors that influence the results of the intervention. Starting psychoanalytic treatment somewhat implies taking a share of responsibility in the condition presented, as it invites the patient to talk about themselves and to be encouraged to build hypotheses and undertake investigative work regarding the symptomatic manifestations, making them take responsibility for their part in the formation of symptoms.

## CONCLUSION

This study showed the effectiveness of individual psychoanalytic treatment conducted with patients with PNES and may be considered an essential form of care for a decrease or cessation of seizures.

The constant connection between subjectivity and organism, as shown and proven in individuals diagnosed with PNES, calls health professionals to reflect on the pre-

sence of the unconscious in the medical setting, making it clear that behind or beyond technology, subjectivity manifests itself and asks to be listened to and to be treated.

## RESUMO

Crises não epilépticas psicogênicas e tratamento psicanalítico: resultados.

**Introdução:** estima-se que o número de casos de pacientes com crises não epilépticas psicogênicas (CNEP) seja de 2 a 33 por 100 mil habitantes. O índice de CNEP corresponde ainda a, aproximadamente, 19% dos pacientes tratados como epilépticos. Os pacientes com CNEP são tratados como portadores de epilepsia refratária, chegando ao limite máximo do tratamento medicamentoso e sem a obtenção de resultados satisfatórios.

**Objetivo:** relatar os efeitos do tratamento psicanalítico individual em pacientes com CNEP de forma a avaliar a evolução do quadro clínico de CNEP e verificar sua associação com gênero, tempo de crise, prejuízos sociais, afetivos e profissionais, bem como término do tratamento.

**Métodos:** a casuística foi composta por 37 pacientes com diagnóstico de CNEP feito por meio da monitoração por vídeo-EEG. Foram realizadas sessões de tratamento psicanalítico: atendimento clínico individual com frequência semanal, com duração aproximada de 50 minutos e duração total de 48 sessões em 12 meses.

**Resultados:** este estudo constatou elevado índice de sucesso no tratamento dos pacientes com CNEP: 29,7% (n = 11) de cessação/cura dos sintomas e 51,4% (n = 19) de redução das crises convulsivas. Foi constatada associação entre cessar ou reduzir as crises e gênero (p<0,01), religião (p<0,01) e término do tratamento (p<0,01).

**Conclusão:** este estudo apontou eficácia do tratamento psicanalítico individual realizado com pacientes com CNEP, podendo ser considerada uma forma de assistência essencial para que haja decréscimo ou cessação das crises.

**Palavras-chave:** crise não epiléptica psicogênica; transtorno conversivo; psicanálise; tratamento.

## REFERENCES

1. Benbadis SR, Hauser WA. An estimate of the prevalence of psychological non-epileptic seizures. *Seizures*. 2000;9(4):280-1.
2. Reuber M, Elger CE. Psychogenic nonepileptic seizures: review and update. *Epilepsy Behav*. 2003;4(3):205-16.
3. Dworetzky BA, Mortati KA, Rossetti AO, Vaccaro B, Nelson A, Bromfield EB. Clinical characteristics of psychogenic nonepileptic seizure status in the long-term monitoring unit. *Epilepsy Behav*. 2006;9(2):335-8.
4. Kanner AM. Is the neurologist's role over once the diagnosis of psychogenic nonepileptic seizures is made? No! [editorial]. *Epilepsy Behav*. 2008;12(1):1-2.
5. Iriarte J, Parra J, Urrestarazu E, Kuyk J. Controversies in the diagnosis and management of psychogenic pseudoepilepsies. *Epilepsy Behav*. 2003;4:354-9.
6. De Timary P, Fouchet P, Sylin M, Indriets JP, De Barys T, Lefebvre A, et al. Non-epileptic seizures: delayed diagnosis in patients presenting with electroencephalographic (EEG) or clinical signs of epileptic seizures. *Seizure*. 2002;11(3):193-7.
7. Jirsch JD, Ahmed SN, Maximova K, Gross DW. Recognition of psychogenic nonepileptic seizures diminishes acute care utilization. *Epilepsy Behav*. 2011;22(2):304-7.
8. Szaflarski JP, Hughes C, Szaflarski M, Ficker DM, Cahil WT, Li M, et al. Quality of life in psychogenic nonepileptic seizures. *Epilepsia*. 2003;44(2):236-42.
9. O'Sullivan SS, Spillane JE, McMahon EM, Sweeney BJ, Galvin RJ, McNamara B, et al. Clinical characteristics and outcome of patients diagnosed with psychogenic nonepileptic seizures: a 5-year review. *Epilepsy Behav*. 2007;11(1):77-84.
10. Gates JR. Epidemiology and classification of non-epileptic events. In: Gates JR, Rowan AJ, editors. *Non-epileptic seizures*. 2<sup>nd</sup> ed. Boston: Butterworth-Heinemann; 2000. p.3-14.
11. LaFrance WC Jr, Devinsky O. Treatment of non-epileptic seizures. *Epilepsy Behav*. 2002;3:S19-S23.
12. Benbadis SR, Tatum WO, Vale FL. When drugs don't work: an algorithmic approach to medically intractable epilepsy. *Neurology*. 2000;55(12):1780-4.
13. Benbadis SR, LaFrance WC Jr. Clinical features and the role of video-EEG monitoring. In: Shachter SC, LaFrance WC Jr, editors. *Gates and Rowan's nonepileptic seizures*. 3<sup>rd</sup> ed. Published by Cambridge University Press; 2010.
14. Castro LHM. Epilepsia: atualização no diagnóstico e tratamento. In: Miotto EC, Lucia MCS, Scaff M, organizadores. *Neuropsicologia e as interfaces com a neurociência*. São Paulo: Casa do Psicólogo; 2007.
15. Scévola L, Teitelbaum J, Oddo S, Centurión E, Loidl CF, Kochen S, et al. Psychiatric disorders in patients with psychogenic nonepileptic seizures and drug-resistant epilepsy: a study of an Argentine population. *Epilepsy Behav*. 2013;29(1):155-60.
16. Levy JK, Thomas M. Biofeedback therapy for psychogenic movement disorders. *Psychogenic Movement Disorders* 2006;343 (abstract).
17. Moene FC, Spinhoven P, Hoogduin KA, Van Dyck R. A randomized controlled clinical trial of a hypnosis-based treatment for patients with conversion disorder, motor type. *Int J Clin Exp Hypn*. 2003;51(1):29-50.
18. Van Nuenen BF, Wohlgemuth M, Wong Chung RE, Abdo WF, Bloem BR. Acupuncture for psychogenic movement disorders: treatment or diagnostic tool? *Mov Disord*. 2007;22(9):1353-5.
19. Chastan N, Parain D, Verin E, Veber J, Faure MA, Marie JP. Psychogenic aphonia: spectacular recovery after motor cortex transcranial magnetic stimulation. *J Neurol Neurosurg Psychiatr*. 2009;80(1):94.
20. Bodde NMG, Brooks JL, Baker GA, Boon PAJM, Hendriksen JGM, Mulder OG, et al. Psychogenic non-epileptic seizures: definition, etiology, treatment and prognostic issues: a critical review. *Seizure*. 2009;18(8):543-53.
21. Prigatano GP, Stonnington C, Fisher R. Psychological factors in the genesis and management of nonepileptic seizures: clinical observations. *Epilepsy Behav*. 2002;3(4):343-9.
22. LaFrance WC Jr, Barry JJ. Update on treatments of psychological nonepileptic seizures. *Epilepsy Behav*. 2005;7(3):364-74.
23. Metin SZ, Ozmen M, Metin B, Talasman S, Yeni SN, Ozkara C. Treatment with group psychotherapy for chronic psychogenic nonepileptic seizures. *Epilepsy Behav*. 2013;28(1):91-3.
24. Wolanczyk T, Brynska A. Psychogenic seizures in obsessive-compulsive disorder with poor insight: a case report. *Pediatr Neurol*. 1998;18(1):85-6.
25. LaFrance WC Jr, Marinis AJ, Webb AF, Machan JT, Rusch MD, Kanner AM. Comparing standard medical care for nonepileptic seizures in Chile and the United States. *Epilepsy Behav*. 2012;25(1):224-9.
26. Kalogjera-Sackellares D. *Psychodynamics and psychotherapy of pseudoepilepsies*. United Kingdom: Crown House Publishing; 2004.
27. Herrmann F. *Pesquisa psicanalítica*. Ciênc Cult. 2004;56(4):25-8.

28. Patidar Y, Gupta M, Khwaja GA, Chowdhury D, Batra A, Dasgupta A. Clinical profile of psychogenic non-epileptic seizures in adults: a study of 63 cases. *Ann Indian Acad Neurol*. 2013;16(2):157-62.
29. Howell SJ, Owen L, Chadwick DW. Pseudostatus epilepticus. *Q J Med*. 1989;71(266):507-19.
30. Reuber M, Fernández G, Bauer J, Helmstaedter C, Elger C. Diagnostic delay in psychogenic nonepileptic seizures. *Neurology*. 2002;58(3):493-5.
31. McDade G, Brown SW. Non-epileptic seizures: management and predictive factors of outcome. *Seizure*. 1992;1(1):7-10.
32. King DW, Gallagher BB, Murvin AJ, Smith DB, Marcus DJ, Hartiagi LC, et al. Pseudoseizures: diagnostic evaluation. *Neurology* 1982;32(1):18-23.
33. Thompson N, Connely L, Peltzer J, Nowack WJ, Hamera E, Hunter EE. Psychogenic nonepileptic seizures: a pilot study of a brief educational intervention. *Perspect Psychiatr Care*. 2013;49(1):78-83.
34. Mayor R, Howlett S, Grünewald R, Reuber M. Long-term outcome of brief augmented psychodynamic interpersonal therapy for psychogenic nonepileptic seizures: seizure control and health care utilization. *Epilepsia*. 2010;51(7):1169-76.
35. Schmutz M. Dissociative seizures -- a critical review and perspective. *Epilepsy Behav*. 2013;29(3):449-56.

# Intrauterine growth restriction in monochorionic-diamniotic twins

RITA DE CÁSSIA ALAM MACHADO<sup>1</sup>, MARIA DE LOURDES BRIZOT<sup>1\*</sup>, SEIZO MIYADAHIRA<sup>1</sup>, ROSSANA PULCINELI VIEIRA FRANCISCO<sup>1</sup>,

VERA LÚCIA JORNADA KREBS<sup>2</sup>, MARCELO ZUGAIB<sup>1</sup>

<sup>1</sup>Department of Obstetrics, Hospital das Clínicas, University of São Paulo's Medical School, São Paulo, SP, Brazil

<sup>2</sup>Department of Pediatrics, Hospital das Clínicas, University of São Paulo's Medical School, São Paulo, SP, Brazil

## SUMMARY

**Objective:** to evaluate neonatal morbidity and mortality in monochorionic-diamniotic (MCDA) twin pregnancies complicated by selective intrauterine growth restriction (sIUGR) and non-selective intrauterine growth restriction (nsIUGR).

**Methods:** neonatal morbidity parameters and mortality were analyzed in 34 twins with IUGR (< 10<sup>th</sup> percentile on twins' growth charts): 18 with sIUGR and 16 with nsIUGR. The sIUGR group was made up of 18 pregnancies in which growth was restricted in only one fetus (n = 18). The nsIUGR group was composed of 8 pregnancies in which both fetuses presented restricted growth (n = 16). Cases of twin-to-twin transfusion syndrome and fetal malformation were not included in the study.

**Results:** the MCDA twin pregnancies with sIUGR had a higher rate of orotracheal intubation (p = 0.001) and mechanical ventilation (p = 0.0006), as well as longer than average fasting time (p = 0.014) compared to those in which the fetuses had nsIUGR. A higher incidence was also observed of types II and III umbilical artery Doppler velocimetry patterns in the sIUGR cases (p = 0.002). There was no significant difference between the two groups as to mortality during pregnancy and the neonatal period (p = 0.09).

**Conclusion:** in MCDA twin pregnancies, sIUGR presents more severe umbilical artery Doppler velocimetry abnormalities and worse morbidity than nsIUGR.

**Keywords:** monozygotic twins, disease in twins, fetal growth retardation, laser Doppler flowmetry, morbidity, newborn infant.

Study conducted at Hospital das Clínicas,  
University of São Paulo, São Paulo, SP

Article received: 7/19/2013

Accepted for publication: 2/3/2014

**\*Correspondence:**

Departamento de Obstetrícia e  
Ginecologia, Instituto Central,  
Hospital das Clínicas  
Address: Av. Dr. Enéas de Carvalho Aguiar,  
255, 10o andar, cj. 10.037  
Postal Code: 05403-000  
São Paulo – SP  
Phone: (11) 2661-6209  
Fax: (11) 2661-6445  
mlbrizot@uol.com.br

<http://dx.doi.org/10.1590/1806-9282.60.06.019>

Conflict of interest: none

## INTRODUCTION

Intrauterine growth restriction (IUGR) in monochorionic pregnancies may affect one (selective IUGR, sIUGR) or both fetuses (non-selective IUGR, nsIUGR). However, when affecting both fetuses, IUGR morbidity, as compared with sIUGR morbidity in MCDA pregnancies, remains unknown.<sup>6</sup>

Selective intrauterine growth-restriction (sIUGR) affects 12-15% of monochorionic pregnancies.<sup>1</sup> The monochorionic placenta structure accounts for most of the morbidity associated with these pregnancies. A greater incidence of marginal or velamentous umbilical cord insertion, unequal sharing of the placental bed, and unbalanced arterio-venous anastomoses, with consequent compensatory mechanisms, make each monochorionic placenta an individual and atypical arrangement.<sup>2,3</sup>

Gratacos et al.,<sup>4</sup> in 2004, initiated a series of studies demonstrating increased neonatal morbidity in monochorionic and diamniotic (MCDA) pregnancies affected by sIUGR with abnormalities in Doppler velocimetry. In 2007, Gratacos et al.,<sup>5</sup> comparing groups of sIUGR-affected MCDA pregnancies with different umbilical artery Doppler velocimetry patterns (normal Doppler, persistent absent or reversed end diastolic velocity flow, intermittent absent or reversed end diastolic velocity flow), reported, in the group with the latter pattern, a higher rate of intrauterine death (IUD) in the smaller fetus and of brain lesions in the larger fetus.

Gao et al.,<sup>7</sup> evaluated neonatal morbidity in 7 pregnancies with IUGR in both fetuses and 71 cases of sIUGR; the control group consisted of 217 cases without

IUGR. In their study, conducted with a mixed sample of mono and dichorionic twin pregnancies, monochorionicity turned out to be a higher risk factor for IUGR, especially sIUGR ( $p < 0.001$ ). The groups associated with IUGR had a higher incidence of intrauterine death (IUD) and neonatal death (ND) ( $p < 0.001$ ).

However, there are no studies in the literature, specifically complicated by sIUGR compared to nsIUGR in MCDA pregnancies.

The aim of the current study was to evaluate prenatal evolution as well as perinatal morbidity and mortality in MCDA twin pregnancies complicated by sIUGR in contrast with nsIUGR.

## METHODS

This was a retrospective cohort study involving 34 monochorionic-diamniotic fetuses with IUGR ( $< 10^{\text{th}}$  percentile, according to the Alexander et al.<sup>8</sup> growth chart). We included cases that were followed up in our twin clinic and delivered in our hospital between 2004 and 2010. The study was approved by the Hospital's Ethics Committee (0092/10).

The sIUGR group comprised 18 pregnancies in which only one fetus was restricted in growth ( $n = 18$ ). The nsIUGR group was composed of 8 pregnancies in which both fetuses presented restricted growth ( $n = 16$ ).

Cases with twin-to-twin transfusion syndrome (TTTS) ( $n = 43$ ), fetal malformation ( $n = 36$ ), as well as three cases of sIUGR and IUD prior to 26 weeks that did not deliver in our institution and chorionicity not determined were not included in the study.

In our twin clinic, management of monochorionic twin pregnancies includes serial evaluations of fetal biometry, Doppler velocimetry, and biophysical profile, as well as monitoring of TTTS signs and amniotic fluid volume.

Ultrasound examination was performed transabdominally using a 3.5-5.0 MHz curvilinear-array transducer (Envisor - Phillips; Voluson Expert- GE). Fetal weight was estimated using the four-parameter formula (head and abdominal circumferences, biparietal diameter, and femur length) described by Hadlock et al.<sup>9</sup> Gestational age was estimated based on the date of the last menstrual period and on first-trimester or two consecutive second-trimester ultrasound scans. Selective IUGR was defined as estimated fetal weight below the 10<sup>th</sup> percentile in one twin according to a nomogram for twins.<sup>8</sup>

Oligohydramnios was defined as the deepest vertical pocket (DVP) of 2 cm or less and polyhydramnios as the DVP of 8 cm or greater prior to 20 weeks and 10 cm or greater after 20 weeks.<sup>10</sup> Diagnosis criteria for TTTS was

considered as previously described.<sup>11</sup> Chorionicity was determined by first-trimester ultrasound examination and/or pathoanatomical examination in all cases.

Doppler examination of the umbilical artery (UA) was performed in a free loop of the umbilical cord near the respective fetus. Whenever the UA was altered, evaluation was performed in three other areas of the umbilical cord. Abnormal UA Doppler was classified according to the characteristics of diastolic flow:<sup>5</sup> type I (positive with increased pulsatility index, PI); type II (persistent absent or reversed end diastolic velocity flow, AREDF), and type III (intermittent absent or reversed end diastolic velocity flow, iAREDF).

Cases with IUGR but normal UA Doppler were followed every two weeks. Cases with abnormal Doppler and gestational age below 26 weeks were examined weekly. In our nursery, viability is considered after 26 weeks of gestation; therefore, cases with type I Doppler were monitored weekly and cases with type II or III were admitted to the hospital and monitored daily with Doppler velocimetry of UA, middle cerebral artery, and *ductus venosus* in combination with biophysical profile and fetal heart rate measurements. All cases were managed expectantly as they were not subjected to laser therapy or selective fetocide.

Delivery indication due to fetal deterioration was considered before 28 weeks when there was AREDF in the *ductus venosus*; after this period, if any of the following parameters were present: *ductus venosus* PI persistently above 1.0,<sup>12</sup> persistently abnormal fetal heart rate traces, and maintenance of abnormal biophysical profile ( $< 6$ ) in evaluations 6 hours apart. Cases with AREDF or iAREDF not presenting fetal deterioration were delivered at 34 weeks of gestation. For type I, in accordance with our protocol for monochorionic twin pregnancy, delivery was scheduled at 36 weeks or earlier if fetal deterioration was observed.

Indicated preterm delivery was carried out based on either maternal or fetal conditions. Prophylactic antenatal corticosteroids (2 daily IM 12mg betamethasone) were administered only if preterm delivery ( $< 34$  weeks) was anticipated. All cases were delivered in our institution and the neonates were kept in the nursery adjacent to the maternity ward. The placentas underwent pathoanatomical examination; however, perfusion studies of the vascular shunts were not performed.

Major perinatal outcomes of the siblings in each group were compared. Outcome variables related to neonatal morbidity were gestational age at hospital admittance, gestational age at birth, birth weight, five-minute Apgar

score < 7, length of hospital stay, length of stay in neonatal intensive care unit (ICU), fasting time, orotracheal intubation, mechanical ventilation, and the presence of respiratory diseases (hyaline membrane, iatrogenic pneumothorax, emphysema, pulmonary hypertension, wet lung syndrome, pneumonia and/or bronchopulmonary dysplasia), infectious diseases (pneumonia, sepsis), neurological disorders (intraventricular hemorrhage, IVH; periventricular leukomalacia, PVL; multicystic leukoencephalomalacia), and blood disorders (anemia, neutropenia, polycythemia). Variables of perinatal outcome were also recorded, such as hospital discharge, intra-uterine death, and death during nursery admission.

The chi-square test or Fisher exact test were used to test the homogeneity of the groups in terms of proportions. Mean differences between the two groups were compared using Student *t* test or Mann-Whitney test. The level of significance was set at 5% for all tests.

## RESULTS

Eighteen twins with sIUGR and 16 with nsIUGR were analyzed with respect to neonatal morbidity and mortality.

Mean maternal age was lower in the sIUGR group ( $p < 0.001$ ). Otherwise, groups did not differ from each other: parity, previous miscarriages and rates of gestational *diabetes mellitus*, chronic hypertension, and preeclampsia were similar (Table 1).

Table 2 displays the neonatal morbidity and mortality data. It can be seen that mean gestational age at hospital admittance for control of fetal surveillance was lower in the sIUGR group ( $p = 0.024$ ) and that there was longer time of fasting in the nursery ( $p = 0.014$ ) as well as a higher need for orotracheal intubation ( $p = 0.001$ )

and use of mechanical ventilation ( $p = 0.0006$ ) among the newborns with sIUGR. Mean gestational age at delivery, mean birth weight and total length of nursery and neonatal ICU stay did not differ significantly between the two groups.

Three fetuses with restricted growth (2 with sIUGR and 1 with nsIUGR) progressed to IUDs; all had REDF in the umbilical artery (type II). One fetal death occurred at 26 weeks of gestation with *ductus venosus* PI equaling 1.44 at the last evaluation. The fetus was receiving corticotherapy for lung maturation; the non-restricted twin was also dead. Another fetus died at 28 weeks of gestation; the *ductus venosus* PI (0.82) and biophysical profile parameters were normal 24 hours prior to death. The co-twin was delivered at 32 weeks of gestation (nsIUGR). In the third case, fetal death was diagnosed at 32 weeks of gestation, and, as in the previous case, the *ductus venosus* PI (0.85) and biophysical profile parameters were normal 24 hours prior to death; delivery of the co-twin was performed soon after detection of the fetal death of the growth-restricted one. There was no difference in the incidence of IUD and ND between the two groups ( $p = 0.092$ ; Table 2).

Table 3 shows the distribution of Doppler velocimetry patterns in the sIUGR and nsIUGR groups. Type I UA Doppler velocimetry was more frequent in the nsIUGR group, whereas type II and type III UA Doppler velocimetry occurred more often in the sIUGR group.

## DISCUSSION

Although the two study groups were no different regarding gestational age at delivery and birth weight, the MCDA pregnancies complicated by sIUGR had a higher incidence of neonatal morbidity than the nsIUGR group.

**TABLE 1** Characteristics of the study population. sIUGR = selective intrauterine growth restriction; nsIUGR = non-selective intrauterine growth restriction

	sIUGR (n = 18)	nsIUGR (n = 16)	p value
Male (n, %)	11 (61.1)	12 (75.0)	0.387*
Parity (mean, SD)	0.33 ± 1.50	1.50 ± 2.78	0.429**
Miscarriages (mean, SD)	0.39 ± 0.78	0.13 ± 0.35	0.531**
Maternal age (mean, SD)	25.83 ± 6.97	35.00 ± 7.07	0.001***
Gestational diabetes (n, %)	2 (11.1)	2 (12.5)	1.000****
Chronic hypertension (n, %)	5 (27.8)	4 (25.0)	1.000****
Preeclampsia (n, %)	7 (38.9)	6 (37.5)	0.933*

\* Chi-square test.

\*\* Parametric Mann-Whitney test.

\*\*\* Student *t* test.

\*\*\*\* Fisher exact test.

**TABLE 2** Neonatal morbidity and mortality parameters in selective and non-selective intrauterine growth restriction (sIUGR; nsIUGR). GA: gestational age; ICU: intensive care unit

	sIUGR (n = 18)	nsIUGR (n = 16)	p value
GA at hospitalization (weeks, mean, SD)	29.8 (2.8)	31.4 (2.1)	0.024*
GA at delivery (weeks, mean, SD)	33.4 (1.6)	33.4 (1.6)	0.953*
Birth weight (g, mean, SD)	1093.4 (341.3)	1274.7 (264.7)	0.111**
Length of stay (days, mean, SD)	35.2 (10.2)	45.4 (34.8)	0.707*
Neonatal ICU stay (days, mean, SD)	14.7 (16.0)	21.9 (19.4)	0.271*
Fasting time (days, mean, SD)	7.5 (7.8)	3.0 (6.9)	0.014*
Apgar < 7 – 5 <sup>th</sup> minute (n, %)	2 (12.5)	1 (6.6)	1.000***
Orotracheal intubation (n, %)	10 (62.5)	1 (6.6)	0.001****
Mechanical ventilation (n, %)	12 (75.0)	2 (13.3)	0.0006****
Neonatal ICU (n, %)	13 (81.2)	9 (60.0)	0.252***
Infection (n, %)	10 (62.5)	7 (46.6)	0.376****
Intraventricular hemorrhage (n, %)	3 (18.7)	5 (33.3)	0.433***
Blood disorders (n, %)	12 (75.0)	9 (60.0)	0.457***
Respiratory disease (n, %)	14 (87.5)	8 (53.3)	0.092***
Outcome			0.092***
Intrauterine fetal death	2 (11.1)	1 (6.2)	
Neonatal death	6 (33.3)	1 (6.2)	

\* Parametric Mann-Whitney test.

\*\* Student *t* test.

\*\*\* Fisher exact test.

\*\*\*\* Chi-square test (oro-tracheal intubation, power = 0.94 and mechanical ventilation, power = 0.97).

**TABLE 3** Distribution of umbilical artery Doppler patterns<sup>5</sup> in selective and non-selective intrauterine growth restriction (sIUGR; nsIUGR)

	sIUGR		nsIUGR		p value
	n	%	n	%	
Type I	2	11.1	11	68.8	0.002
Type II	11	61.1	4	25	
Type III	5	27.8	1	6.2	
Total	18	100	16	100	

Fisher exact test

Selective IUGR was associated with postnatal need for intubation and mechanical ventilation and longer fasting time during nursery stay than that of the nsIUGR group.

The reports by Gratacos et al.<sup>4,5,13</sup> showed that sIUGR is associated with intermittent UA flow pattern (type III) and that the type of Doppler alteration is related to the number and diameter of artery-artery anastomoses. That prompted us to investigate if there were any differences between the sIUGR and nsIUGR groups regarding Doppler flow pattern.

In our study, type II and type III UA Doppler flow patterns were more frequently in sIUGR twins than in nsIUGR twins. On the other hand, type I UA pattern was more

often seen in nsIUGR twins than in sIUGR twins. Our findings led us to question whether sIUGR and nsIUGR arise from different mechanisms regarding placental angio-structure, the former being related to vascular communication, as described in previous studies,<sup>3,5,14,15</sup> and the latter to placental insufficiency. Also, we wondered if the older maternal age in the nsIUGR-related cases is a predictor of placental insufficiency. The non-assessment of placental vascularization in our study, however, prevents the confirmation of these hypotheses.

All three IUD cases (2 cases of sIUGR and 1 case of nsIUGR) reported herein were associated with UA Doppler velocimetry type II (REDF). Our data agree with those by Ishi et al.,<sup>16</sup> who reported a higher risk for IUD and ND in IUGR cases with persistent AREDF. No difference was found between the study groups in relation to IUD or ND. However, our findings suggest a tendency towards higher mortality in the sIUGR group: a total of 8 cases of IUD and ND (44.4%) as against the 2 cases in the nsIUGR group (12.5%). A larger number of cases may be necessary to evaluate with greater certainty the seemingly discrepant mortality rates of the two groups.

Our results were similar to those by Ishi et al.<sup>16</sup> who observed a higher risk of death in cases below the 3<sup>rd</sup> centile of the normal curve for singleton pregnancies, but instead, we chose to use a specific twin curve in order to identify the most severe cases.<sup>8</sup>

It was thus possible to observe, in the sIUGR group, a higher rate of neonatal morbidity and of severe UA Doppler velocimetry patterns, perhaps due to the greater seriousness of placental dysfunction as characterized by UA Doppler velocimetry (AREDF and iAREDF pattern – types II and III according to categorization by Gratacos et al.).<sup>5</sup> Therefore, sIUGR points toward the need for closer fetal surveillance given the risk of neonatal complications and IUD in such cases.

The gestational age at delivery in sIUGR reported by previous studies<sup>16</sup> was lower (32 weeks) compared to the present study (33.36 weeks), showing that less severe cases were included in our study owing to late referral of such cases to a tertiary center. Probably, several of the severe cases had died *in utero* before reaching our center.

The present study reflects data from a single tertiary Center without discrepancies in the management of the cases. Therefore, we present a small number of cases as compared to multicenter studies.<sup>5,13,16</sup> However, we found significant association of sIUGR with mechanical ventilation and orotracheal intubation (0.97 and 0.94, respectively).

The present series was not submitted to laser therapy or selective fetocide, showing the natural evolution of the cases.

There are no studies comparing neonatal outcome in cases of sIUGR and nsIUGR in MCDA pregnancies. Gao et al.,<sup>7</sup> when evaluating IUGR in mono and dichorionic pregnancies, observed that monochorionicity was a risk factor for IUGR. In the present study, MCDA twin pregnancies with sIUGR presented higher rate of severe UA Doppler abnormalities leading to a worse neonatal prognosis compared to MCDA twin pregnancies with nsIUGR.

## RESUMO

Restrição de crescimento intrauterino em gêmeos monochorionicos diamnioticos.

**Objetivo:** avaliar a morbidade e mortalidade neonatal em gestações monochorionicas e diamnioticas (MCDA) acometidas pela restrição de crescimento fetal seletiva (RCFS) e não seletiva (RCFNS).

**Métodos:** os parâmetros de morbidade e mortalidade neonatais foram avaliados em 34 gêmeos com RCF (abaixo do percentil 10 de uma curva de crescimento para gêmeos): 18 com RCFS e 16 com RCFNS. O grupo com RCFS teve origem em 18 gestações, em que somente um feto apresentava RCF. O grupo com RCFNS teve origem em 8 gestações em que ambos os fetos apresentavam RCF. Foram excluídos deste estudo casos da síndrome da transfusão feto-fetal e malformações fetais.

**Resultados:** os gêmeos de gestações MCDA com RCFS apresentaram maior frequência de entubação orotraqueal ( $p=0,001$ ), ventilação mecânica ( $p=0,0006$ ) e maior tempo em jejum durante internação ( $p=0,014$ ), quando comparados aos gêmeos de gestações MCDA com RCFNS. No grupo com RCFS, também foram observados maior frequência de tipos II e III de dopplervelocimetria de artéria umbilical ( $p=0,002$ ). Não houve diferença significativa entre os grupos quanto à mortalidade neonatal ( $p=0,09$ ).

**Conclusão:** em gestações gemelares MCDA, a RCFS representa maior frequência de alterações severas na velocimetria Doppler da artéria umbilical e piores resultados na morbidade neonatal.

**Palavras-chave:** gêmeos monozigóticos, doenças em gêmeos, retardo do crescimento fetal, fluxometria por *laser* Doppler, morbidade, recém-nascido.

## REFERENCES

- Lewi L, Van Schoubroeck D, Gratacós E, Witters I, Timmerman D, Deprest J. Monochorionic diamniotic twins: complications and management options. *Curr Opin Obstet Gynecol.* 2003;15:177-94.
- Machin GA: Vascular anatomy of monochorionic twin placentas; In: Blickstein I, Keith LG, editors. Multiple pregnancy: epidemiology, gestation & perinatal outcome. 2<sup>nd</sup> ed. Andover: Thomson Publishing Services; 2005. p. 193-200.
- Lopriore E, Pasmán SA, Klumper FJ, Middeldorp JM, Walther FJ, Oepkes D. Placental characteristics in growth-discordant monochorionic twins: a matched case-control study. *Placenta.* 2012;33:171-4.
- Gratacos E, Lewi L, Carreras E, Becker J, Higuera T, Deprest J, Cabero L. Incidence and characteristics of umbilical artery intermittent absent and/or reversed end-diastolic flow in complicated and uncomplicated monochorionic twin pregnancies. *Ultrasound Obstet Gynecol.* 2004;23:456-60.
- Gratacos E, Lewi L, Munoz B, Acosta-Rojas R, Hernandez-Andrade E, Martinez JM, et al. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin. *Ultrasound Obstet Gynecol.* 2007;30:28-34.
- Valsky DV, Eixarch E, Martinez JM, Crispi F, Gratacos E. Selective intrauterine growth restriction in monochorionic twins: pathophysiology, diagnostic approach and management dilemmas. *Semin Fetal Neonatal Méd* 2010;15:342-8.
- Gao Y, Zhiming He, Yanmin L, Sun H, Huang L, Li M, et al. Selective and non-selective intrauterine growth restriction in twin pregnancies: high risk factors and perinatal outcome. *Arch Gynecol Obstet.* 2012;285:973-8.
- Alexander GR, Michael K, Martin J, Papiernick E. What are the fetal growth patterns of singletons, twins and triplets in the United States? *Clin Obstet Gynecol.* 1998;41:115-25.
- Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body and femur measurements – A prospective study. *Am J Obstet Gynecol.* 1985;151:333-7.
- Senat M, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion Syndrome. *N Engl J Med.* 2004;351:136-44.

11. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. *J Perinatol* 1999;19:550-55.
12. Francisco RPV, Miyadahira S, Zugaib M: Predicting pH at birth in absent or reversed end-diastolic velocity in the umbilical arteries. *Ultrasound Obstet Gynecol.* 2006;107:1042-7.
13. Gratacós E, Diemert A, Hecher K, Lewi P, Depres J. Clinical outcome and placental characteristics of monochorionic diamniotic twin pairs with early and late-onset discordant twin. *Am J Obstet Gynecol.* 2008;199:511e1-e7.
14. Lewi L, Cannie M, Blickstein I, Jani J, Huber A, Hecker K, et al. Placental sharing, birth weight discordance, and vascular anastomoses in monochorionic diamniotic twin placentas. *Am J Obstet Gynecol.* 2007;197:587e1-e8.
15. Lewi L, Gucciardo L, Huber A, Jani J, Miegheem TV, Doné E, et al. Clinical outcome and placental characteristics of monochorionic diamniotic twin pairs with early and late-onset discordant twin. *Am J Obstet Gynecol.* 2008;199:511e1-e7.
16. Ishi K, Murakoshi T, Hayashi S, Saito M, Sago M, Takahashi Y, et al. Ultrasound predictors of mortality in monochorionic twins with selective intrauterine growth restriction. *Ultrasound Obstet Gynecol.* 2011;37:22-6.

# Distortion-product otoacoustic emission growth curves in neonates

TANIA ALVES BARBOSA<sup>1</sup>, ALESSANDRA SPADA DURANTE<sup>2</sup>, LIDIO GRANATO<sup>3</sup>

<sup>1</sup>Speech Therapist, Master in Health Sciences, Faculty of Medical Sciences of Santa Casa de São Paulo, São Paulo, SP, Brazil

<sup>2</sup>Professor Assistant, Faculty of Medical Sciences of Santa Casa de São Paulo, São Paulo, SP, Brazil

<sup>3</sup>Professor, Department of Otorhinolaryngology, Faculty of Medical Sciences of Santa Casa de São Paulo, São Paulo, SP, Brazil

## SUMMARY

**Background:** The recording of otoacoustic emissions (OAE) enabled us to prove that the cochlea is able not only to receive sounds but also to produce acoustic energy. Through the use of distortion-product otoacoustic emission measurements, the growth of the response was seen according to the intensity of the sound stimulus presented (growth curve).

**Objective:** to determine the thresholds for the emergence of distortion-product otoacoustic emissions (DPOAE) on frequencies of 2000 and 4000 Hz with a stimulus varying from 20 to 65dB SPL, and to establish the slope values obtained in the growth curves.

**Methods:** 39 neonates aged 5 to 28 days without risk indicators of hearing loss were studied. The DPOAE growth curves were obtained on the frequencies from 2000 Hz and 4000 Hz with a level of intensity ranging from 20 to 65dB SPL divided into two paradigms (20 to 40dB SPL and 40-65dB SPL).

**Results:** there was a statistically significant difference in the thresholds for the emergence of DPOAE depending on the criteria used. The thresholds were on average higher at 4000 Hz than 2000 Hz and the slope was higher on average at 2000 Hz than 4000 Hz, although not statistically significant in either case.

**Conclusion:** the thresholds were on average 30dB SPL at 2000Hz and 35dB SPL at 4000Hz. The slope values varied between 3 and 4 on average, reaching 15 in some cases.

**Keywords:** spontaneous otoacoustic emissions, hearing tests, hearing, newborn.

Study conducted at Hospital Nossa Senhora da Conceição and at the Faculty of Medical Sciences, Santa Casa de São Paulo, São Paulo, SP

Article received: 3/1/2013

Accepted for publication: 2/20/2014

\*Correspondence:

Address: Rua Dr Cesário Motta Jr  
nº 61, 8º andar  
São Paulo – SP

Postal Code: 01221-020  
tania.abc@glubo.com

<http://dx.doi.org/10.1590/1806-9282.60.06.020>

Conflict of interest: none

## INTRODUCTION

The recording of otoacoustic emissions (OAE) is a method used for the detection of hearing changes of cochlear origin.<sup>1</sup> Among other functions, the cochlea amplifies sounds, which is performed nonlinearly in healthy cochlea, that is, there is a compression mechanism within the cochlea that enables the amplification to occur at different proportions depending on the intensity of the stimulus (weak, medium and strong). For weak sounds the amplification is linear, and for medium intensity sounds the amplification is lower, which is called cochlear compression, Ruggero.<sup>2</sup>

Direct measurements of cochlear nonlinearity are not possible. As a result, access to the nonlinearity of the human cochlea has to be undertaken with noninvasive and indirect measures, according to Gorga et al.<sup>3</sup>

With the measurement of distortion-product otoacoustic emissions (DPOAE) it is possible to verify the growth in the response according to the level of intensity of the sound stimulus presented (growth curve), as per Abdala.<sup>4</sup>

The study of the DPOAE growth function has proven to be a very favorable instrument for access to and

understanding of cochlear physiology, especially compression mechanisms and cochlear nonlinearity, as well as the function of outer hair cells. The realization of the DPOAE growth curve, also known as the input/output (IO) growth function makes it possible to obtain the DPOAE threshold.<sup>5</sup> The occurrence of DPOAE compression in newborns can be interpreted as an indication of reduction in gain from cochlear amplification with an increase in the stimulus level. The presence of compression in this phase, in addition to suggesting cochlear integrity, is a strong indicator that already at birth the peripheral function enables greater amplification of sounds with a low intensity level, favoring auditory tasks that require temporal resolution ability. Nonlinearity is important for recognizing speech in a noisy environment.<sup>6</sup> The sounds are dynamic, with constant changes in the spectrum, amplitude, spatial location and duration parameters. The process of perceiving quick changes in the pattern of the stimulus, integrating information occurring over time, is denominated temporal processing. Knowledge of the occurrence of this pattern at birth confirms the hypothesis of maturity in the peripheral auditory system in the neonatal phase, predisposing the development of temporal resolution ability in this phase.<sup>7</sup>

Thus, importance of research on the possible clinical applications of this test emerges. Cochlear physiology represents an important subject for study and has become a major motivation in this work: to obtain a more specific understanding of the cochlea and its operation, thereby collaborating when there are losses to these cochlear functions, mainly aimed at the neonatal population, where intervention and early stimulation measures can be developed, as well as complementing newborn hearing screening (NHS). Non-linear amplification of the sound made by the cochlea indicates that it is working normally, especially in relation to the OHC function, and a linear amplification for all levels of stimulus intensity indicates a cochlea with abnormalities.<sup>8</sup>

In alterations to the middle ear only, the function of the OHCs is not compromised, so the growth curve obtained will have the same configuration as a normal examination, i.e. with nonlinear amplification, presenting only an increased DPOAE threshold. The realization of DPOAE growth curves in babies who “fail” the Newborn Hearing Screening Program would be important and useful to differentiate the presence of amniotic fluid/vernix in the EAM (external auditory meatus) and/or tube dysfunction from a cochlear abnormality,<sup>9</sup> optimizing the referral for audiological diagnosis.

Obtaining the thresholds for the emergence of DPOAE helps in the recommendation of hearing aids in the cases of mild to moderate hearing losses, increasing the information provided to the professional who will perform this procedure.<sup>10</sup>

In addition to its possible applications, this line of research has not been well explored in newborns, meaning that studies in this area and on this specific population are justified.

## OBJECTIVE

To determine the DPOAE emergence thresholds at the frequencies of 2000 Hz and 4000 Hz with a variation in the stimulus of 20 to 65dBNPS.

To establish the slope values obtained in the growth curves at the frequencies of 2000 Hz and 4000 Hz as a function of the intensity.

## METHODS

This is a prospective, cross-sectional and descriptive study. This was approved by the Research Ethics Committee of São Paulo’s Holy House of Mercy Brotherhood (project 277/10) and was conducted at the institution’s Speech Pathology Sector, with newborns born between March and August 2011. All of the newborns tested were born at São Paulo’s Holy House of Mercy Brotherhood and were tested after being discharged from hospital. At that time, the parents or guardians received a referral for realization of newborn hearing screening at the hospital’s Speech Pathology Sector, at scheduled dates and times, within 4 weeks of birth, enabling investigation within the neonatal period.

### Case-based reasoning

Inclusion criteria:

- Neonates born to term, over 37 weeks based on the New Ballard Score classification.<sup>11</sup>
- No risk indicator for hearing loss according to the JCIH.<sup>12</sup>
- With OAE by transient stimuli and/or distortion product present in the newborn hearing screening program.
- Signed informed consent form.

Exclusion criteria:

- Newborns who did not sleep or woke up during the exam.

This study included 39 newborns. A total of 14 exams were conducted on each newborn. The total assessment

period was an average of 30 minutes per newborn in a single session.

### Characterization of the sample

51 newborns were invited to participate in the study, however 12 did not maintain the conditions required to realize the exam either because they woke up during the assessment, did not sleep for testing to begin, or did not respond in the newborn hearing screening after otoacoustic emissions. Thus, 39 newborns participated in the study, 21 (53.8%) male and 18 (46.2%) female. The perinatal characteristics of the newborns can be viewed in Table 1.

### Equipment

The equipment used for the collection of the data in the study was the ILO V6 Otodynamics Analyzer, Cochlear Emissions Analyzer ILO292 DP Echoport Version 6, Otodynamics, London. A newborn probe was used for insertion (SGS-8) connected to channel A of the external unit of the ILO equipment.

### Procedure

The exams were performed in a soundproof booth. The shape of the stimulus curve was monitored in the ear in 'real-time', ensuring the quality and reliability of the data collected. The probe was acoustically calibrated daily in a cubic centimeter cavity, for assessment of newborns. No otoscopy was conducted before the procedure.

In a state of natural sleep, the newborn was positioned to conduct the assessment, starting 50% of the exams in the right ear and 50% in the left ear, thus ensuring no interference from the first ear tested.

The probe was adapted to capture DPOAE growth curves (GC) in the first ear to be tested, results being recorded with the following order of procedures:

- DPOAE GC at 2000Hz general paradigm
- DPOAE GC at 2000Hz paradigm 1

- DPOAE GC at 2000Hz paradigm 2.
- DPOAE GC at 4000Hz paradigm 1.
- DPOAE GC at 4000Hz paradigm 2.

Where:

- Paradigm 1 (P1): L2 from 20 to 40 dB NPS.
- Paradigm 2 (P2): L2 from 40 to 65 dB NPS.
- General Paradigm (GP): L2 from 35 to 65 dB NPS

Next, the same procedures were repeated in the second ear.

The DPOAE GC were obtained for paradigms P1 and P2 based on the hypothesis that the slope would be higher (greater incline of the curve) in weak sounds (20 to 40dB SPL) and lower (lower incline of the curve) in midrange sounds (40 to 65dB SPL).

The quality of each exam was observed, ensuring equal assessment conditions with regard to the placement of the probes, stimulus intensity, stability and noise level. Thus, although the study of OAE in the neonatal population is delicate, the reliability of the response observed as increased.

The DPOAE growth curve was obtained for both ears. Two pure tones with primary frequencies denominated F1 and F2 were presented. The responses for analysis were obtained at 2F1-F2, with  $F1/F2 = 1.22$ . The F2 frequencies chosen were 2000 Hz and 4000 Hz for being the frequencies used most often in studies with this population.<sup>13</sup>

The intensities (L2) ranged from 20 to 65 dB SPL divided into three paradigms:

- **Paradigm1:** L2 (intensity of frequency F2) varied from 20 to 40 dB SPL with a 3 dB interval.
- **Paradigm2:** L2 (intensity of frequency F2) varied from 40 to 65 dB SPL with a 3 dB interval.
- **General paradigm:** L2 (intensity of frequency F2) varied from 35 to 65 dB SPL with a 5 dB interval.

**TABLE 1** Baseline characteristics

	Weight (g)	Gestational age (weeks)	Days of life upon assessment	1 minute Apgar	5 minute Apgar
Mean	3337.4	39.2	12.72	-	-
Median	3375	39	10	9	10
SD	471.2	0.9	5.75	0.6	0.5
Minimum	2290	38	5	7	9
Maximum	4085	41	28	9	10

SD: standard deviation; N: number of newborns.

- The intensity of L1 (intensity of frequency 1) was adjusted using the formula  $L1 = 0.4L2 + 39$  from Kummer et al.<sup>14</sup>

The exams were finalized when the background noise was equal to or lower than 0 dB SPL after a minimum of three scans.

The following criteria were adopted to analyze the response in the signal to noise ratio (S/N):

- **Lim0:** intensity at which the S/N ratio is greater than or equal to zero – this was called Lim0 (threshold zero).
- **Lim6:** intensity at which the S/N ratio is greater than or equal to six – this was called Lim6 (threshold six).

To obtain the slope, three criteria were established in accordance with the intensities established:

- **GP** = intensity varying from 35 to 65 dB SPL at 2kHz in 5 dB intervals.
- **P1** = intensity varying from 20 to 40 dB SPL at 2000 Hz and 4000 Hz in 3 dB intervals.
- **P2** = intensity varying from 40 to 65 dB NPS at 2000 Hz and 4000 Hz in 3 dB intervals.

#### Statistical analysis

The statistical analysis was undertaken using the program SPSS version 13.0.

The sample calculation was performed using Prime software, considering a significance level of 0.05.

For the descriptive analysis, the summary measures for quantitative variables were calculated. For qualitative varia-

bles, absolute and relative frequencies were obtained and boxplot graphs were generated, as well as Wilcoxon signed-rank test, adopting a significance level of 5% for all tests.

## RESULTS

### Study of DPOAE emergence thresholds obtained with the growth curve

The Lim0 and Lim6 thresholds (described in Methods) on the right and left ears at frequencies of 2000 Hz and 4000 Hz were compared (Table 2). It was noted that the differences between the parameters used in the research (Lim0 and Lim6) were significant at the frequencies of 2000 Hz and 4000 Hz in both ears, but when comparing the left ear and right ear the differences were not significant.

### Descriptive study of the slope obtained with the DPOAE growth curve

A descriptive analysis was undertaken of the slope values obtained with the realization of the DPOAE GC at frequencies of 2000 Hz and 4000 Hz in the three paradigms used in the study (Table 3 and 4).

The values of the slope obtained in paradigms P1 and P2 at 2000 Hz in the right ear and the left ear were compared, and no significant differences were found between them in both ears. When comparing the values of the slope obtained in paradigms P1 and P2 at 4000 Hz in the right ear and the left ear, no significant difference was observed between them. We compared the slope values obtained at frequencies of 2000 Hz

**TABLE 2** Distribution of emergence thresholds in decibels obtained in the 2 parameters (Lim0 and Lim6) by ear and by frequency

	Right ear				Left ear			
	2000 Hz		4000 Hz		2000 Hz		4000 Hz	
	L0	L6	L0	L6	L0	L6	L0	L6
Minimum	22	25	28	28	19	19	19	19
Average	28.13	32.32	34.69	38.66	28.97	33.27	33.62	37.21
SD	6.25	7.7	6.8	8	6.4	7.2	8.4	9.4
Median	25	28	31	37	28	32.5	31	37
Maximum	53	53	59	44	44	50	62	62
	p<0.001		p<0.001		p<0.001		p<0.001	

L0: threshold where the signal to noise ratio is greater than or equal to zero; L6: threshold where the signal to noise ratio is greater than or equal to six; SD: standard deviation; p: significance level.

**TABLE 3** Distribution of the slope values obtained at 2000 Hz in the 3 paradigms for the right ear and left ear

	2000Hz					
	Right ear			Left ear		
	P1	P2	GP	P1	P2	GP
Minimum	-0.15	-0.62	2.15	0.33	0.9	1.51
Mean	3.55	3.91	10.05	3.51	4.26	8.85
SD	2.08	2.56	6.2	3.1	2.42	4.38
Median	3.16	3.21	8.98	2.33	3.74	9.16
Maximum	8.08	9.19	28.06	14.59	10.96	17.03

SD: standard deviation; P1: 1 paradigm (stimulus intensity ranging from 20 to 40 dB SPL); P2: paradigm 2 (stimulus intensity ranging from 40 to 65 dB SPL); GP: general paradigm (stimulus intensity ranging from 35 to 65 dB SPL).

**TABLE 4** Distribution of the slope values obtained at 4000 Hz in the 2 paradigms for the right ear and left ear

	4000Hz			
	Right ear		Left ear	
	P1	P2	P1	P2
Minimum	0.54	-1.38	-0.04	0.2
Mean	3.97	3.7	3.01	3.06
SD	3.17	3.51	2.65	2.84
Median	2.6	2.68	2.4	2.51
Maximum	11.58	15.9	12.33	14.44

SD: standard deviation; P1: 1 paradigm (stimulus intensity ranging from 20 to 40 dB SPL); P2: paradigm 2 (stimulus intensity ranging from 40 to 65 dB SPL).

and 4000 Hz in paradigm 1 in the right ear, and no significant difference between the frequencies was obtained, with the same occurring in paradigm 2. When comparing the slope values obtained at frequencies of 2000 Hz and 4000 Hz in paradigm 1 and paradigm 2, on the left ear, a significant difference was not obtained between frequencies.

## DISCUSSION

The same sequence presented in the results was maintained for the presentation of the discussion.

Cochlear activity is characterized by the absolute signal of the response, and the criterion for identification of the response depends on signal to noise ratio. Therefore, for analysis of the presence of DPOAE, it is necessary for the cochlear response to be above the noise. There is no consen-

sus in the literature about the recommended signal/noise ratio. Some studies have used an S/N ratio greater than or equal to 3dB, such as Neely et al.<sup>15</sup> and Tiradentes et al.<sup>16</sup> and there are others who have used an S/N ratio greater than 6dB, such as Gorga et al.<sup>8</sup> and Boege and Janssen.<sup>17</sup>

The equipment used in this study - the ILO V6, analyzes the presence of noise for each pair of frequencies tested considering its mean plus 1 standard deviation. Therefore, the noise level displayed on the monitor screen is higher than the average noise by 6 dB, and therefore the presence of a response can be considered when the S/N ratio is greater than or equal to zero, according to the manufacturer's protocol.

Analyzing the results when obtaining the DPOAE emergence thresholds with the GC, the results showed a significant difference between the two criteria used (Lim0 and Lim 6) at the two frequencies (2000 Hz and 4000 Hz) in both ears, with the thresholds obtained in Lim0 smaller on average than those obtained in Lim6. According to a study by Dubno,<sup>6</sup> significant differences were noted in the emergence thresholds of the DPOAE GC according to the criterion used at 2000 Hz and 4000 Hz. Comparing the results of the emergence thresholds according to the two criteria used (Lim0 and Lim6) significant differences at 2000 Hz were noted in both ears, as well as at 4000 Hz, also in both ears, therefore always observing the criterion used in the study should be emphasized for possible comparisons of results.

The emergence thresholds at 2000 Hz were 30 dB on average, and 35 dB on average at 4000 Hz according to the criteria used (Table 2). These thresholds were lower than those obtained by Dubno<sup>6</sup> where the responses emerged

at 50 dB at 2000 Hz and 60 dB at 4000 Hz. In this study we considered three thresholds denominated Threshold1, Threshold2 and Threshold3 where:

- Threshold1 (Lim1) = lowest intensity studied where the signal/noise ratio is greater than or equal to 3dB;
- Threshold2 (Lim2) = lowest intensity studied where the signal/noise ratio is greater than or equal to 3dB and 2F1-F2 with a positive value; and
- Threshold3 (Lim3) = lowest intensity studied where the signal/noise ratio is greater than or equal to 3dB and subsequent intensities also present a S/N ratio greater than or equal to 3dB, with the emergence threshold considered when it appeared in 70% of cases.

Therefore, the responses were better at 2000 Hz compared to 4000 Hz such as those obtained in the aforementioned study.

When comparing the left ear with the right ear, the differences were not significant due to the number of newborns composing the sample, which was not sufficient for this purpose. These results compare to those obtained by Leme and Carvalho<sup>18</sup> and Costa et al.<sup>19</sup> There are studies already established in the literature that show that OAE responses are better in the right ear for the female gender compared to the left ear for the male gender, Leme and Carvalho,<sup>18</sup> Aidan et al.<sup>20</sup> and Durante et al.<sup>21</sup>

The results obtained in the DPOAE growth curves in this study were used to calculate the mean responses for each intensity, using 2F1-F2 and the signal to noise ratio at the frequencies of 2000 Hz and 4000 Hz, in order to obtain an average curve profile for newborns and to identify the occurrence of any compression pattern for the responses in this age group. To obtain the mean, the grouped results of the left and right ears at each intensity and frequency were used, given that there was no significant difference between them in this study.

The DPOAE GC were obtained for paradigms P1 and P2 based on the hypothesis that the slope would be higher (greater incline of the curve) in weak sounds (20 to 40dB SPL) and lower (lower incline of the curve) in midrange sounds (40 to 65dB SPL). According to Gorga et al.<sup>8</sup> cochlear gain is higher for weaker stimulus levels, decreasing as the level increases. That is, the cochlea is more com-

pressive when stimuli are of medium intensity. In this work, the slope values obtained at 2000 Hz were lower in P1 than P2 in both ears, and at 4000 Hz in the right ear P1 was higher than P2, and in the left ear P1 was lower than P2, as in 2000 Hz. These differences were not significant. However, visually, the slope in P1 is greater than in P2. The slope value was higher on average at 2000 Hz than 4000 Hz (except for the slope obtained in P1 in the right ear at 4000 Hz, which was greater than the corresponding slope at 2000 Hz). If the DPOAE growth curve enables detection of the presence of cochlear compression upon calculating the slope, the numerical results of this study did not make it possible to prove the presence of cochlear compression in the sample, though looking at the growth curve graphs a decrease was seen in the slope of the curves at midrange intensities.

It was not possible to make comparisons with other slope studies obtained in two paradigms, as no work using DPOAE GC in this way was found in the literature. However, a study by Almeida<sup>7</sup> noted a change in the incline of the curve of the slope from 65 dB, which would be the compression point for the frequencies studied (the DPOAE GC was outlined with stimuli a variation range between 35 and 75 dB with 5 dB intervals at 2000 Hz and 4000 Hz). Comparing these results with the present study was not possible, because 65dB was the largest stimulus used in the paradigms presented. In studies with adults, the compression point was between 50 and 60 dB.<sup>3,15,22</sup>

When using the general paradigm the slope values were higher than those obtained in paradigms 1 and 2, but the comparison was not made because of the use of different criteria.

The slope values varied from 3 to 4 on average, reaching 15 in some cases. These maximum values can be attributed to the fact that they were obtained in the newborn population where the OAE responses are better than in other age groups. This fact was discussed with the technical team of the equipment manufacturer (Otodynamic), Peter Bray and Lee Van Middlesworth, who still have no explanation for this finding due to the small number of studies performed with the newborn population. The general paradigm was only applied to part of the sample, and only at 2000 Hz; therefore, it was not compared with the other paradigms (P1 and P2), and the General P slope values were higher than those obtained in P1 and P2. The mean General P slope value was 10.05 in the right ear and 8.85 in the left ear.

## CONCLUSION

The emergence thresholds were on average 30 dB SPL at 2000 Hz and 35 dB SPL at 4000 Hz, therefore the best emergence thresholds were at a frequency of 2000 Hz compared to 4000 Hz.

No difference in the slope values obtained in the DPOAE growth curves were noted, but slopes were steeper at the weakest intensities (P1) and more linear at the moderate intensities (P2) suggesting that the visual analysis of the graph reflects cochlear compression.

## ACKNOWLEDGEMENTS

Peter Bray and Lee Van Middlesworth at Otodynamic, who collaborated with technical knowledge whenever consulted. Prof. Erika Fukunaga for the statistical analysis. Mirtes, Sonia and Daniel, postgraduate secretaries, for their constant and indispensable help. Sadia Hussein Mustafá for the articles obtained and cataloging data. The Faculty of Medical Sciences at the Santa Casa de São Paulo and São Paulo's Holy House of Mercy Brotherhood. Capes for the scholarship grant provided. To those responsible for the newborns that accepted the invitation to participate in this study.

## RESUMO

Curva de crescimento das emissões otoacústicas produto de distorção em neonatos.

**Introdução:** o registro das emissões otoacústicas permitiu comprovar que a cóclea, além de receber os sons, produz energia acústica. Com a medida das emissões otoacústicas – produto de distorção (EOAPD), verifica-se o crescimento da resposta de acordo com a intensidade do estímulo sonoro apresentado (curva de crescimento).

**Objetivo:** determinar os limiares de surgimento das EOAPD nas frequências de 2.000 e 4.000 Hz com estímulo de 20 a 65 dB NPS e estabelecer os valores de *slope* obtidos nas curvas de crescimento.

**Métodos:** foram estudados 39 neonatos com 5 a 28 dias de vida sem indicadores de risco para perda auditiva. A captação das curvas de crescimento das EOAPD foi realizada em 2.000 e 4.000 Hz com nível de intensidade variando de 20 a 65 dB em dois paradigmas (20 a 40 dB NPS e 40 a 65 dB NPS).

**Resultados:** houve diferença estatística significativa dos limiares de surgimento das EOAPD dependendo do cri-

tério utilizado. Os limiares foram, em média, mais elevados em 4.000 Hz do que em 2.000 Hz, e o *slope* foi, em média, maior em 2.000 Hz do que em 4.000 Hz; porém, com diferença não significativa em ambos os casos.

**Conclusão:** os limiares de surgimento foram, em média, 30 dB NPS em 2.000 Hz e 35 dB NPS em 4.000 Hz. Os valores do *slope* variaram, em média, entre 3 e 4, chegando a 15 em alguns casos.

**Palavras-chave:** emissões otoacústicas espontâneas; testes auditivos; audição; recém-nascido.

## REFERENCES

1. Kemp DT. Stimulated acoustic emissions from within the human auditory system. *J Acoust Soc Am.* 1978;64(5):1386-91.
2. Ruggiero M, Rich N, Naryan SS, Robles L. Basilar-membrane responses to tones at the base of the chinchilla cochlea. *J Acoust Soc Am.* 1997;101(4):2151-63.
3. Gorga MP, Neely ST, Dierking DM, Kopun J, Jolkowski K, Groenenboom K, et al. Low-frequency and high-frequency cochlear nonlinearity in humans. *J Acoust Soc Am.* 2007;122(3):1671-80.
4. Abdala C. Distorsion product otoacoustic emission (2f1-f2) amplitude growth in human adults and neonates. House Ear Institute. *J Acoust Soc Am.* 2000; 107(1):446-56.
5. Kemp DT. Otoacoustic emissions, their origin in cochlear function, and use. *Br Med Bull.* 2002;63:223-41.
6. Dubno JR, Horwitz AR, Ahlstrom JB. Estimates of basilar-membrane nonlinearity effects on masking of tones and speech. *Ear Hear.* 2007;28(1):2-17.
7. Almeida PP. Crescimento das emissões otoacústicas evocadas-produto de distorção: estudo em neonatos [Dissertação] São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2010.
8. Gorga MP, Neely ST, Dorn PA, Konrad-Martin D. The use of distortion product otoacoustic emission suppression as an estimate of response growth. *J Acoust Soc Am.* 2002;111(1):271-84.
9. Gehr DD, Janssen T, Michaelis CE, Deingruber K, Lamm K. Middle ear and cochlear disorders result in different DPOAE growth behaviour: implications for the differentiation of sound conductive and cochlear hearing loss. *Hear Res.* 2004;193(1-2):9-19.
10. Janssen T, Niedermeyer HP, Arnold W. Diagnostics of the cochlear amplifier by means of distortion product otoacoustic emissions. *ORL J Otorhinolaryngol Relat Spec.* 2006;68(6):334-9.
11. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. Joint Committee on Infant Hearing 2007 Position Statement. *ASHA.* 1994;36:38-41.
12. Haddad GG, Green TP. Diagnostic approach to respiratory disease. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. *Nelson textbook of pediatrics.* 19th Philadelphia: Saunders Elsevier; 2011. chapter 366.
13. Almeida PP, Sanches SGG, Carvalho RMM. Limiar da função de crescimento das emissões otoacústicas por produto de distorção em neonatos *Pró Fono.* 2010;22(4):409-14.
14. Kummer P, Janssen T, Wolfgang A. The level and growth behavior of 2f1-f2 distortion product otoacoustic emission and its relationship to auditory sensitivity in normal hearing and cochlear hearing loss. *J Acoust Soc Am.* 1998;103(6):3431-44.
15. Neely ST, Johnson TA, Kopun J, Dierking DM, Gorga MP. Distortion-product otoacoustic input/output characteristics in normal-hearing and hearing-impaired human ears. *J Acoust Soc Am.* 2009;126(2):728-38.
16. Tiradentes JB, Coube CZV, Costa Filho OA. Estudo do padrão de respostas das curvas de crescimento (dp growth) das emissões otoacústicas produto

- de distorção em indivíduos com audição normal. *Rev Bras Otorrinolaringol.* 2002;68(1):21-6.
17. Boege P, Janssen T. Pure-tone threshold estimation from extrapolated distortion product otoacoustic emission I/O- functions in normal and cochlear hearing loss ear. *J Acoust Soc Am.* 2002;111(4):1810-8.
  18. Leme VN, Carvalho RMM. Nível de emissões otoacústicas por estímulo transiente e por produto de distorção em neonatos com e sem risco para perda auditiva. *J Bras Fonoaudiol.* 2005;(23):388-93.
  19. Costa JMD, Almeida VF, Oliveira CACP, Sampaio ALL. Emissões otoacústicas por estímulo transiente e por produto de distorção em recém-nascidos prematuros. *Arq Int Otorrinolaringol.* 2009;13 (3); 309-16.
  20. Aidan D, Lestang P, Avan P, Bonfils P. Characteristics of transient evoked otoacoustic emissions (TEOEs) in neonates. *Acta Otolaryngol.* 1997;117(1):25-30.
  21. Durante AS, Carvalho RMM, Costa FS, Soares JC. Characteristics of transient evoked otoacoustic emission in newborn hearing screening program. *Pró-Fono.* 2005;17(2):133-40.
  22. Sanches SGG, Sanchez TG, Carvalho RMM. Influence of cochlear function on auditory temporal resolution in tinnitus patients. *Audiol Neurootol.* 2010;15(5):273-81.

# Diagnostic accuracy of respiratory diseases in primary health units

BRUNO PIASSI DE SÃO JOSÉ<sup>1\*</sup>, PAULO AUGUSTO MOREIRA CAMARGOS<sup>2</sup>, ÁLVARO AUGUSTO SOUZA DA CRUZ FILHO<sup>3</sup>, RICARDO DE AMORIM CORRÊA<sup>4</sup>

<sup>1</sup>Master and Doctoral student of medicine - Postgraduate degree in Infectology and Tropical Medicine, Federal University of Minas Gerais Medical School - Physician at the Hospital das Clínicas -UFMG Pneumology Outpatient Clinic, Belo Horizonte, MG, Brazil

<sup>2</sup>Visiting Professor at the Pediatric Department - UFMG Medical School, Belo Horizonte, MG, Brazil

<sup>3</sup>ProAr - Center for Excellence in Asthma, Federal University of Bahia, Salvador, BA, Brazil

<sup>4</sup>Adjunct Professor IV- UFMG Medical School, Belo Horizonte, MG, Brazil

## SUMMARY

Respiratory diseases are responsible for about a fifth of all deaths worldwide and its prevalence reaches 15% of the world population. Primary health care (PHC) is the gateway to the health system, and is expected to resolve up to 85% of health problems in general. Moreover, little is known about the diagnostic ability of general practitioners (GPs) in relation to respiratory diseases in PHC. This review aims to evaluate the diagnostic ability of GPs working in PHC in relation to more prevalent respiratory diseases, such as acute respiratory infections (ARI), tuberculosis, asthma and chronic obstructive pulmonary disease (COPD). 3,913 articles were selected, totaling 30 after application of the inclusion and exclusion criteria. They demonstrated the lack of consistent evidence on the accuracy of diagnoses of respiratory diseases by general practitioners. In relation to asthma and COPD, studies have shown diagnostic errors leading to overdiagnosis or underdiagnosis depending on the methodology used. The lack of precision for the diagnosis of asthma varied from 54% underdiagnosis to 34% overdiagnosis, whereas for COPD this ranged from 81% for underdiagnosis to 86.1% for overdiagnosis. For ARI, it was found that the inclusion of a complementary test for diagnosis led to an improvement in diagnostic accuracy. Studies show a low level of knowledge about tuberculosis on the part of general practitioners. According to this review, PHC represented by the GP needs to improve its ability for the diagnosis and management of this group of patients constituting one of its main demands.

**Keywords:** respiratory tract diseases, primary health care, diagnosis, general practitioners, review.

Study conducted at the Post-Graduation Program of Infectology and Tropical Medicine, Medical School, Federal University of Minas Gerais Belo Horizonte, MG

Article received: 3/8/2014

Accepted for publication: 3/24/2014

\*Correspondence:

Address: Rua Nunes Vieira 304/1303, Santo Antonio

Postal Code: 30350-120

Belo Horizonte - MG

niraldo@usp.br

niraldosp@uol.com.br

<http://dx.doi.org/10.1590/1806-9282.60.06.021>

Conflict of interest: none

## INTRODUCTION

According to the World Health Organization (WHO), 20% of the 59 million annual deaths by all causes are due to respiratory tract diseases.<sup>1,2</sup> Among these, acute respiratory infections (ARI) occupy third place (3.6 million deaths; 6.1% of the total), while chronic obstructive pulmonary disease (COPD) occupies fourth place, with 3.28 million deaths (5.8% of the total), and will reach third place by 2030 according to projections.<sup>3-5</sup>

More than a billion people worldwide - 15% of the global population - suffer from some kind of chronic res-

piratory disease, with half affected by one of the two most prevalent conditions: asthma (235 million)<sup>6</sup> or COPD (210 million).<sup>7</sup> Owing to this, around a third of appointments at primary health care (PHC) units worldwide are due to respiratory diseases.<sup>1</sup>

Among the difficulties encountered in PHC in relation to this group of diseases, we can mention imprecision in the diagnosis of asthma and COPD<sup>8-10</sup> and excessive prescription of antibiotics for the treatment of acute respiratory diseases.<sup>1,11,12</sup> In general, little is known about

diagnostic ability and the elaboration of treatment plans for these conditions by PHC physicians, as well as the factors influencing them.

This article presents a review of the literature with respect to the diagnostic accuracy of general physicians in PHC in relation to the most prevalent respiratory diseases and those of greatest interest for public health, including ARI, tuberculosis, asthma and COPD.

## METHODS

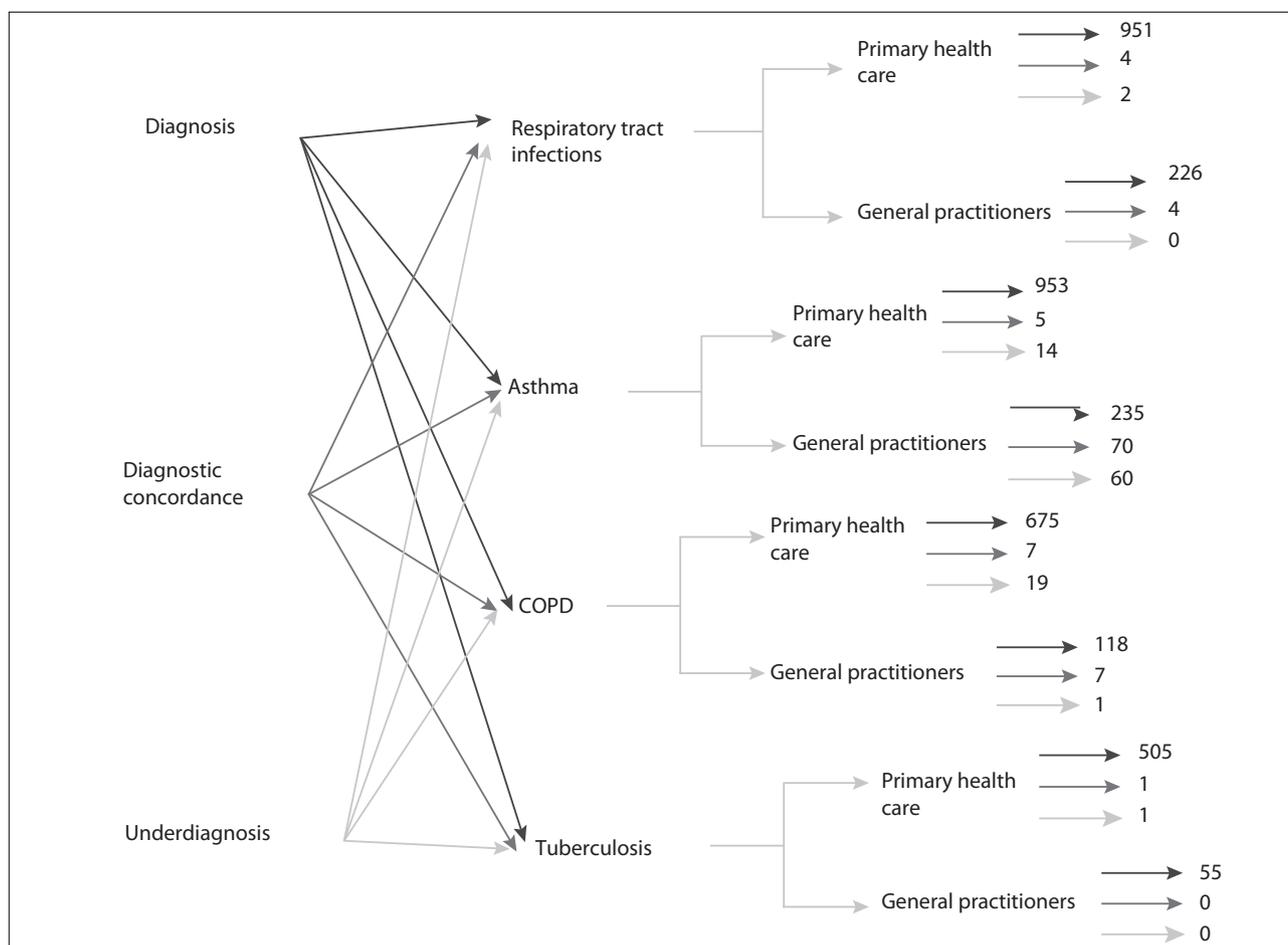
A search of the literature was undertaken for articles assessing the concordance between the diagnosis by PHC physicians and specialists in respiratory diseases for the main respiratory illnesses in PHC services. The review also included studies using supplementary reference exams (spirometry) for asthma and COPD; acid-fast bacilli (AFB) tests for tuberculosis and C-reactive protein (CRP) and procalcitonin for ARI or for making clinical decisions, such as prescribing antibiotics.

The literature review was conducted using the PUBMED database covering the period from 1/1/1992 to 8/1/2012, limited to studies conducted on humans and published in Portuguese, English and Spanish.

In the selection, cross-referencing was performed using these groups of MeSH keywords with free terms (FT) of relevance to the research: “diagnosis” (MeSH), “underdiagnosis” (TL) e “diagnostic concordance” (TL) com “respiratory tract infections” (MeSH), “asthma” (MeSH), “COPD” (MeSH) and “tuberculosis” (MeSH) with “primary health care” (MeSH) and “general practitioners” (MeSH; Figure 1).

As a result of the lack of studies about this issue in the literature, differences in methodology or the definitions of conditions were not used as exclusion criteria, as will be discussed below.

The diseases included in this review were ARI, asthma, COPD and tuberculosis. Articles that included other diseases such as sleep apnea, lung cancer and other respiratory diseases were excluded.



**FIGURE 1** System for searching articles according to the keywords and number of articles found in each cross-reference.

## RESULTS

Thirty of the 3,913 articles encountered were selected according to the following flowchart (Figure 2).

Articles assessing the diseases of interest were not found in this set. The methodological heterogeneity encountered did not meet the criteria for conducting a meta-analysis. The results will be presented organized as follows: acute respiratory infections, tuberculosis, asthma, COPD, and asthma and COPD in conjunction.

### Acute respiratory infections - ARI

#### Upper respiratory tract infections

Among studies of upper respiratory tract infections (URTI), two used C-reactive protein (CRP) or used it as diagnostic aid, or as a reference method for assessment of diagnostic accuracy.

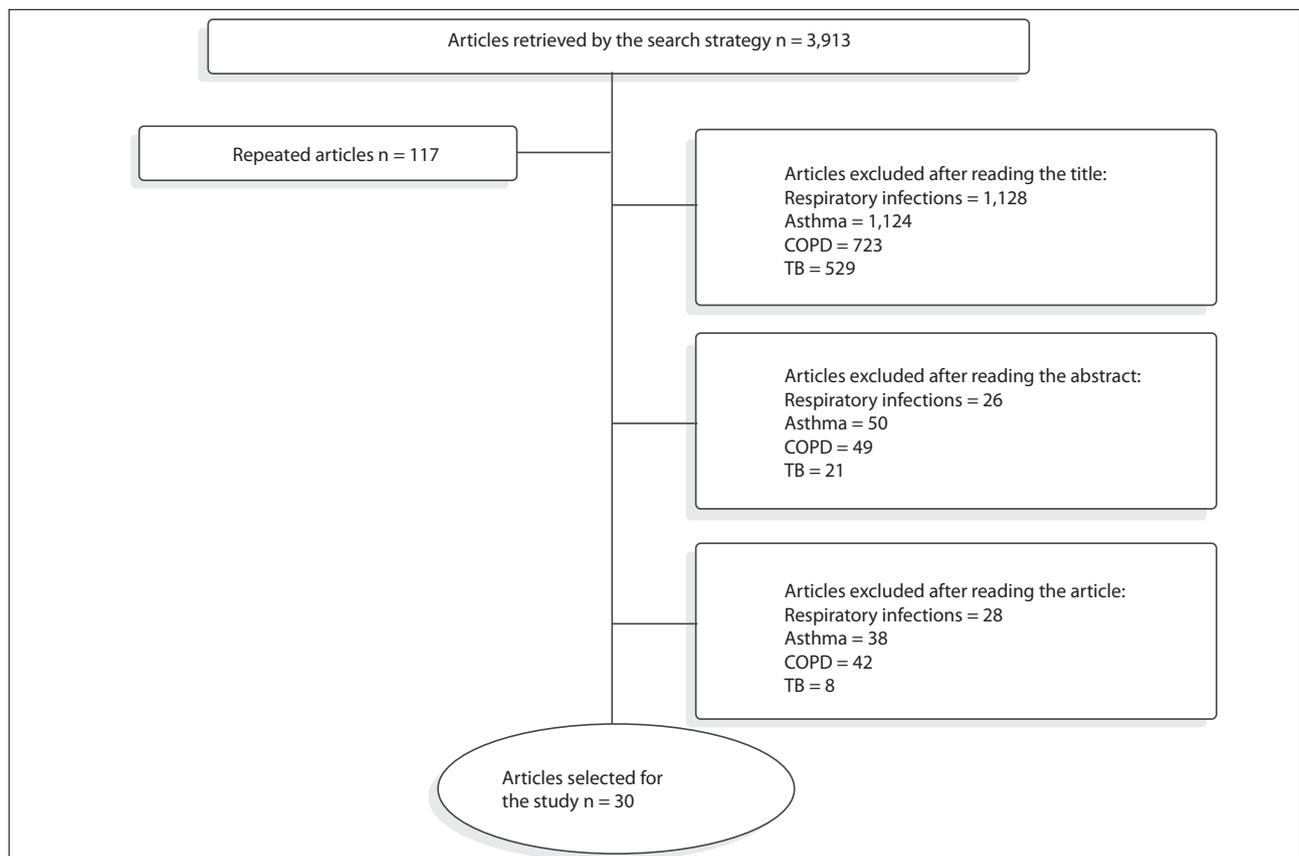
A single study verified the accuracy of the upper respiratory tract disease diagnosis. The authors evaluated the accuracy of the clinical diagnosis of pharyngitis using CRP dosage and leukocyte count in the two phases of the

study.<sup>13</sup> Another study also used the CRP as an auxiliary tool in the diagnosis of acute bacterial rhinosinusitis and prescription of antibiotics.<sup>14</sup>

Only one study assessed the concordance between general practitioners and specialists (pediatricians and ENT specialists) through a standardized questionnaire in the management of children with recurrent tonsillitis. There was disagreement between the signs and symptoms evaluated by the ENT specialists and general practitioners in the diagnosis of tonsillitis, pharyngitis or upper respiratory tract infection.<sup>15</sup>

#### Lower respiratory tract infections

Studies assessing the concordance or comparing the diagnosis and conduct of general physicians and specialists for lower respiratory tract infections were not encountered. The few studies encountered compared the diagnosis by general practitioners with a reference exam and are grouped in Table 1.<sup>11</sup>



**FIGURE 2** Flowchart for selection of articles according to the criteria adopted in the review.

**TABLE 1** Synopsis of the articles relating to acute respiratory tract infections (ARI), tuberculosis, asthma, COPD, and asthma and COPD in conjunction

Ref. <sup>1</sup>	Author, year, country	Main objective	Reference method	Study design	N° of patients; age group; mean age	N° of physicians	Results
ARI Upper tract	13	Gulich et al., 1999, Germany To assess whether the measurement of CRP <sup>2</sup> improves the accuracy of diagnosis of pharyngitis	CRP <sup>2</sup> and leukocyte count in the blood	Cross-sectional	Phase I: 179 Phase II: 161; 16-75; 34.3	15 phase I 14 phase II	Improvement in accuracy from 70 to 81% when they had access to exams. The ROC curve <sup>3</sup> showed that the diagnostic value of CRP <sup>2</sup> was better than the leukocyte counts (area under the curve = 0.85 versus 0.68)
	14	Bjerrum et al., 2004, Denmark To assess whether generalists using CRP <sup>2</sup> in their practice prescribe fewer antibiotics for sinusitis that generalists who do not	CRP <sup>2</sup>	Cross-sectional	1,444; 31-53; 40	367	Physicians who requested the test prescribed 20% fewer antibiotics. The request and the level of CRP <sup>2</sup> had a strong influence on prescribing antibiotics for sinusitis
	15	Capper et al., 2001, United Kingdom To assess agreement between general practitioners, pediatricians and ENT specialists on the conduct among children with recurrent tonsillitis	Non previously validated questionnaire answered by doctors	Cross-sectional	Does not apply	71 GPs, 57 pediatricians, 42 ENT specialists	Little agreement among GPs, pediatricians and ENT specialists about the diagnosis of tonsillitis and indication for tonsillectomy
ARI Lower tract	11	Hopstaken et al., 2002, Netherlands To evaluate the diagnostic value of signs, symptoms, ESR <sup>4</sup> and CRP <sup>2</sup> for pneumonia	Chest X-ray	Cross-sectional	246; 18-89; 52	25	Of the 246 patients included, 32 (13%) had radiographs consistent with pneumonia. GPs diagnosed pneumonia in 21 patients using only clinical examination. Antibiotics were prescribed for 193 (78.4%) patients. The authors concluded that the prescriptions could have been avoided in 80 (41%) patients with probable diagnosis of acute bronchitis who received unnecessary antibiotics

(continues)

**TABLE 1** Synopsis of the articles relating to acute respiratory tract infections (ARI), tuberculosis, asthma, COPD, and asthma and COPD in conjunction (continuation)

ARI Upper and lower tract	12	Briel et al., 2008, Switzerland	To compare the usual approach to approach guided by PCT(5)	PCT <sup>5</sup>	Randomized trial	458; 33-63; 48	53	The 458 patients with acute respiratory infections that, in their physicians' opinion, needed antibiotics were randomized to either a group of usual care or a group of care guided according to the results of PCT. <sup>5</sup> When PCT was used by GPs as a discriminating factor in relation to clinical assessment, those who used it received 72% less antibiotic prescriptions than the other group
	16	Cirit et al., 2003, Turkey	Assessment of knowledge of GPs and pulmonary specialists on diagnosis and treatment of tuberculosis	Analysis of a questionnaire completed by professionals	Cross-sectional	Does not apply	203	Significant difference on knowledge of the diagnosis and treatment of tuberculosis among specialists and generalists in primary care. The main differences were in combination of drugs for treatment, infection duration, and medical management in cases of resistance
Tuberculosis	17	Al-Maniri et al., 2008, Oman	To evaluate suspicion of tuberculosis by GPs in units of public and private health	Questionnaire related to five clinical cases	Cross-sectional	Does not apply	257	The general index of suspicion was only 37.7% of GPs and public hospitals had a better degree of suspicion compared to private units (27.3 versus 53.4%, p = 0.001)
	18	Hong et al., 1995, South Korea	Knowledge, attitudes and practices of GPs	Responses to questionnaire	Cross-sectional	Does not apply	923	More than 50% do not consider the sputum examination essential for diagnosis, and 75% to monitor response to treatment. For initial treatment of active tuberculosis, only 11% prescribed in accordance with government guidelines. More than 73% were using treatment regimens that are not recommended and 16% unacceptable regimens
	19	Singla et al., 1998, India	Knowledge, attitudes and practices of doctors in the private system	Responses to questionnaire	Cross-sectional	Does not apply	204	In suspected cases of tuberculosis only 22 (12%) of GPs requesting sputum AFB smear <sup>6</sup> for diagnosis. Only 66 (18%) search contacts, and 39 (19.5%) guide the patient to regular treatment

(continues)

**TABLE 1** Synopsis of the articles relating to acute respiratory tract infections (ARI), tuberculosis, asthma, COPD, and asthma and COPD in conjunction (continuation)

20	Marklund et al., 1999, Sweden	To estimate the frequency of diagnostic errors in asthma by GPs	Review by allergy specialist, spirometry and bronchial challenge test whenever there is diagnostic uncertainty	Cross-sectional	123; >18 years; no reports	6	One hundred and twenty three patients completed the inclusion criteria and were invited for further consultation. Eighty six of these (70%) accepted the invitation. At the end, 51/86 (59%) had asthma, six (7%) had asthma combined with COPD, and 29 (34%) had no asthma
21	Montnémy et al., 2002, Sweden	Assess whether the low prevalence of asthma was caused by underdiagnosis in primary care. The study also assessed the validity of the first diagnosis of asthma by GPs in primary care	Evaluated by pulmonary specialists	Cross-sectional	3,025; ≥18 years; no reports	100	99 patients were diagnosed with asthma and were reevaluated by pulmonologists. The diagnosis of asthma was validated on 52 cases (76.5%), with a sensitivity of 0.59 (95% CI 0.31-0.81) and specificity of 0.99 (95% CI 0.99-1.00). These results indicated that 23.5% of patients were diagnosed as asthmatic by GPs without actually having the disease
9	Adams et al., 2003, Australia	To compare the clinical diagnosis of asthma by GPs with spirometry	Spirometry	Cross-sectional	3,422; ≥18 years; no reports	Not informed	Of the 3,422 individuals interviewed, 2,523 (74%) agreed to participate in the clinical assessment, and 292 (11.6%) had asthma according to spirometric criteria. Of this total, 236 (9.3%) had a previous, self-reported, diagnosis of asthma, and 56 (2.3%) were unaware of the diagnosis and were defined as having asthma according to spirometric criteria. Thus, the group diagnosed with asthma by spirometry, 56 (19.2%) had no previous diagnosis of asthma
10	Hahn et al., 1994, United States	Describe the epidemiology of diagnosis, and the possible underdiagnosis of asthma	Responses to questionnaire	Cross-sectional	14,127; All age groups; 15	59	Of the total sample, 13,542 (95.5%) answered the questionnaire properly. Of this total, 10.3% reported having previous medical diagnosis of asthma. The study revealed that 6.5% of patients who had wheezing had no previous diagnosis of asthma (underdiagnosis)

(continues)

Asthma

**TABLE 1** Synopsis of the articles relating to acute respiratory tract infections (ARI), tuberculosis, asthma, COPD, and asthma and COPD in conjunction (continuation)

Asthma	22	Ward et al., 2004, United Kingdom	Assessed the under- and overdiagnosis of asthma in patients aged 16-55 years in primary care	Analysis of questionnaire answered by the patients themselves	Cross-sectional	833 patients and 831 controls; 16-55; 34.3 average	8	The response rate was 79.1% (659/833). Among the respondents, 60.5% (399/659) had symptoms of bronchial hyperactivity; among those without bronchial hyperactivity, 73.1% (190/260) were considered asthmatic according to a review of their medical records. The authors concluded that there is a chance of 89.4% that patients with this diagnosis reported in their medical records do in fact have asthma
	23	Bednarek et al., 2008, Poland	To investigate the prevalence and severity of COPD in primary units	Responses to a questionnaire and spirometry	Cross-sectional	2,250; 40-93; 56.7	2	Out of the 183 (9.3% of total) patients diagnosed with COPD based on responses to a questionnaire and spirometry, only 34 (18.6%) had a previous diagnosis
COPD	24	Geijer et al., 2005, Netherlands	To determine the prevalence of underdiagnosis of airflow obstruction according to the GOLD criteria <sup>7</sup>	Responses to a questionnaire and spirometry	Cross-sectional	3,985; 40- 65; 50	Not informed	Among the 702 who responded and possessed an acceptable and reproducible spirometry, 201 (29.9%) had an obstructive pattern not previously detected
	26	Roberts et al., 2009, United Kingdom	To define the predictive value of clinical diagnosis or suspicion of COPD in primary care patients presenting spirometric criteria for diagnosis according to GOLD <sup>7</sup>	Spirometry	Cross-sectional	677; Not defined; 63.8	Not informed	Of the 503 who had clinical diagnosis and were referred for evaluation of disease severity, 141 (28%) patients presented normal spirometry. The remaining 302/503 (60%) had obstruction of air flow and possible COPD according to the GOLD criteria, <sup>7</sup> stage 2. The positive predictive value of the diagnosis of COPD in primary care was 0.62 for patients referred for severity assessment and 0.56 for patients referred for diagnostic testing
	27	Zwar et al., 2011, Australia	Comparison of the clinical diagnosis of COPD in primary care GPs with spirometry	Spirometry	Cross-sectional	1,144; 40-80; 65	56	Of the 1,144 patients identified, 445 (38.9%) agreed to participate, undergoing spirometry. Of these, 257 (57.8%) had spirometry consistent with COPD; i.e., in this study, there was about 40% overdiagnosis and many patients were treated unnecessarily

(continues)

**TABLE 1** Synopsis of the articles relating to acute respiratory tract infections (ARI), tuberculosis, asthma, COPD, and asthma and COPD in conjunction (continuation)

28	Walters et al., 2011, Australia	To evaluate the diagnostic errors of COPD in primary units	Spirometry	Cross-sectional	1,200; Not informed; 65	31	Of the 1,200 patients identified, 341 (58%) underwent spirometry and 234 (69%) had a confirmed diagnosis. In 31% of cases, diagnostic errors were found
29	Hamers et al., 2006, Brazil	To assess the competence of GPs in primary care regarding the diagnosis of COPD	Spirometry	Cross-sectional	350; ≥ 15 years; 46.8	34	Of the 142 (44.9%) patients who underwent spirometry, 94 (66%) had been correctly diagnosed by the GPs (Kappa = 0:55), nine with confirmed COPD and 85 without COPD. The remaining 48 (34%) were discordant: 27 had COPD according to the spirometry and were not diagnosed by the GPs, and 21 were false positives
30	Joo et al., 2011, United States	To examine the characteristics associated with the use of spirometry in primary care with increased risk for COPD and to determine the diagnostic accuracy of spirometry in patients with COPD	Spirometry	Cohort	1,052; ≥ 35; 57	Not informed	A total of 1,052 patients were identified and 527 (50%) had spirometry. Of the 159 patients identified as COPD, 93 (58.5%) met the GOLD criteria. <sup>7</sup> Of the 362 without a diagnosis of COPD, 93 (25.7%) had COPD according to the same criteria. It was also found that chronic cough or dyspnea were more associated with a request for spirometry than current or previous smoking habits
31	Hill et al., 2010, Canada	To measure the prevalence of COPD in patients aged over 40 years with a smoking history	Spirometry and clinical assessment	Cross-sectional	1,459; ≥40; 60	Not informed	Of the 1,459 eligible patients, 1,003 underwent spirometry and completed a questionnaire. Of these, 208 (20.7%) had spirometric criteria for COPD according to GOLD <sup>7</sup> , 2, FEV1/FVC<0.70 <sup>8,9</sup> and FEV1<0.80). <sup>8</sup> Only 67 (32.7%) had a previous diagnosis of COPD
32	Pearson et al., 2003, United Kingdom	To assess the impact of spirometry and clinical evaluation in the diagnosis of airway diseases	Spirometry and questionnaire applied by the nursing staff	Cross-sectional	61,191; ≥40; 66.7	1,003	The evaluation showed improper base diagnosis with change in 54% of diagnoses of asthma, COPD in 14% and 63% for other conditions

(continues)

**TABLE 1** Synopsis of the articles relating to acute respiratory tract infections (ARI), tuberculosis, asthma, COPD, and asthma and COPD in conjunction (continuation)

33	Melbye et al., 2011, Norway	To describe symptoms and lung function in patients diagnosed with asthma or COPD in primary care and to describe how the results of spirometry fit the diagnoses made by GPs	Spirometry	Cross-sectional	367; ≥40; 62	Not informed	<p>The diagnosis of COPD was confirmed by spirometry and according to GOLD<sup>7</sup> criteria in 68.1% of patients, while the diagnosis of asthma was confirmed in 17.1%. The kappa agreement between the diagnosis of COPD in the medical record with the spirometric diagnosis was 0.50. Spirometry helped confirm that patients had a mixed disease but did not discriminate between asthma and COPD in all cases</p>
34	Izquierdo et al., 2010, Spain	Goal was to analyze the diagnostic accuracy in patients receiving inhaled medications in primary care	Spirometry	Cross-sectional	9,931; ≥18; 58.3	1,449	<p>4,188 (42.9%) had a diagnosis of asthma, 4,175 (42.8%) had a diagnosis of COPD, and 1,389 had non-identifiable diagnoses. Among patients aged over 40 years with diagnoses of COPD and spirometry (50.9%), only 13.9% met the GOLD criteria<sup>7</sup></p>
35	Weidinger et al., 2009, Sweden	To assess adherence to guidelines in primary care in patients with asthma and COPD	Swedish national guidelines for asthma and COPD	Cross-sectional	623; All age groups; not informed	Not informed	<p>Adhesion was found in 130/499 (26%) of patients with initial diagnosis of asthma and 35/124 (28%) of patients with initial diagnosis of COPD</p>
36	Raghunath et al., 2006, United Kingdom	To assess differences in the interpretation of spirometry and peak expiratory flow (PEF) between primary care GPs and pulmonary specialists in patients with a previous diagnosis of asthma or COPD	Pulmonologists	Cohort	102; ≥45 years; not informed	Not informed	<p>The concordance between the diagnoses of generalists and specialists (Kappa) in the evaluation of tests was 0.20</p>

(continues)

**TABLE 1** Synopsis of the articles relating to acute respiratory tract infections (ARI), tuberculosis, asthma, COPD, and asthma and COPD in conjunction (continuation)

37	Starren et al., 2012, United Kingdom	To check the operation of a unit of reference for respiratory conditions by reviewing the diagnoses of referrals from GPs	Pulmonologists	Cross-sectional	1,156; All age groups; 61.3	28	Of the 1,156 patients referred, COPD was the most common cause (445/666; 66.8%); over one third of the diagnoses suggested by GPs were incorrect (161/445; 36%)
38	Lucas et al., 2012, Netherlands	To assess what criteria GPs use to justify their diagnostic hypothesis of asthma and COPD; whether the evaluations by experts cause changes in diagnoses of GPs; and whether to make GPs justify their diagnostic hypotheses, influences the diagnosis given in the reference center	Pulmonologists	Cross-sectional	284; 2-88; 51	17	Only 50% of diagnostic hypotheses were confirmed by the specialized service. The chances of asthma were confirmed more frequently (62%) than those of COPD (40%). The justifications for the diagnostic hypotheses of GPs did not influence the results
39	Broekhuizen et al., 2010, Netherlands	To determine the frequency of asthma or COPD in people aged over 50 years who consult their GPs because of persistent cough	Panel with an experienced GP and a pulmonary specialist	Cross-sectional	353; ≥50; 63	73	After evaluation of pulmonary function tests and discussion of clinical data by a panel of two doctors, it was concluded that 29% of patients had a diagnosis of COPD, 7% had asthma, and 4% were diagnosed with mixed disease. It should be reiterated that these diagnoses were new, that is, they were not previous diagnoses made by assistant GPs

<sup>1</sup>Ref. - Reference, <sup>2</sup>CRP - C-reactive Protein, <sup>3</sup>ROC - receiver operating characteristics curve, <sup>4</sup>ESR - Erythrocyte sedimentation rate, <sup>5</sup>PCT - Procalcitonin <sup>6</sup>AFB - Acid-fast bacilli, <sup>7</sup>GOLD - Global Initiative for Lung Chronic Obstructive, <sup>8</sup>FEV1 Forced expiratory volume in 1 second, <sup>9</sup>FVC- Forced vital capacity.

### *Pulmonary tuberculosis*

Few studies about tuberculosis that fulfilled the inclusion criteria were encountered (Table 1). Only one reported the degree of suspicion of diagnosis or knowledge on the part of general practitioners and specialists, though this was not the main focus of the article and not directly assessed,<sup>16</sup> while the other studies only assessed the knowledge or degree of suspicion of tuberculosis by general practitioners.<sup>17-19</sup>

### *Asthma*

In the case of asthma, only two studies evaluated the diagnostic ability of general practitioners through a follow up evaluation by experts (Table 1).<sup>20,21</sup>

The first, conducted in Sweden in 1994 included patients aged over 18 years visiting general practitioners in selected PHC, verifying the frequency of errors in relation to asthma diagnosis by general practitioners. The patients with this diagnosis established in the medical records were invited to be examined by allergists. The diagnoses were discussed by a group that included a general practitioner and a nurse, in addition to the allergist. One hundred and twenty-three patients fulfilled the inclusion criteria and were invited to another consultation. 86 of these (70%) accepted the invitation. At the end, 51/86 (59%) had their asthma diagnosis confirmed, six (7%) were diagnosed with an asthma-COPD association and 29 (34%) did not have asthma, i.e. they were initially wrongly diagnosed.<sup>20</sup>

The second, also conducted in Sweden, investigated whether the low level of asthma diagnoses was due to underdiagnosis in PHC, as well as assessing the validity of the first asthma diagnosis by general practitioners. Over the course of three months in 1997, all patients seeking medical assistance at PHC units in the district of Lund with upper or lower respiratory tract infections, prolonged cough, allergic rhinitis, dyspnea or a first positive diagnosis of asthma were recorded (n=3,025). Ninety-nine were diagnosed with asthma and reassessed by pulmonologists. The results indicated that 23.5% of patients were mistakenly considered as asthmatic by general practitioners.<sup>21</sup>

Three other articles were evaluated: one assessed the concordance between the clinical diagnosis of asthma undertaken previously by the general practitioner with the spirometry results;<sup>9</sup> the other two assessed the underdiagnosis of asthma and used an non-validated questionnaire as a diagnostic tool, without specialized clinical assessment or spirometry.<sup>10,22</sup>

In the five studies selected, overdiagnosis varied from 10.6<sup>22</sup> to 34%<sup>20</sup> and underdiagnosis from 6.5<sup>10</sup> to 19.2%.<sup>9</sup>

### *COPD*

Studies whose main focus was to assess the concordance between the diagnosis by PHC physicians and specialists were not encountered. The selected studies, which compared the diagnosis by general practitioners and spirometry results revealed mistakes in the diagnosis, characterized by both under and overdiagnosis.

In the eight studies selected<sup>23-31</sup> overdiagnosis varied from 28<sup>26</sup> to 40%<sup>23</sup> while underdiagnosis, from 25.7<sup>30</sup> to 81.4%.<sup>23</sup>

A study conducted in Brazil assessed the concordance between the diagnosis by PHC general practitioners and spirometry according to the criteria established by the GOLD initiative. 94 (66%) of the 142 (44.9%) of patients undergoing spirometry had concordant diagnoses with that of the general practitioners (Kappa = 0.55), with 9 having a confirmed diagnoses and 85 without COPD. The remainder (48; 34%) was discordant: 27 had COPD according to the spirometry and were not diagnosed by the general practitioners, and 21 were false positives. In this study, the variables associated with the spirometric diagnosis of COPD were: being male, having a rural origin, the presence of dyspnea and cough, being a current smoker, being over 55 years, and exposure to smoke from wood stoves.<sup>29</sup>

### *Asthma and COPD*

The studies encountered that evaluated asthma and COPD in conjunction are heterogeneous in relation to the methodologies employed. In the eight studies recovered,<sup>32-39</sup> the variation in the overdiagnosis of COPD was 36<sup>37</sup> to 86.1%,<sup>34</sup> while for asthma this was 38<sup>38</sup> to 74%.<sup>35</sup> The variation in the underdiagnosis of COPD was 14<sup>32</sup> to 29%,<sup>39</sup> while for asthma this was 7<sup>39</sup> to 54%.<sup>32</sup> The majority used an evaluation of the database followed by reassessment of patients, with the exception of one study based on the patient's symptoms at a spontaneous visit to a primary care unit.<sup>39</sup>

For example, the Cadre study (*COPD and Asthma Diagnostic/management Reassessment*), conducted in the United Kingdom involved more than a thousand GPs and included over 60 thousand patients who had been treated for a respiratory condition and were reassessed using a standardized questionnaire applied by nurses, as well as spirometry. An experienced GP then evaluated the questionnaire, spirometry results and made the diagnosis. This new assessment showed incorrect diagnosis, with a 54%

increase in the diagnosis of asthma, 14% increase in COPD and 63% increase in other diseases.<sup>32</sup>

Broekhuizen et al.<sup>39</sup> assessed patients aged over 50 with persistent cough lasting more than 14 days without a previous diagnosis of asthma or COPD. After evaluating the lung function tests and discussing the clinical data in a panel formed by two physicians, it was concluded that 29% of patients had a diagnosis of COPD, 7% had asthma and 4% an overlapping condition. It should be reiterated that these diagnoses were new, that is, there was no previous diagnosis made by assistant general practitioners (Table 1).<sup>39</sup>

## DISCUSSION

This comprehensive literature review found that despite the methodological heterogeneity of the studies encountered, the accuracy of acute and chronic respiratory disease diagnoses elaborated by general practitioners in primary health care is low.

Even those approaching the conditions separately presented different methodological delineations and aspects, which hindered the interpretation and elaboration of definitive conclusions. As an example, the imprecision of the asthma diagnosis varied from 54% underdiagnosis to 34% overdiagnosis,<sup>32,20</sup> while for COPD there was 81% underdiagnosis up to 86.1% overdiagnosis.<sup>23,34</sup> This heterogeneity may have occurred, at least in part, because the studies were not randomized, due to the diversification in sampling and definitions of each disease, and the variables considered in the populations analyzed.

In relation to ARI, the use of auxiliary diagnostic exams almost always resulted in improved diagnostic accuracy and consequent decrease in the prescription of antibiotics.<sup>12,14</sup>

In relation to tuberculosis, the better results from specialists over those from general practitioners in primary care seem obvious and natural, but as it is a condition of interest to national and international public health, a better performance was expected from general practitioners.<sup>16</sup> The studies encountered prove the low level of knowledge about tuberculosis by general practitioners working in primary care.<sup>18,19</sup>

Underdiagnosis and thus under-treatment may present a significant impact on the increased morbidity and mortality of respiratory diseases.<sup>40,41</sup> Similarly, overdiagnosis may lead to increased costs and possible collateral effects related to unnecessary treatment.

The literature reviewed places the general practitioner as the key player in the context of mistaken diagnosis, whether through lack or excess. In both cases, the degree of lia-

bility of accidents for the mistakes cannot be determined. It is also difficult to determine on what proportion it can be defined as systematic errors relating to difficulties accessing exams, or cognitive errors by general practitioners - errors owing to interpretation of signs and symptoms when the patient presents them. In other words, some authors interrogate if under diagnosis is due to the inappropriate interpretation of symptoms by the physician or the patients' failure to express their symptoms to the doctor.<sup>42-45</sup>

Another point to consider is that the slow and progressive nature of diseases such as asthma and COPD seems to lead to a decreased perception of their manifestations. Cough and reduced tolerance to exercise may be seen as normal phenomena in certain age ranges. As a result, patients do not seek general practitioners and in an eventual appointment may fail to report such symptoms to their physician.<sup>46</sup>

For around 50 years it was thought impossible for blood pressure to be measure by nurses or nursing technicians. Nowadays the importance of these professionals in official blood pressure control programs is recognized. Thus, a multi-professional strategy in the detection of high prevalence diseases should be implemented as opposed to focusing solely on experts, a common approach at present.<sup>46</sup> For example, the incorporation of simple questions in the routine of health professionals, such as "Do you smoke? Do you want to stop smoking?", as part of a program could significantly increase the diagnosis of COPD and the effectiveness of programs for smoking cessation.

The common sense that the context of PHC is less complex than those with medium to high complexity seems incorrect. PHC has the most extensive clinical practice and is where interventions of high complexity should be undertaken, such as those relating to changes in behavior and lifestyles in relation to health, including stopping smoking, adopting healthy eating behaviors and physical activity, among others. The secondary and tertiary levels of care include practices with higher technological density, but not necessarily higher complexity. This distorted view of complexity, whether singular or systematic, leads politicians, managers, health professionals and the population as a whole, to overvalue the practices that are carried out at the secondary and tertiary levels of health care and, consequently, to a trivialization of PHC.<sup>47</sup>

In the cases of the most prevalent diseases and those of major interest in the management of public health, it is expected that PHC physicians should obtain high detection rates, or at least higher levels of sensitivity, considering the fact that they provide front line medical atten-

tion, where the lack of a medical diagnosis will result in increased morbidity or the occurrence of acute and chronic complications. Specialists have a supporting role in the diagnosis and monitoring of the more complex cases. The detection process should be primarily the responsibility of primary care, which presupposes adequate training of GPs and the implementation of a horizontal care program including the provision of medication and supplementary exams to diagnostics so that respiratory diseases can be identified and treated at an early stage.

This review includes some limitations which should be discussed. Some studies about ARI only compared prescriptions for antibiotics and did not verify the quality and accuracy of the diagnosis.<sup>11,12,14</sup> Other works assessed accuracy as a secondary outcome.<sup>15</sup> Methodological differences within the same group may have compromised these results, at least in part. Various differences can be highlighted, since the stage of inclusion criteria: database or spontaneous demand reviews, age, history of smoking, through to definition of the COPD diagnosis, with some using the GOLD 1 (FEV1/FVC <70) criteria, others GOLD 2 (FEV1/FVC <70 and FEV1 <80%), while in others the criteria were not clearly defined. Another limitation that can be cited is the extraction of data by a single researcher, which may have affected the reproducibility of the results.

## CONCLUSION

The results prove, in a general manner, that there are diagnostic errors and that the level of knowledge of respiratory diseases by general practitioners in various countries is lower than desired. To better understand the reality of healthcare in PHC, further studies with methodologies better defined regarding inclusion criteria and assessment tools, should be conducted. Their results could support the adoption of consistent policies for improving healthcare as a whole.

## RESUMO

Precisão diagnóstica de doenças respiratórias em unidades primárias de saúde.

As doenças respiratórias acometem 15% da população do planeta e respondem por 1/5 dos óbitos no mundo. Espera-se que a atenção primária à saúde (APS), primeira instância da assistência médica, solucione até 85% dos problemas de saúde em geral. Pouco se sabe a respeito da habilidade de médicos generalistas da APS em relação ao diagnóstico das doenças respiratórias. Esta revisão refere-se à habilidade diagnóstica de médicos ge-

neralistas que atuam na APS em relação às doenças respiratórias mais prevalentes, como doenças respiratórias agudas (IRA), tuberculose, asma e doença pulmonar obstrutiva crônica (DPOC). Dentre 3.913 artigos, 30 foram selecionados após aplicação dos critérios de inclusão e exclusão. Ficou demonstrada a carência de dados consistentes sobre a acurácia dos diagnósticos de doenças respiratórias elaborados por generalistas. Em relação à asma e à DPOC, os estudos demonstram erros diagnósticos que levam ao sobrediagnóstico ou ao subdiagnóstico, dependendo da metodologia usada. A imprecisão do diagnóstico de asma variou de 54% de subdiagnóstico a 34% de sobrediagnóstico; para DPOC, houve variação de 81% de subdiagnóstico a 86,1% de sobrediagnóstico; para IRA, verificou-se que a inclusão de exame complementar de auxílio diagnóstico melhora sua acurácia. Os estudos demonstram um baixo nível de conhecimento sobre tuberculose por parte dos generalistas. De acordo com esta revisão, a APS, na figura do médico generalista, necessita aprimorar sua capacidade de diagnóstico e o manejo desse grupo de pacientes, que constitui uma de suas principais demandas.

**Palavras-chave:** doenças respiratórias; atenção primária à saúde; diagnóstico; médicos de atenção primária; revisão.

## REFERENCES

- Ottmani S, Scherpier R, Chaulet P. Respiratory care in primary care services. A survey in 9 countries. Geneva: WHO; 2004. Document WHO/HTM/TB/n. 333.
- The global burden of disease: 2004 update. WHO Library Cataloguing-in-Publication Data. [cited 2012 dec 10]. Available from: [http://www.who.int/healthinfo/global\\_burden\\_disease/GBD\\_report\\_2004update\\_full.pdf?ua=1](http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf?ua=1).
- The top 10 causes of death Fact sheet N° 310. Updated June 2011. [cited 2012 dec 10]. Available from: <http://www.who.int/mediacentre/factsheets/fs310/en/>.
- World health statistics 2008. WHO Library Cataloguing-in-Publication Data. [cited 2012 dec 10]. Available from: [http://www.who.int/whosis/whostat/EN\\_WHS08\\_Full.pdf](http://www.who.int/whosis/whostat/EN_WHS08_Full.pdf).
- World Health Statistics 2008. WHO Library Cataloguing-in-Publication. [cited 2012 dec 10]. Available from: [http://www.who.int/respiratory/copd/World\\_Health\\_Statistics\\_2008/](http://www.who.int/respiratory/copd/World_Health_Statistics_2008/).
- World Health Organization. Asthma. Media Centre. Fact sheet N° 307. Updated May 2011. [cited 2013 mar 15]. Available from: <http://www.who.int/mediacentre/factsheets/fs307/en/index.html>.
- Bousquet J, Khaltaev N, editors. Global surveillance, prevention and control of chronic respiratory diseases. A comprehensive approach. [cited 2012 dec 10]. Available from: <http://www.who.int/gard/publications/GARD%20Book%202007.pdf>.
- Nascimento OA, Camelier A, Rosa FW, Menezes AMB, Pérez-Padilla R, Jardim JR, Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) Group. Chronic obstructive pulmonary disease is underdiagnosed and undertreated in São Paulo (Brazil). Results of the PLATINO Study. *Braz J Med Biol Res.* 2007;40:887-95.
- Adams R, Wilson D, Appleton S, Taylor A, Dal Grande E, Chittleborough C, et al. Underdiagnosed asthma in South Australia. *Thorax.* 2003;58:846-50.
- Hahn DL, Beasley JW and the Wisconsin Research Network (WRn) Asthma Prevalence Study Group. Diagnosed and possible undiagnosed asthma: A Wisconsin Research Network (WRn) Study. *J Fam Pract.* 1994;38:373-9.

11. Hopstaken RM, Muris JW, Knottnerus JA, Kester AD, Rinkens PE, Dinant GJ. Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection. *Br J Gen Pract.* 2003;53(490):358-64.
12. Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, Périat P, et al. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. *Arch Intern Med.* 2008;1681:2000-7.
13. Gulich MS, Matschiner A, Glück R, Zeitler HP. Improving diagnostic accuracy of bacterial pharyngitis by near patient measurement of C-reactive protein (CRP). *Br J Gen Pract.* 1999;49(439):119-21.
14. Bjerrum L, Gahrn-Hansen B, Munck AP. C-reactive protein measurement in general practice may lead to lower antibiotic prescribing for sinusitis. *Br J Gen Pract.* 2004;54(506):659-62.
15. Capper R, Canter RJ. Is there agreement among general practitioners, paediatricians and otolaryngologists about the management of children with recurrent tonsillitis? *Clin Otolaryngol Allied Sci.* 2001;26:371-8.
16. Cirit M, Orman A, Unlü M. Physicians approach to the diagnosis and treatment of tuberculosis in Afyon, Turkey. *Int J Tuberc Lung Dis.* 2003;7:243-7.
17. Al-Maniri AA, Al-Rawas OA, Al-Ajmi F, De Costa A, Eriksson B, Diwan VK. Tuberculosis suspicion and knowledge among private and public general practitioners: Questionnaire Based Study in Oman. *BMC Public Health.* 2008;26:177.
18. Hong YP, Kwon DW, Kim SJ, Chang SC, Kang MK, Lee EP, et al. Survey of knowledge, attitudes and practices for tuberculosis among general practitioners. *Tuber Lung Dis.* 1995;76:431-5.
19. Singla N, Sharma PP, Singla R, Jain RC. Survey of knowledge, attitudes and practices for tuberculosis among general practitioners in Delhi, India. *Int J Tuberc Lung Dis.* 1998;2:384-9.
20. Marklund B, Tunsater A, Bengtsson C. How often is the diagnosis bronchial asthma correct? *Fam Pract.* 1999;16:112-6.
21. Montnémy P, Hansson L, Lanke J, Lindholm L-H, Nyberg P, Löfdahl C-G, et al. Accuracy of a first diagnosis of asthma in primary health care. *Fam Pract.* 2002;19:365-8.
22. Ward DG, Halpin DM, Seamark DA. How accurate is a diagnosis of asthma in a general practice database? A review of patients' notes and questionnaire-reported symptoms. *Br J Gen Pract.* 2004;54:753-8.
23. Bednarek M, Maciejewski J, Wozniak M, Kuca P, Zielinski J. Prevalence and underdiagnosis of COPD in the primary care setting. *Thorax.* 2008;63:402-7.
24. Geijer RM, Sachs AP, Hoes AW, Salomé PL, Lammers JW, Verheij TJ. Prevalence of undetected persistent airflow obstruction in male smokers 40-65 years old. *Fam Pract.* 2005;22:485-9.
25. Global initiative for chronic obstructive lung disease - COPD. Global strategy for diagnosis, management, and prevention of chronic obstructive pulmonary disease (Revised 2011). [cited 2012 dec 12]. Available from: <http://www.goldpoc.com.br>.
26. Roberts CM, Abedi MKA, Barry JS, Williams E, Quantrill SJ. Predictive value of primary care made clinical diagnosis of chronic obstructive pulmonary disease (COPD) with secondary care specialist diagnosis based on spirometry performed in a lung function laboratory. *Prim Health Care Res Dev.* 2009;10:49 AM 53.
27. Zwar NA, Marks GB, Hermiz O, Middleton S, Comino EJ, Hasan I, et al. Predictors of accuracy of diagnosis of chronic obstructive pulmonary disease in general practice. *Med J Aust.* 2011;195:168-71.
28. Walters JA, Walters EH, Nelson M, Robinson A, Scott J, Turner P, et al. Factors associated with misdiagnosis of COPD in primary care. *Prim Care Respir J.* 2011;20:396-402.
29. Hamers R, Bontemps S, van den Akker M, Souza R, Penaforte J, Chavannes N. Chronic obstructive pulmonary disease in Brazilian primary care: diagnostic competence and case-finding. *Prim Care Respir J.* 2006;15:299-306.
30. Joo MJ, Au DH, Fitzgibbon ML, McKell J, Lee TA. Determinants of spirometry use and accuracy of COPD diagnosis in primary care. *J Gen Intern Med.* 2011;26:1272-7.
31. Hill K, Goldstein RS, Guyatt GH, Blouin M, Tan WC, Davis LL, et al. Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care. *CMAJ.* 2010;182:673-8.
32. Pearson M, Ayres J, Sarno M, Massey D, Price D. Diagnosis of airway obstruction in primary care in the UK: the CADRE (COPD and Asthma Diagnostic/management REassessment) programme 1997-2001. *Int J Chron Obstruct Pulmon Dis.* 2006;1:435-43.
33. Melbye H, Drivenes E, Dalbak L, Leinan T, Hoegh-Henrichsen S, Ostrem A. Asthma, chronic obstructive pulmonary disease, or both? Diagnostic labeling and spirometry in primary care patients aged 40 years or more. *Int J Chron Obstruct Pulmon Dis.* 2011;6:597-603.
34. Izquierdo JL, Martín A, Lucas P, Moro J, Almonacid C, Paravisini A. Misdiagnosis of patients receiving inhaled therapies in primary care. *Int J Chron Obstruct Pulmon Dis.* 2010;5:241-9.
35. Weidinger P, Nilsson JL, Lindblad U. Adherence to diagnostic guidelines and quality indicators in asthma and COPD in Swedish primary care. *Pharmacoepidemiol Drug Saf.* 2009;18:393-400.
36. Raghunath A, Innes A, Norfolk L, Hannant M, Greene T, Greenstone M, et al. Difficulties in the interpretation of lung function tests in the diagnosis of asthma and chronic obstructive pulmonary disease. *J Asthma.* 2006;43:657-60.
37. Starren ES, Roberts NJ, Tahir M, OByrne L, Haffenden R, Patel IS, et al. A centralised respiratory diagnostic service for primary care: a 4-year audit. *Prim Care Respir J.* 2012;21:180-6.
38. Lucas AE, Smeenk FJ, Smeele IJ, van Schayck OP. Diagnostic accuracy of primary care asthma/COPD working hypotheses, a real life study. *Respir Med.* 2012;106:1158-63.
39. Broekhuizen B, Sachs A, Hoes A, Moons K, Van Den Berg J, Dalinghaus W, et al. Undetected chronic obstructive pulmonary disease and asthma in people over 50 years with persistent cough. *Br J Gen Pract.* 2010;60(576):489-94.
40. Fletcher C, Peto R, Tinker C. The natural history of chronic airflow obstruction. *BMJ.* 1977;1:1645-8.
41. Speight AN, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. *BMJ.* 1983;286:1253-6.
42. Van Schayck CP, Chavannes NH. Detection of asthma and chronic obstructive pulmonary disease in primary care. *Eur Respir J Suppl.* 2003;39:16s-22s.
43. Levy M. Delay in diagnosing asthma. Is the nature of general practice to blame? *J Royal Coll Gen Pract.* 1986;36:52-3.
44. Kendrick AH, Hoggs CMB, Whitfield MJ, Laszlo G. Accuracy of perception of severity of asthma patients treated in general practice. *BMJ.* 1993;307:422-4.
45. Bijl-Hofland ID, Cloosterman SGM, Folgering HThM, Akkermans RP, van Schayck CP. Relation of the perception of airway obstruction to the severity of asthma. *Thorax.* 1999;54:5-19.
46. Van Schayck CP, Van der Heijden FMMA, Van den Boom G, Tirimanna PRS, Van Herwaarden CLA. Underdiagnosis of asthma: is the doctor or the patient to blame? The DIMCA project. *Thorax.* 2000;55:562-5.
47. Mendes EV. As redes de atenção à saúde. Brasília (DF): Organização Pan-Americana da Saúde; 2011. p.311-320.