

# World Journal of *Clinical Pediatrics*

*World J Clin Pediatr* 2012 December 8; 1(4): 20-39



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**AIM AND SCOPE** *World Journal of Clinical Pediatrics (World J Clin Pediatr, WJCP)*, online ISSN 2219-2808, DOI: 10.5409) is a bimonthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 100 experts in pediatrics from 31 countries.

The aim of *WJCP* is to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of congenital and hereditary neonatal diseases and abnormalities. *WJCP* covers fetal diseases, inborn, newborn diseases, infant diseases, genetic diseases, diagnostic imaging, endoscopy, traditional medicine, integrated Chinese and Western medicine, evidence-based medicine and epidemiology. The journal also publishes original articles and reviews that report the results of applied and basic research in fields related to pediatrics, such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

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**NAME OF JOURNAL**  
*World Journal of Clinical Pediatrics*

**ISSN**  
ISSN 2219-2808 (online)

**LAUNCH DATE**  
June 8, 2012

**FREQUENCY**  
Bimonthly

**EDITING**  
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**PUBLISHER**  
Baishideng Publishing Group Co., Limited  
Room 1701, 17/F, Henan Building,  
No.90 Jaffe Road, Wanchai, Hong Kong, China  
Fax: +852-31158812  
Telephone: +852-58042046  
E-mail: bpgoffice@wjgnet.com  
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**PUBLICATION DATE**  
December 8, 2012

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## Maternal mental disorders in pregnancy and the puerperium and risks to infant health

Priscila Krauss Pereira, Lúcia Abelha Lima, Letícia Fortes Legay, Jacqueline Fernandes de Cintra Santos, Giovanni Marcos Lovisi

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Supported by Brazil Higher Education Consortia Program (CAPES)

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Received: March 3, 2012 Revised: September 6, 2012

Accepted: September 13, 2012

Published online: December 8, 2012

### Abstract

Prenatal and postnatal period presents the highest prevalence of mental disorders in women's lives and depression is the most frequent one, affecting approximately one in every five mothers. The aggravating factor here is that during this period psychiatric symptoms affect not only women's health and well-being but may also interfere in the infant's intra and extra-uterine development. Although the causes of the relationship between maternal mental disorders and possible risks to a child's health and development remain unknown, it is suspected that these risks may be related to the use of psychotropic drugs during pregnancy, to substance abuse and the mother's lifestyle. Moreover, after delivery, maternal mental disorders may also impair the ties of affection (bonding) with the newborn and the ma-

ternal capacity of caring in the post-partum period thus increasing the risk for infant infection and malnutrition, impaired child growth that is expressed in low weight and height for age, and even behavioral problems and vulnerability to presenting mental disorders in adulthood. Generally speaking, research on this theme can be divided into the type of mental disorder analyzed: studies that research minor mental disorders during pregnancy such as depression and anxiety find an association between these maternal disorders and obstetric complications such as prematurity and low birth weight, whereas studies that evaluate severe maternal mental disorders such as schizophrenia and bipolar disorder have found not only an association with general obstetric complications as well as with congenital malformations and perinatal mortality. Therefore, the success of infant growth care programs also depends on the mother's mental well being. Such findings have led to the need for new public policies in the field of maternal-infant care geared toward the population of mothers. However, more research is necessary so as to confirm the association between all factors with greater scientific rigor.

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**Key words:** Maternal welfare; Mental disorders; Pregnancy; Puerperium; Infant health

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Pereira PK, Lima LA, Legay LF, de Cintra Santos JF, Lovisi GM. Maternal mental disorders in pregnancy and the puerperium and risks to infant health. *World J Clin Pediatr* 2012; 1(4): 20-23 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v1/i4/20.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v1.i4.20>

## INTRODUCTION

For many years now, it is largely believed that a pregnant woman's emotions can affect her child's health<sup>[1-4]</sup>, that is, her nutritional, hormonal, metabolic, psychological and social conditions during pregnancy have a direct relationship with the newborn's health<sup>[5-9]</sup>. However, this issue has only been researched around the world in the past few decades<sup>[10-14]</sup>.

Mental disorders are currently considered a global public health problem and affect approximately 10% of the world population, with over 25% prevalence over a lifetime, and are one of the leading causes for years lived with disability<sup>[15,16]</sup>. Prenatal and postnatal period presents the highest prevalence of these disorders in women's lives and depression is the most frequent one<sup>[17-21]</sup>, affecting approximately one in every five mothers<sup>[22-26]</sup>. The aggravating factor here is that during this period psychiatric symptoms affect not only women's health and well-being but may also interfere in the infant's intra and extra-uterine development<sup>[27-31]</sup>.

## CLINICAL AND EPIDEMIOLOGICAL ASPECTS

Although the causes of the relationship between maternal mental disorders and possible risks to a child's health and development remain unknown, it is suspected that these risks may be related to the use of psychotropic drugs during pregnancy<sup>[32,33]</sup>, to substance abuse (alcohol, tobacco and other drugs)<sup>[34]</sup>, the mother's lifestyle (unsatisfactory maternal diet and self-care, sedentary lifestyle and general bad health habits)<sup>[3,13]</sup> and to the precarious socioeconomic status in which they tend to live, more particularly, women with severe mental disorders who have very little material and social resources<sup>[34]</sup>.

Moreover, due to the psychiatric symptoms themselves, mothers with mental disorders during pregnancy may often present less concern with their health status<sup>[35]</sup>. They have difficulty in following medical orientation and getting proper antenatal care which has led to higher neonatal morbimortality risks especially in developing countries<sup>[36]</sup>. After delivery, maternal mental disorders may also impair the ties of affection (bonding) with the newborn<sup>[37]</sup> and the maternal capacity of caring in the post-partum period thus increasing the risk for infant infection and malnutrition<sup>[38]</sup> and impaired child growth that is expressed in low weight and height for age<sup>[10,13]</sup>, and even behavioral problems and vulnerability to presenting mental disorders in adulthood<sup>[39-41]</sup>.

Generally speaking, research on this theme can be divided into the type of mental disorder analyzed. Studies that research minor mental disorders during pregnancy such as depression and anxiety find an association between these maternal disorders and obstetric complications such as prematurity and low birth weight<sup>[1,14,42-44]</sup>. Such studies point to a biological mechanism that could explain this relationship since the hypothalamic-pituitary-

adrenal axis, the mediator of the association between maternal stress and low fetal growth<sup>[45]</sup>, is activated in response to physical and psychological stressors<sup>[46]</sup>. Maternal hypercortisolemia resulting from these mental disorders can change the cortisol cycle leading to an early peak in corticotropin-releasing hormone and consequently to preterm gestation<sup>[47,48]</sup>. Likewise, the resulting increase in fetal cortisol through the placental barrier can inhibit intra-uterine growth when it is present in high concentrations<sup>[49,50]</sup>.

It is worthwhile noting that a large number of these studies present a longitudinal design<sup>[51-55]</sup> and was carried out in developed countries<sup>[56-60]</sup>. However, most do not use standard instruments for the diagnosis of the disorders<sup>[61-64]</sup>-they commonly use screening instruments for depression and anxiety-related symptoms such as the Edinburgh Postnatal Depression Scale<sup>[65]</sup>, the Beck Depression Inventory<sup>[66]</sup> and the Hospital Anxiety and Depression Scale<sup>[67]</sup>, nor lab tests to assess cortisol levels.

On the other hand, studies that evaluate severe maternal mental disorders such as schizophrenia and bipolar disorder have found not only an association with general obstetric complications as well as with congenital malformations and perinatal mortality<sup>[3,6,9,12,68-70]</sup>. Studies on the outcomes of pregnancies of women with psychotic disorders demonstrate a two-fold increase in the risks for malformation in their newborns; when compared to children of mothers with no history of mental disorders, namely cardiovascular diseases and fatal congenital defects, although there are no plausible hypotheses for this association with one or other type of malformation<sup>[6,10,13]</sup>.

However, the vast majority of studies that evaluate the outcomes of pregnancies of mothers with severe psychiatric disorders are based on secondary data, drawing linkages between obstetric and psychiatric data bases in which the control of confounding variables may have been jeopardized since oftentimes there is no information regarding women's socioeconomic status, their use of alcohol, tobacco and other drugs during pregnancy, nor on their psychopharmacological treatment<sup>[3,6,10,12,13]</sup>. As was shown in one study, schizophrenic mothers are in average older than those without the disorder. Moreover, diseases such as diabetes and hypertension are also more frequent among mothers with severe mental disorders such as schizophrenia when compared to those without any mental disorders<sup>[10]</sup>. Such diseases, as well as advanced maternal age, in and of themselves, are renowned risk factors for obstetric complications and infant congenital malformations.

## CONCLUSION

There has been a growing epidemiological and clinical recognition of the importance of maternal mental health, since several studies have presented evidence that mental disorders during pregnancy and post-partum have an impact not only on the mother's health but also affect the newborn's health and development, thus making this

theme an essential one in the field of maternal-infant care. Moreover, the success of infant growth care programs also depend on the mother's mental well being<sup>[1]</sup>. Such findings have led to the need for new public policies for care geared toward the population of mothers. However, more research is necessary so as to confirm the association between all factors with greater scientific rigor, differentiated study designs, primary data-preferably longitudinal; and standardized and validated instruments to assess both exposure and outcome, in addition to associated factors, thus enabling greater control of possible confounding variables and a better understanding of the causal mechanisms involved in the relationship between maternal mental health and the newborn's health.

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S- Editor Jiang L L- Editor A E- Editor Zheng XM

## Profound deafness and the acquisition of spoken language in children

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Received: December 29, 2011 Revised: September 13, 2012

Accepted: December 5, 2012

Published online: December 8, 2012

### Abstract

Profound congenital sensorineural hearing loss (SNHL) is not so infrequent, affecting 1 to 2 of every 1000 newborns in western countries. Nevertheless, universal hearing screening programs have not been widely applied, although such programs are already established for metabolic diseases. The acquisition of spoken language is a time-dependent process, and some form linguistic input should be present before the first 6 mo of life for a child to become linguistically competent. Therefore, profoundly deaf children should be detected early, and referred timely for the process of auditory rehabilitation to be initiated. Hearing assessment methods should reflect the behavioural audiogram in an accurate manner. Additional disabilities also need to be taken into account. Profound congenital SNHL is managed by a multidisciplinary team. Affected infants should be bilaterally fitted with hearing aids, no later than 3 mo after birth. They should be monitored until the first year of age. If they are not progressing linguistically, cochlear implantation can be considered after thorough preoperative assessment. Prelingually deaf children develop significant speech perception and production abilities, and speech intelligibility over time, following cochlear implantation. Age at intervention and oral communication, are the most important determi-

nants of outcomes. Realistic parental expectations are also essential. Cochlear implant programs deserve the strong support of community members, professional bodies, and political authorities in order to be successful, and maximize the future earnings of pediatric cochlear implantation for human societies.

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**Key words:** Hearing loss; Sensorineural; Deafness; Pediatric; Children; Hearing aid; Cochlear implant

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Vlastarakos PV. Profound deafness and the acquisition of spoken language in children. *World J Clin Pediatr* 2012; 1(4): 24-28 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v1/i4/24.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v1.i4.24>

### GENERAL CONSIDERATIONS

The development of spoken language is one of the most spectacular accomplishments of a child. Language is central to most aspects of the child's life, and plays a role in the acquisition of a sense of self, and the achievement of social identity<sup>[1]</sup>. In addition, the ability to share information about intentions, ideas and feelings plays a vital role in human interaction<sup>[2]</sup>, and finally results in social integration.

It is widely accepted that if listening is not developed during the critical language learning years, the acquisition of spoken language is severely compromised<sup>[1]</sup>. Profound congenital sensorineural hearing loss (SNHL) is not so infrequent, as it is estimated to affect 1 to 2 of every 1000 newborns in western countries. More than 50% of cases of congenital SNHL are thought to be of genetic origin. Up to 80% of cases are inherited in a recessive manner,

and up to 70% are non-syndromic. A mutation in the gap junction  $\beta$ -2 (*GJB2*) gene, which controls protein connexin 26, an important regulator of potassium flow in the inner ear, is responsible for 30%-50% of congenital non-syndromic SNHL. On the other hand, syndromes associated with congenital SNHL include: (1) Pendred's syndrome (accompanying feature: goiter); (2) Alport's syndrome (accompanying feature: renal failure); (3) Usher's syndrome (accompanying feature: retinitis pigmentosa); (4) Waardenburg syndrome (accompanying feature: white tuft in the area of the forehead); (5) CHARGE syndrome (accompanying features: coloboma, heart defects, choanal atresia, retardation, genitourinary abnormalities); and (6) Jervell and Lange-Nielsen syndromes (accompanying features: long Q-T on ECG, arrhythmias). Despite the relatively high incidence of congenital SNHL, however, universal hearing screening programs have not been widely applied, and most countries have only established screening programs for high-risk infants. By contrast, metabolic diseases such as phenylketonuria, with an incidence of approximately 1 in 15 000 births, are routinely detected through newborn screening.

Early identification, referral, and diagnosis of children with hearing loss are necessary to initiate the process of auditory rehabilitation, which can ensure in turn that the hearing impaired child will receive the maximum amount of auditory information during the critical periods for spoken language development, thus reducing the effects of auditory deprivation.

Indeed, the sheer basis of our evolutionary advantage is the ability to increase our knowledge through our use of language. Language, however, does not just happen in an instance, but is a time-dependent process<sup>[3]</sup>.

Three general conditions are widely accepted in the area of the acquisition of a first language in children: (1) babies are exposed to language from birth onwards. This occurs in conversational settings, and is provided by those close to them; (2) a first language is acquired by infants through communicative interaction with competent users of that language; and (3) the language addressed to the child displays some characteristics which make it especially helpful for the young language learner, who is an immature conversational partner. These characteristics do not only include the structural and semantic features of the language, but also particular communicative behaviours, such as the management of the child's attention by the adult, who is trying to communicate with the child<sup>[1]</sup>.

In fact, with regard to the latter condition, there seems to be a triangular scheme of communication leading to vocal development. The child's and caregiver's lines of visual regard form two sides of the triangle, and the language input from the caregiver, which is received by the child through audition, forms the third side. A communication link is formed, as the caregiver communicates with the child, while the child is looking at something, making their interaction meaningful. When a baby is profoundly deaf, the third side of the triangle is practically absent<sup>[4]</sup>.

Given the three aforementioned conditions, which are almost always present in the early lives of normally developing infants in all cultures, receiving enough, and good enough language input for successful language development is rarely a problem for them. Language acquisition is a robust process for normally developing children, which fails only in cases of extreme deprivation<sup>[5]</sup>.

## SNHL AND LANGUAGE DEVELOPMENT

The development of language appears to follow a hierarchical progression. It includes first the sound of words-phonology. It is then followed by the meaning of words-semantics, and finally by the rules of grammar-syntax. Semantics and syntax are, therefore, dependent on appropriate and timely phonological input. They can, however, develop further in the years to come. Both intrinsic (hearing, processing, neuroplasticity) and extrinsic mechanisms (linguistic input, social and cultural influences) affect the development of spoken language. Language acquisition seems, in fact, to be a product of both nature and nurture<sup>[3]</sup>.

The CNS has an ability to adapt to sensory changes, which appears to be inversely proportional to age. It seems that for a child to become linguistically competent, some form linguistic input should be present before the first 6 mo of life. In addition, the acquisition of a normal language is guaranteed for children up to the age of six, is steadily compromised from then until shortly after puberty, and is rare thereafter<sup>[6]</sup>.

Many studies have shown that hearing-impaired children use excessively high pitches<sup>[7,8]</sup> and inappropriate variations in the fundamental frequency of their voice<sup>[9]</sup>. Reduced sound repertoires, containing multiple errors, are also characteristic of profoundly hearing-impaired children. Substitutions of one sound for another, omissions, and distortions frequently occur<sup>[10]</sup>. Syllabic structures are adversely influenced, and fail to show the variety of features associated with normal-hearing speakers. Consonant and vowel productions also are replete with errors, and contribute to reductions in overall speech intelligibility<sup>[11]</sup>. Visible consonants produced in the front of the mouth are used more frequently, than less visible consonants produced in the back of the mouth<sup>[12,13]</sup>. Front vowels appear to be produced with more errors than back vowels, thus suggesting that profoundly hearing-impaired children may have difficulty with the position of the tongue<sup>[13]</sup>.

With regard to vocabulary growth, although there is not a universal agreement as to the extent of normal variation between hearing children, estimates range from 2000 to 10 000 words for a 5-year-old. Most children encounter new words by the tens of thousands per year, and learn thousands of them. By comparing these numbers to those of a deaf child, some indication is given of the ensuing handicap. Di Carlo<sup>[14]</sup> estimated that a "typical five-year-old deaf child" has approximately 25 words! In fact, in the absence of any rehabilitation, congenitally deaf children will have little concept of the existence of verbal language, and effectively no experience of it, by the time

they reach school age<sup>[15]</sup>. By the time these children reach the end of their school career, and again in the absence of appropriate rehabilitation, their English vocabulary may not actually exceed that of a 6-year-old hearing child.

For people who are deaf, the chances of misunderstandings occurring during everyday interactions are far greater than for normal-hearing people. Conversations between the deaf and normal hearing can be fraught with difficulty. However, society tends to categorize people, and subsequently decide upon what is normal for each person in these categories<sup>[16]</sup>. In effect, we make assumptions about people and how we expect them to be, and if someone doesn't fit in with these expectations, he/she is then demoted to a "not-so-good-as-us" level, and may be stigmatised accordingly. As peers constitute a significant part in a child's life, there is a strong possibility that hearing-impaired children will begin to perceive themselves as "different" from an early age, and run the risk of becoming stigmatized.

## DIAGNOSIS OF SNHL IN INFANTS

Early referral, timely diagnosis and appropriate management of infants with profound SNHL are now considered of paramount importance in the developed world. It is, therefore, essential that the related methods accurately reflect the behavioural audiogram<sup>[17]</sup>.

Behavioural observation techniques based on the presentation of a loud sound, and the observation of the baby's response, have been largely superseded by more objective hearing tests<sup>[18]</sup>. Nevertheless, they may still prove useful to General Pediatricians and Practitioners, albeit needing some experience in interpreting the variety of possible responses. The related tests include: (1) induction of the sound blinking reflex, with the baby quickly blinking his/her eyelids, or shutting them more tightly, when stimulated by a sudden sound of 105-115 decibel (dB); (2) the startle reflex (Moro reflex), a rapid movement of the infant's head, with symmetrical extension of his/her extremities, while forming a C shape with the thumb and forefinger, when the infant is stimulated by a sudden noise of 80-85 dB in intensity. This is followed by a return to a flexed position with the extremities against the body; and (3) Rattle or bell tests, with the baby turning towards the sound, or widening his/her eyes with sound. The obtained response is not reflexive, and sometimes even normally-hearing infants are unable to make reliable direct head turn responses towards sound sources<sup>[19]</sup>.

The progress of clinical audiology during the last decades has been remarkable, nevertheless, none of the three objective tests typically performed in most specialist centers (otoacoustic emissions-OAEs, auditory brainstem responses-ABRs, and auditory steady state responses-ASSRs) are perfect<sup>[20]</sup>. Additional disabilities (i.e., autism), which may not be able to be detected early in life<sup>[21]</sup>, also need to be taken into account.

Apart from scientific dilemmas, reliable diagnosis is also very important to parents and family. Parents may indeed experience significant emotional stress during and

following hearing assessment. Hence, both the diagnostic process and the certainty of the diagnosis are considered central for them, to accept the problem, and participate in future management<sup>[22]</sup>. In addition, parental and family bonding and behaviour towards the infant, along with their trust to physicians, may be disturbed, when the diagnosis is inaccurate or doubtful<sup>[23]</sup>.

## MANAGEMENT OF SNHL IN INFANTS AND CHILDREN: THE ROLE OF COCHLEAR IMPLANTS

Hearing loss in the profoundly deaf can range, by definition, from a low of 90 dB to a high in the region of 120 dB. People with 120 dB hearing losses are probably totally deaf, and respond to sound only through the sense of touch<sup>[24]</sup>.

Profound congenital SNHL is managed by a multi-disciplinary team (MDT), which includes the pediatrician, the ENT surgeon, the genetic scientist, the clinical audiologist, the speech and language therapist, the psychologist, the teacher for the deaf, and the social worker. Ideally, infants with profound congenital SNHL should be bilaterally fitted with hearing aids, no later than 3 mo after birth. The child's progress should be monitored by the speech and language therapist and the teacher for the deaf, which should report their findings to the MDT.

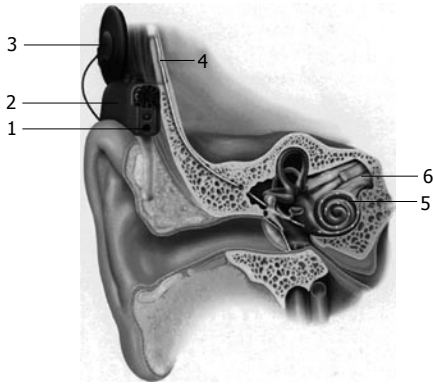
If the child is profoundly deaf and is not progressing linguistically, despite the consistent use of bilateral hearing aids, and the intensive speech and language therapy, a cochlear implantation can be considered after thorough preoperative assessment. Neuroplasticity and neurolinguistic issues have led cochlear implant centers to the decision of implanting children younger than 12 mo of age. Despite the relative lack of robust and reliable outcome measures of monitoring implanted infants<sup>[25]</sup>, it has been reported that implanted infants demonstrate improved auditory, speech language and cognitive performances compared to children implanted later<sup>[26]</sup>.

Cochlear implants represent one of the most important achievements of modern medicine, as for the first time in history an electronic device is able to restore a lost sense-hearing<sup>[27]</sup>.

A cochlear implant system comprises of the following components (Figures 1 and 2): (1) A multi-channel receiver - stimulator, which has several electrodes, and is placed under the skin behind the ear at the time of surgery (cortical mastoidectomy and posterior tympanotomy). The other end of the receiver (the electrodes) is delicately placed in the scala tympani of the cochlea; (2) A transmitter coil - a small external device (usually about 30 mm in diameter), which is held securely in place over the internal receiver/stimulator by magnetic attraction; (3) A microphone which is fitted behind the ear; and (4) A speech processor-a device that looks like a post-auricular hearing aid.

The microphone picks up sounds from the environ-





**Figure 1 Cochlear implant (schematic presentation).** 1: Microphone; 2: Speech processor; 3: Receiver/stimulator; 4: Electrodes; 5: Cochlea (electrodes inserted); 6: Cochlear nerve.



**Figure 2 Nucleus-freedom.** A: Nucleus-freedom receiver-stimulator; B: Nucleus-freedom behind-the-ear speech processor.

ment and sends them to the speech processor, through a thin cord that connects them. The speech processor converts the sounds into electronic signals, which are sent to the transmitter coil, through a cable. The transmitter sends these signals to the receiver across the intact skin, *via* an FM carrier wave. The signals are then converted back into electronic signals, and stimulate the implanted electrodes, and the cochlear nerve fibers. The nerve fibers send the signals to the brain, and a sensation of hearing is experienced. Hence, unlike a hearing aid, a cochlear implant can by-pass the damaged inner ear, and directly stimulate the auditory nerve fibers, in order to restore hearing<sup>[28]</sup>.

## COCHLEAR IMPLANTATION: OUTCOMES AND PREDICTORS

It is essential that parents have realistic expectations prior to embarking on cochlear implantation. In addition, parents and carers should be informed in detail about the need for long-term commitment to the child's rehabilitation.

However, the results regarding the acquisition of spoken language in implanted children with profound deafness are astonishing. Prelingually deaf children develop significant speech perception and production abilities

over time. These achievements may appear limited in the first two years, but show significant improvement after the second year of implantation, and do not reach a plateau, even 5 years following implantation<sup>[29]</sup>.

Prelingually deaf children also develop significant speech intelligibility, but a long period of cochlear implant use (sometimes more than 5 years) is needed prior to the emergence of intelligible speech<sup>[30]</sup>.

The age at intervention, and the mode of communication are the most important determinants of outcomes following cochlear implantation in young prelingually deaf children<sup>[31]</sup>. Implanted children ought to be operated early in life, and placed in an environment that has a strong oral component, in order to maximize the respective outcomes. Children implanted prior to educational placement are significantly more likely to go to mainstream schools following implantation, than those implanted when they are already in school<sup>[32]</sup>.

It needs to be mentioned as a concluding remark that the selection of the appropriate pediatric population, the existence of a dedicated cochlear implant MDT, with long-term commitment to the rehabilitation of the young patients, the adequacy of resources, and the strong support of the implant program by parents, community members, professional bodies, and political authorities, are the necessary parameters for the acquisition of spoken language by the prelingually deaf children following cochlear implantation, thus maximizing the future earnings of pediatric cochlear implantation for human societies.

## ACKNOWLEDGEMENTS

To my Mentor, Professor Nikolopoulos TP, for everything he's taught me. To Charis, the little angel that changed my life for ever.

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S- Editor Gou SX L- Editor A E- Editor Zheng XM

## Fever management: Evidence vs current practice

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Received: February 14, 2012 Revised: September 15, 2012  
Accepted: December 5, 2012  
Published online: December 8, 2012

### Abstract

Fever is a very common complaint in children and is the single most common non-trauma-related reason for a visit to the emergency department. Parents are concerned about fever and its potential complications. The biological value of fever (i.e., whether it is beneficial or harmful) is disputed and it is being vigorously treated with the belief of preventing complications such as brain injury and febrile seizures. The practice of alternating antipyretics has become widespread at home and on paediatric wards without supporting scientific evidence. There is still a significant contrast between the current concept and practice, and the scientific evidence. Why is that the case in such a common complaint like fever? The article will discuss the significant contrast between the current concepts and practice of fever management on one hand, and the scientific evidence against such concepts and practice.

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**Key words:** Acute childhood illnesses; Fever phobia; Physicians; Febrile seizure

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El-Radhi ASM. Fever management: Evidence vs current practice.

World J Clin Pediatr 2012; 1(4): 29-33 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v1/i4/29.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v1.i4.29>

### CURRENT CONCEPTS AND PRACTICE THAT FEVER IS HARMFUL

#### Current concepts among parents

Acute childhood illnesses are often associated with fever, which is considered by parents and by many doctors as a major and harmful sign of illness, sometimes as an illness itself rather than a symptom and a host defense response. Parents worry when their child is feverish and feel that fever may spiral upwards with a possible fatal outcome. As a result, they are convinced that antipyretic measures must be used to lower fever. Fever phobia, an exaggerated fear of fever in their children, is common among parents<sup>[1,2]</sup>. Parents have a poor understanding of fever and little or no information about its beneficial role in diseases<sup>[3]</sup>. As antipyretics do not normalize body temperature or prevent recurrences of fever, parents' concerns increase leading to increased use of antipyretics and health services. Pharmaceutical companies and the media may also be contributing to myths and fears of fever with comments or advertisements such as "If you love your child, get rapid relief with this medicine" or "if you care about the comfort of your child use this medicine", etc. By giving children the antipyretic medication the child soon feels better. The parent is then relieved that the lowered fever is the cause of the improvement in her/his child. But, this is most likely simply due to the reduction in pain and discomfort caused by the medication (see below).

#### Current concepts among physicians

There is often a wide perception among pediatricians that fever is dangerous. The majority (65%) of pediatricians in Massachusetts, USA, believe that fever itself could be dangerous to a child with seizures; death and brain dam-

age being the most serious complications of fever if the temperature is 40 °C or greater<sup>[4]</sup>. Although most pediatricians agree that treatment of a febrile child with antipyretics is mostly for the relief of the symptoms of fever, many tend to prescribe antipyretics for any child with fever. Pediatricians may be contributing to fever phobia by prescribing antipyretics for children who are only mildly febrile or by recommending the use of paracetamol alternating with ibuprofen. The biological value of fever (i.e., whether it is beneficial or harmful) is disputed among physicians and it is being vigorously treated with the belief of preventing its complications.

### **Risk of febrile seizure**

Febrile seizure (FS) has been one of the diseases where antipyretic treatment has strongly been advocated. In a study from the USA, 49% of pediatricians considered convulsions to be a principal danger of fever and 22% believed that that brain damage could result from typical FS<sup>[5]</sup>. Early literature reported a mortality rate of 11% in children with FS<sup>[6]</sup>.

As fever is generally considered to be an essential precursor of a FS, medical professionals have concluded that antipyretic measures should prevent febrile seizures. Antipyretics continue to be among the most commonly prescribed medications, especially for children at risk of such seizures. Parents are usually advised that the administration of antipyretics to at risk child may reduce the risk of further convulsions.

The current practice considers the liberal use of antipyretics a necessity and demands measures to abolish fever, even for a low degree of fever<sup>[7]</sup>. Antipyretics are parents' preferred method of managing fever and there has been an increase in this preference over the past two decades from 67% to more than 90% (91% to 95%)<sup>[2,8,9]</sup>. Of concern to health professionals is that parents' antipyretic administration is often incorrect both in dose and frequency<sup>[10,11]</sup>. Underdosing increases health service usage and encourages alternating antipyretics to maintain normal temperature. Overdosing is potentially harmful. The practice of alternating antipyretics has become widespread on pediatric wards and doctors are not sure whether this practice is supported by evidence and are there complications as a result. Parents reported to use this practice rising from 27% in 2001 to between 52% and 67% in 2007<sup>[12]</sup>. Pediatricians who work with children in hospitals have come to accept that antipyretics are very often automatically prescribed on the treatment sheet for the single indication, that is, the presence of fever. A febrile child who is playful on the ward, and a child with significant discomfort due to fever, both receive antipyretics.

It is possible that the negative views about fever have their roots historically. Throughout most of history fever was feared by ordinary people as a manifestation of punishment, induced by evil spirits or a marker of death<sup>[13]</sup>. Claude Bernhard (1813-1878), the great French physiologist, recognised that body temperature was regulated in

healthy organisms by the balancing of heat production and loss. He demonstrated that animals died quickly when the body temperature exceeded the normal level by 5-6 °C, thus suggesting that fever may be harmful and that antipyretics, which were introduced later, may be beneficial<sup>[14]</sup>. William Osler (1849-1919) declared that 'the humanity has three enemies, fever, famine and war, but fever is by far the greatest'.

## **EVIDENCE THAT FEVER IS BENEFICIAL**

Fever per se is self-limiting and rarely serious provided that the cause is known and fluid loss is replaced. With fever, unlike hyperthermia, body temperature is well regulated by a hypothalamic set-point that balances heat production and heat loss so effectively that the temperature does not climb up relentlessly and does not exceed an upper limit of 42 °C. Within this upper range, 40 °C to 42 °C, there is no evidence that the fever is injurious to tissue. About 20 percent of children seen in the emergency room have temperatures over 40 °C but they usually have a full recovery. If there is morbidity or mortality, it is due to the underlying disease. The associated fever may well be protective.

### **Furthermore**

Fever exerts an overall adverse effect on the growth of bacteria and on replication of viruses<sup>[15,16]</sup>. It also enhances immunological processes, including activity of interleukin-1 (IL-1), T-helper cells, cytolytic T-cells, B-cell and immunoglobulin synthesis<sup>[17]</sup>. The mobility, phagocytosis and killing of bacteria by polymorphonuclear leukocytes are significantly greater at temperatures above 40 °C. Elevated temperatures of 38 °C and 39 °C have a direct positive effect on lymphocyte transformation, the generation of cytolytic cells, B-cell activity, and immunoglobulin synthesis<sup>[18]</sup>. IL-1 is more active at febrile temperature than at an afebrile temperature. Interferon (INF), a potent antiviral agent, has enhanced antiviral activity above 40 °C<sup>[19]</sup>.

Human studies are also in support that fever may be beneficial. Fever was the principal form of treatment for syphilis and gonorrhoea about a century ago. A study from Japan<sup>[20]</sup> found that the frequent administration of antipyretics to children with bacterial diseases led to a worsening of their illness. A study of 102 children with salmonella gastroenteritis from Finland<sup>[21]</sup> demonstrated a significant negative correlation between the degree of fever and the duration of excretion of organisms. In a series of children presenting with severe infection, such as pneumonia or septicaemia, it was found that the lower the body temperature, the higher the mortality<sup>[22]</sup>. Insufflations of humidified air at 43 °C (three 30-min sessions at 2-3 h intervals) into the nasal passages of patients suffering from coryza resulted in the suppression of symptoms in 78 per cent of patients<sup>[23]</sup>. In human volunteers infected with rhinovirus, the use of antipyretics was associated with suppression of serum antibody response,

increased symptoms and signs and a trend towards longer duration of viral shedding<sup>[24]</sup>. In a study of children with chickenpox, half of whom received paracetamol four times a day, and half received a placebo, the time to total scabbing was slightly shorter in the placebo group (5.6 d) than in the paracetamol group (6.7 d)<sup>[25]</sup>.

Concerning the risk of FS, there is now abundant evidence indicating that antipyretics have no effect on preventing further FS<sup>[26]</sup>. Children with high risk of recurrences of FS (positive family history of FS, age < 1 year, complicated FS, low grade fever at the onset of FS) develop frequent recurrences while those without these risk factors rarely develop recurrences. Antipyretics are used for both groups of children, suggesting that it is the risk factors, and not the antipyretics, which predispose to recurrences. Several randomized, placebo-controlled trials on children at risk of FS found no evidence that the antipyretic paracetamol or ibuprofen, with or without diazepam, was effective in preventing FS during subsequent febrile episodes<sup>[27-29]</sup>. Furthermore, numerous studies show that a temperature > 40 °C is associated with decreased incidence of recurrence while children who develop seizures with lower degrees of fever have lower seizure threshold and therefore high recurrence rate of FS<sup>[30]</sup>. Thus, a high temperature at the onset of FS is a useful predictor of non-recurrence. Furthermore, a Cochrane review concluded that the evidence that paracetamol has a superior effect than placebo is insufficient<sup>[31]</sup>.

Antipyretics are known to cause adverse reactions and some fatalities. In the UK, paracetamol has been one of the most popular choices for suicide attempts in adolescents and adults, causing 100-150 deaths annually. In the USA, paracetamol-associated overdoses account for 56 000 emergency visits, 26 000 hospitalizations, with approximately 450 deaths each year. About 100 of these deaths are unintentional<sup>[32]</sup>.

The benefits of fever may also be found in the hygiene theory. The prevalence of asthma and allergies has increased worldwide for many years and the hygiene theory has been offered to explain the rise<sup>[33]</sup>. The theory proposes that early exposure to infections might protect children against allergic diseases.

### ***In support of this theory are the following findings***

The prevalence of atopy is lower among children of large families or those attending day-care nurseries than among children of small families or those not nurseries. Children with older siblings are less likely to develop allergies than children with younger siblings or none at all. Atopic diseases are rare in countries with parasitic infestation.

### ***Benefits of fever are found among ancient scholars***

The Hippocratic writings contain evidence that fever was thought to be beneficial to the infected host, “fever was beneficial in ophthalmia” and it cured it<sup>[34]</sup>. Since Hippocrates believed in the benefit of fever, he placed little emphasis on the treatment of it. When a disease was

caused by an excess of one of the four bodily humors, the excess humour was then “cooked”, separated and removed by the fever. Rufus of Ephesus, a surgeon who lived at the beginning of the 2nd century AD, strongly advocated the beneficial role of fever. He was the first physician to recommend the use of “fever therapy”, such as by malarial fever, to treat epilepsy. He said: “fever is a good remedy for an individual seized with convulsion, and if there were a physician skilful enough to produce a fever it would be useless to seek any other remedy against disease”<sup>[35]</sup>. For Thomas Sydenham (1624-1689), he clearly regarded fever as beneficial as witnessed by his remark “fever is a mighty engine which nature brings into the world to remove her enemies”<sup>[36]</sup>.

### ***More recent evidence***

It was Wagner von Jauregg in 1917 who gave an enormous impetus to the research with his work that fever was an effective treatment of neurosyphilis with malarial fever<sup>[37]</sup>. One of the most important outcomes of this research in recent years has been the discovery of a single mononuclear cell product, (IL-1, whose effects include induction of fever and activation of T-lymphocytes. Numerous substances from outside the body, exogenous pyrogens (ExPs), initiate the fever cycle. Endotoxin of Gram-negative bacteria is the most potent ExPs. The ExPs stimulate monocytes, fixed-tissue macrophages and reticuloendothelial cells to produce and release endogenous pyrogens, of which IL-1 is the most important. IL-1 acts on the hypothalamic thermoregulatory center through mediators, particularly PGE2, to raise the thermostatic set-point. The hypothalamic center accomplishes heat production by inducing shivering and heat conservation through vaso-constriction. At an established degree, fever is regulated by this centre (even at a temperature of over 41.0 °C) and heat production approximates loss, as in health, though at a higher level of the set-point. Therefore fever does not climb up relentlessly. IL-1 has other functions, including: Playing a primary role in the induction of inflammatory responses, such as neutrophil accumulation and adherence, and vascular changes. Stimulating the liver to synthesis certain proteins, acute-phase proteins, such as fibrinogen, haptoglobin, ceruloplasmin and CRP. T-cell and B-cell proliferation and activation, IL-1 activates T-lymphocytes to produce various factors, such as INF and IL-2, which are vital for immune response.

The production of fever simultaneously with lymphocyte activation constitutes the clearest and strongest evidence in favour of the role of fever.

## **RECOMMENDED FEVER MANAGEMENT**

### ***Education***

Health professionals should consider parental education as the core of fever management with the objective to improve parental knowledge and anxiety and to reduce



unnecessary use of health services. The following advice may be given: Fever is normal part of the body response to fight the infection; The body temperature is well controlled in the brain and does not rise relentlessly. This is in contrast to hyperthermia (e.g., heat stroke) where the body temperature may exceed 42.0 °C; Euthermia is not an objective of antipyretic treatment, but make the child comfortable is so; How sick the child looks (e.g., drowsy, lethargic, not playful, not smiling) is more important than the level of the fever; The primary objective of any antipyretic intervention is to decrease the child's discomfort; Antipyretic drugs such as paracetamol should not be use automatically for any fever and their use needs to be balanced against any harm that might result from this intervention. They have side-effects and should be used cautiously and according to the instruction prescribed; Paracetamol is an effective antipyretic and analgesic and a long history of safety. It should remain the drug of choice to use for febrile children. Ibuprofen has a significant potential side-effects; Sudden fever may cause a harmless "febrile seizures or convulsion in 3%-5% of those genetically susceptible children. The seizure does not cause brain damage. Fever-reducing medicines, even prophylactically, does not prevent further seizures.

#### **Therapy is indicated for following situations**

Symptoms such as pain, discomfort, delirium, excessive lethargy. Antipyretics serve here to improve the child's well-being, allowing the child to take fluid and reduce parental anxiety.

A situation associated with limited energy supply or increased metabolic rate (e.g., burn, cardiovascular and pulmonary diseases, prolonged febrile illness, young children, undernourishment, and postoperative state). Fever can increase the metabolic rate and exert a harmful effect on the disease.

Young children who are at risk of hypoxia because of acute respiratory condition such as bronchiolitis, since the presence of fever may increased oxygen requirement and worsen the disease<sup>[38]</sup>.

**A high degree of fever > 40 °C for the following reasons:** Children with this high degree of fever have rarely been studied; Children with this high degree of fever are likely to be symptomatic and at potentially high risk dehydration and delirium; Not advocating antipyretics for this high degree, would cause controversy among paediatricians and dismay among parents.

**We should not be in support of the following interventions:** Antipyretics for a child who does not have one of the above conditions, that is a febrile child with minimal or no symptoms such as discomfort. This constitutes a substantial proportion of febrile children. Such a recommendation may initially cause some dismay among parents because of their perception that their sick and needy children are not being treated. But, if we are to play a leadership role in our fields, we should help to educate

the public about the results of research; Physical measures such as a fan or tepid sponging are discouraged. These are unnecessary and unpleasant for the child. Their main indication is hyperthermia; The practice of alternating antipyretics (paracetamol and Ibuprofen) should be discouraged for there is no evidence to support this practice. The practice can also increase parents' fever phobia as it increases parental preoccupation with the height of the fever.

## **CONCLUSION**

Despite the controversy of the subject, paediatricians could reach a consensus on the following concepts: The accumulated data now suggest that fever has a protective role in promoting host defence against infection, rather than being a passive by-product. A moderate fever (less than 40 °C) is beneficial. The principal benefit of the antipyretic drug is to make children more comfortable and to relieve the parents' anxiety. Febrile seizures are usually benign and does not cause brain damage. Its prevention is difficult and may not be achievable. Antipyretics can not prevent FS. Evidence-based educational interventions are the best way to treat and prevent fever phobia and reduce unnecessary use of health services. This information is best delivered during routine health checks, as parents' anxiety may interfere with their understanding of facts presented when their child is sick. Parents should be taught how simply to assess the child's wellbeing (e.g., skin colour, activity levels, respiratory rate, and hydration). Media and the magazines have an important role in contributing to instruction and education of caregivers.

Antipyretics should be used with indications, like other drugs, and not for fever per se. Although there is evidence to support the beneficial effects of fever, we should recognize that the issue as to whether fever is beneficial or not is still controversial. We need to know which diseases are likely to benefit from the presence of fever, so that minimal interference during their courses may be considered. On the other hand, we should investigate in which diseases the associated fever may be harmful so that steps are taken to treat it. Also it should be determined what degree of fever is harmful and thus ought to be reduced. Finally, research indicates that we are at a crossroads, divided between strong research evidence accumulated during the past few decades supporting a positive role of fever and the continued pressures of current practice to lower body temperature. When we focus upon "treating" the fever, we are giving the impression to parents and health professionals that fever is harmful and that antipyresis is beneficial. Scientific evidence does not support this practice. To continue the current practice of liberal use of antipyretics may mean that we are ignoring important messages from research.

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## Neonatal risks from *in vitro* fertilization and delayed motherhood

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Received: April 6, 2012 Revised: October 9, 2012

Accepted: October 20, 2012

Published online: December 8, 2012

often praise and endorse DC, disregarding the increase of premature babies born because of DC, a real alarm for public health. Pediatricians should discourage the culture that makes DC a normal event.

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**Key words:** Motherhood; Babies; *In vitro* fertilization

**Peer reviewer:** Dr. Keith James Collard, Peninsula Allied Health Centre, University of Plymouth, Plymouth, PL6 8BH, United Kingdom

Bellieni CV. Neonatal risks from *in vitro* fertilization and delayed motherhood. *World J Clin Pediatr* 2012; 1(4): 34-36 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v1/i4/34.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v1.i4.34>

### Abstract

Delayed childbearing (DC) is common in most Western countries. The average age of first-time mothers increased in United States from 21.4 years in 1970 to 25.0 years in 2006 and from 25.4 to 30.8 years in Australia in the same period. It is commonly believed that this has no ominous consequences. But several negative consequences of this behavior are described: stillbirth, prematurity, twins, birth anomalies. Age also decreases women's fertility, thus many couples undergo *in vitro* fertilization. And we highlight a paradox: medical reproduction techniques decreases their effectiveness with maternal age, but their availability can be an incentive to postpone parenthood. Of course the risks of delayed parenthood involve a minority of cases, but are parents entitled to accept any risk on the behalf of their baby? A complete information would make people cautious before deciding to postpone childbearing, though this is often an obliged rather than a free choice: the consumerist society pressure and the difficulty to find an employment have their heavy weight in this choice. But if this choice is not really free, people's interest is to overcome these pressures and to claim for a real broad choice on when becoming parent, despite the pressures made by their cultural environment to postpone parenthood. Moreover, even reproductive techniques have some risks. Unfortunately, mass media

### DELAYED MOTHERHOOD THROUGHOUT THE WORLD

In most countries, women delay the age of the first pregnancy. A recent survey showed that the average age of first-time mothers increased in United States from 21.4 years in 1970 to 25.0 years in 2006, with a decrease in the rate of those younger than 20 years of age, and a relevant increase of those older than 35<sup>[1]</sup>. In most countries the average age at first birth has increased in the same years, with a minimum increase in Sweden (2.9 years) and the maximum (4.6 years) in Denmark; the average age at first birth in 2006 ranged from 25.0 years in the United States to 29.4 years in Switzerland<sup>[1]</sup>. The median age of women giving birth in Australia reached a low of 25.4 in 1971 and rose to a peak of 30.8 in 2006. Consequences of delayed childbearing (DC) were an increase of sterility in the population, and consequently an increase of fertility treatments: but fertility rates decline with age despite *in vitro* fertilization (IVF) techniques<sup>[2,3]</sup>. Nevertheless, the

number of women older than 35 or even 40 years of age who are using IVF is increasing and the average age of the women attending the clinics is increasing as well<sup>[4]</sup>. DC has become more socially acceptable, with subsequent negative connotations associated with younger motherhood<sup>[5]</sup>.

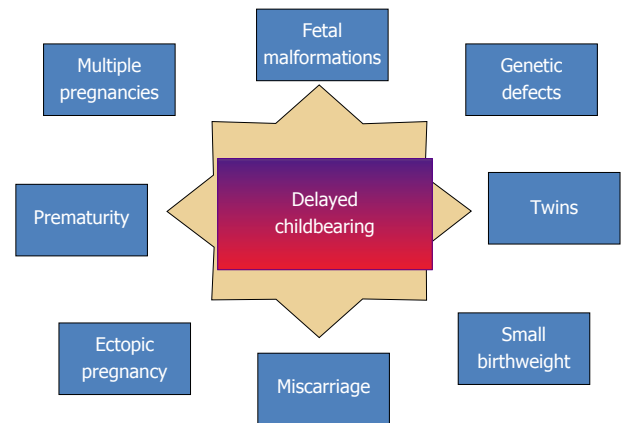
## EXTERNAL PRESSURES

How can this generalized tendency to DC be explained? The first answer is that a pregnancy can interfere with a woman's career<sup>[6]</sup>; this interference is not accepted in a society where women massively enter the job world for equality reasons and also for economic needs. It is well known that financial concerns related to childbirth may affect the take-up of maternity leave allowances<sup>[7]</sup> and that new parents have difficulties in taking maternity leave because of their financial situation<sup>[8]</sup>. Nevertheless, decisions taken under the pressure of economic needs and mass media cultural pressure are far from being a free choice. Women perceive a lack of choice in the timing of when to start a family: "Women do not perceive that they have ultimate control when it comes to the timing of childbearing"<sup>[9]</sup> and some authors report that "the choice to delay motherhood is not so voluntary"<sup>[10]</sup>. Poor understanding of the links between childbearing after age 35, pregnancy complications and increased risk of adverse infant outcomes limit adults' ability to make informed decisions about timing of child bearing<sup>[11]</sup>.

## BABIES' INTERESTS

But, if this is not ultimately a free choice, is DC at least in the interest of babies? Some commentators argue that having a baby late in age can give the baby psychological advantages<sup>[12]</sup>. Nonetheless, DC brings risks to the baby-to-be<sup>[13,14]</sup>: prematurity and consequently higher risk of brain damage<sup>[15]</sup>, aneuploidy, stillbirth, miscarriage are some of the risks (Figure 1). IVF, with a higher rate of prematurity<sup>[16]</sup>, small birth weight<sup>[17]</sup> and malformations<sup>[18]</sup>, as well as risk of imprinting diseases<sup>[19-21]</sup> does not improve this situation. Recent reviews reported these data in detail for DC<sup>[22,23]</sup> and for IVF<sup>[24,25]</sup>, though Davies *et al*<sup>[26]</sup> recently reported that "the increased risk of birth defects associated with IVF was no longer significant after adjustment for parental factors"; nevertheless, "the risk of birth defects associated with intra-cytoplasmic sperm injection remained increased after multivariate adjustment, although the possibility of residual confounding cannot be excluded".

These risks can be accepted by parents, but are parents entitled to accept any risk on the behalf of their baby? When they choose between two healing options, the answer is "yes", if the risk is balanced by possible benefits<sup>[27]</sup>. But choosing DC, they choose between a more risky and a less risky option; this is a paradox, because you should not choose the worst option if its consequences will not affect only you, but also others. Par-



**Figure 1 Possible rare risks of delayed childbearing and of *in vitro* fertilization.** Ectopic pregnancy and miscarriage are not more frequent after *in vitro* fertilization than in the general population

ents have only one option: to behave in the less risky way for the baby, and delaying childbearing beyond a certain threshold is risky. Unfortunately, mass media often praise and endorse DC, disregarding the increase of premature babies induced by several factors, among which DC.

In some cases, DC is not a choice, but is obliged by events: in this case, parents should thoroughly consider their reproductive decisions, trying to take a really autonomous and informed decision.

## PEDIATRIC RESPONSIBILITY

Any parental choice that is not free and that can provoke damages to the babies should be discouraged, and women should be safeguarded from external pressures, when this can harm their babies. Pediatricians and neonatologists should play an active role in this matter<sup>[28]</sup>: they should contrast economic pressures on motherhood, and correctly inform parents-to-be on the pros and cons of DC. They should use their media and agencies to make it clear that an excessive delay in procreating is medically contraindicated in the interest of the babies-to-be. Their message to the information leaders and to politicians should be clear: DC is one of the causes of an epidemic in prematurity and other health risks, ominous for babies, families and social wellbeing.

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S- Editor Song XX L- Editor A E- Editor Zheng XM



## Metabolically obese normal-weight children

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Supported by Fundacion IMSS, AC

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Received: April 16, 2012 Revised: September 13, 2012

Accepted: December 5, 2012

Published online: December 8, 2012

**Key words:** Children; Normal-weight; Cardiovascular risk factors; Screening; Obesity

**Peer reviewers:** Bjelakovic Borisav Bojko, MD, PhD, Associate Professor, Clinic of Pediatrics, Clinic of Pediatrics, Clinical Center, NisZoranaDjindjica 48 Boulevard, Nis 18000, Serbia; Papandreou, Assistant Professor, Department of Intercollege, University of Nicosia, 46 Makedonitis Ave, 1700 Nicosia, 546 36 Thessaloniki, Greece

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### Abstract

Non-obese children with elevated serum insulin levels and metabolic disorders such as, hyperglycemia, hypertension, and/or hypertriglyceridemia are a subset of children in high risk of developing cardiovascular disease later in life. Since usually the health policies for the prevention of the obesity associated disorders in children are based on the screening focused on the obese, frequently the metabolically obese normal-weight (MONW) children are not identified in primary care setting. Given that characterization of the MONW children is an important public health issue, and that a large amount of resources might be unnecessarily used in the screening of metabolic risk of nonobese children; we review data regarding criteria for the early recognition of this subset of children in high risk of developing cardiovascular disease. Results of our review suggests that the presence of family history of type 2 diabetes and/or hypertension, the elevated percentage of body fat, and the high birth-weight should be taken into account as criteria of high cardiovascular risk, irrespective of obesity.

### INTRODUCTION

Non-obese individuals with elevated serum insulin levels and metabolic disorders such as hyperglycemia, hypertension, and/or hypertriglyceridemia have been named metabolically obese normal-weight (MONW) individuals<sup>[1]</sup>, and characterize a subgroup who, irrespective of obesity, exhibited elevated cardiovascular risk.

Because usually the health policies for the prevention of obesity associated disorders in children are based on the screening focused on obese, characterization of the MONW children is an important public health issue. Nonetheless, reports about MONW children are scarce<sup>[2,3]</sup>, and its characteristics and related factors are not well determined in childhood.

Given that a large amount of resources might be unnecessarily used in the screening of metabolic risk of nonobese children, the most important raised question in this regard is which could be the criteria for screening of cardiovascular risk in the non-obese children?

On this regard, it has been reported that non-obese prehypertensive children exhibited significant higher frequency of family history of hypertension and atherogenic lipid profile as compared with non-obese healthy children<sup>[4-7]</sup>. In addition, a positive family history of type 2 diabetes is common in all diabetes types, particularly



type 2 diabetes (83%)<sup>[8]</sup> and had significant effect on individuals with metabolic syndrome as compared with individuals having no family history of diabetes<sup>[9]</sup>. The presence of family history of diabetes is associated with hypertriglyceridemia, hyperinsulinemia, insulin resistance, and impaired fasting glucose, independently of body mass category<sup>[10,11]</sup>. Furthermore, non-obese children (according waist circumference criterion) with family history of hypertension in the maternal branch, show hyperinsulinemia, hypertension, hypertriglyceridemia, and low high-density lipoprotein cholesterol<sup>[12]</sup>. These findings strongly suggest that positive family history of diabetes and/or hypertension could be the first clue for screening of cardiovascular risk factors in non-obese children.

In young women, the relative level of body fatness is related with the presence of abnormal lipid profile and metabolic syndrome irrespective of obesity according to standard body mass index or waist circumference criteria<sup>[13,14]</sup>. This finding strongly suggests that, in order to diagnosis of obesity, clinicians should include the measurement of body fatness as an adjuvant measure to body mass index and waist circumference. It has been shown that reduction of body fatness by lifestyle intervention programmes in the primary prevention of chronic diseases is beneficial at the population level and should not be limited to obese children<sup>[15,16]</sup>. So, it is rationale to consider that the elevated percentage of total body fat might be another criterion for the screening of MONW children.

A growing body of evidence shows that the high birth-weight is a risk factor for cardiovascular disease later in life<sup>[17-21]</sup>. Furthermore, children exposed to maternal obesity are at increased risk of developing metabolic syndrome, irrespective of obesity, which suggests that obese mothers who do not fulfill the clinical criteria for gestational diabetes may still have metabolic factors that affect fetal growth and postnatal outcomes<sup>[18]</sup>. We have found that family history of diabetes in the maternal branch, in combination with the low or high birth-weight is strongly associated with the presence of metabolic syndrome in children and adolescents, irrespective of obesity<sup>[22]</sup>.

Given that non-obese children could display a high prevalence of abnormalities in glucose, insulin levels, and lipid profile<sup>[23-25]</sup>, the screening for cardiovascular risk based in the presence of obesity does not recognize a high proportion of children with atherogenic lipid profile and glucose metabolic disorders. In order to provide the benefits of screening to non-obese children, as part of the public health policies for prevention of cardiovascular disease, we propose that the presence of family history of type 2 diabetes and/or hypertension, the elevated percentage of body fat, and the high birth-weight should be taken into account as criteria of high risk for cardiovascular disease, irrespective of obesity.

The scarce of studies in the field should encourage the research in the field, to validate the criteria of screening for cardiovascular risk in non-obese children.

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ACKNOWLEDGMENTS

## Acknowledgments to reviewers of World Journal of Clinical Pediatrics

We acknowledge our sincere thanks to our reviewers. Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of our World Series Journals. Both the editors of the journals and authors of the manuscripts submitted to the journals are grateful to the following reviewers for reviewing the articles (either published or rejected) over the past period of time.

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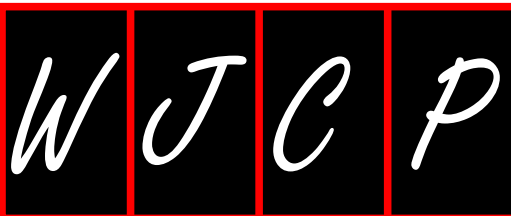
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## Events Calendar 2012

March 7-10, 2013

The 6th International Conference on Ocular Infections (ICOI)  
Santa Monica, CA, United States

May 2-3, 2012

1st Middle East and North Africa Pediatric Orthopaedic Surgery Conference  
Dubai, United Arab Emirates

May 3-4, 2012

IPHOUM 2012 - 13th International Update Meeting Paediatric, Haematology and Oncology  
Edinburgh, United Kingdom

May 3-7, 2013

PAS Annual Meeting 2013  
Washington, WA, United States

May 8-12, 2012

30th Annual Meeting of the European Society of Paediatric Infectious Diseases  
Thessaloniki, Greece

May 11-12, 2012

Best Practices in Primary Care (Baltimore, MD)  
Baltimore, MA, United States

May 17-20, 2012

2nd Global Congress for Consensus in Pediatrics and Child Health  
Moscow, Russia

May 18-20, 2012

Mini-Fellowship in Primary Pediatric Psychopharmacology  
Seattle, WA, United States

May 23-26, 2012

46th Annual Meeting of the Association for European Paediatric and Congenital Cardiology  
Istanbul, Turkey

May 30 - June 1, 2012

The Contribution of Epigenetics in Pediatric Environmental Health  
San Francisco, CA, United States

May 31 - June 2, 2012

Adolescent Health Care  
San Francisco, CA, United States

May 31 - June 2, 2012

Spanish Society of Pediatric Neurology 36th Annual Meeting 2012  
Santander, Spain

June 21-23, 2012

Pediatric - Review for Primary Care  
Sedona, AZ, United States

June 4-6, 2012

Australasian Conference of Child Trauma  
Queensland, Australia

June 7-9, 2012

Neonatal Pharmacology  
Washington, DC, United States

June 20, 2012

9th National Neuroscience Conference: Epilepsy in Children 2012  
London, United Kingdom

June 30 - July 2, 2012

11th International Congress on Pediatric Pulmonology  
Bangkok, Thailand

July 2-6, 2012

20th Annual Primary Care Conference  
Kiawah Island, SC, United States

July 7-14, 2012

33rd World Medical and Health Games - Antalya 2012  
Antalya, Turkey

July 20-21, 2012

4th International Workshop on HIV

Pediatrics

Washington DC, United States

July 23-27, 2012

3rd Essentials in Primary Care CME Conference Session One Palm Coast  
Florida  
Palm Coast, FA, United States

July 30 - August 3, 2012

Essentials in Primary Care CME Conference Session 2 Palm Coast  
Florida  
Palm Coast, FA, United States

August 10-22, 2012

Pediatric Emergency Medicine: Review for Primary Care  
Rome, Italy

August 26-31, 2012

Pediatric Cardiology 2012 Board Review Course  
Dana Point, CA, United States

September 8-9, 2012

International Congress on Paediatric Airway  
Chennai, India

September 11, 2012

Developmental Behavioral Pediatrics Symposium  
Riyadh, Saudi Arabia

September 19-20, 2012

4th conference of the European Paediatric Formulation Initiative  
Prague, Czech Republic

September 20-21, 2012

The Pediatric Emergency Medicine Resource  
Las Palmas, Spain

September 20-23, 2012

ESPE 2012 - European Society for Paediatric Endocrinology Annual Meeting  
Leipzig, Germany

September 24-25, 2012

Pediatric Days 2012  
Chicago, United States

October 5-9, 2012

EAPS 2012 - 4th Congress of the European Academy of Paediatric Societies  
Istanbul, Turkey

October 10-13, 2012

ISPAD 2012 - 38th International Society for Pediatric and Adolescent Diabetes  
Istanbul, Turkey

October 11-12, 2012

Portland Problem Student Problem-Solver Workshop  
Portland, OR, United States

October 23-28, 2012

59th AACAP Annual Meeting  
San Francisco, CA, United States

October 20-23, 2012

American Academy of Pediatrics National Conference and Exhibition  
New Orleans, LA, United States

November 7, 2012

Third Pediatric Infectious Diseases Review Course  
Riyadh, Saudi Arabia

November 10, 2012

3rd International Saudi Pediatric Neurology Conference  
Riyadh, Saudi Arabia

November 14-18, 2012

XVI Latin American Congress of Pediatrics, ALAPE 2012  
Cartagena de Indias, Colombia

November 15-16, 2012

Advanced Pediatric Life Support  
Sevilla, Spain

## GENERAL INFORMATION

*World Journal of Clinical Pediatrics* (*World J Clin Pediatr*, *WJCP*, online ISSN 2219-2808, DOI: 10.5409) is a bimonthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 100 experts in pediatrics from 31 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

### Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJCP* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJCP* is an OA journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJCP* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wis-

dom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

### Aims and scope

The aim of *WJCP* is to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of congenital and hereditary neonatal diseases and abnormalities. *WJCP* covers fetal diseases, inborn, newborn diseases, infant diseases, genetic diseases, diagnostic imaging, endoscopy, traditional medicine, integrated Chinese and Western medicine, evidence-based medicine and epidemiology. The journal also publishes original articles and reviews that report the results of applied and basic research in fields related to pediatrics, such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

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The columns in the issues of *WJCP* will include: (1) Editorial: To introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (6) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (7) Original Articles: To originally report the innovative and valuable findings in pediatrics; (8) Brief Articles: To briefly report the novel and innovative findings in pediatrics; (9) Case Report: To report a rare or typical case; (10) Letters to the Editor: To discuss and make reply to the contributions published in *WJCP*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: To introduce and comment on quality monographs of pediatrics; and (12) Guidelines: To introduce consensus and guidelines reached by international and national academic authorities worldwide on the research in pediatrics.

### Name of journal

*World Journal of Clinical Pediatrics*

### ISSN

ISSN 2219-2808 (online)

### Editor-in-Chief

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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462

PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

*Both personal authors and an organization as author*

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

*Issue with no volume*

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

*No volume or issue*

- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

### Books

*Personal author(s)*

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

*Chapter in a book (list all authors)*

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

*Author(s) and editor(s)*

- 12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wicczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

*Conference proceedings*

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

*Conference paper*

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

**Electronic journal (list all authors)**

- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

**Patent (list all authors)**

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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