Биомаркеры

при критических состояниях в акушерстве

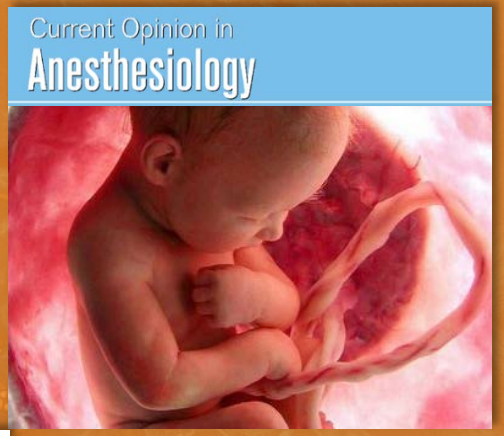
Проф. Е. М. Шифман

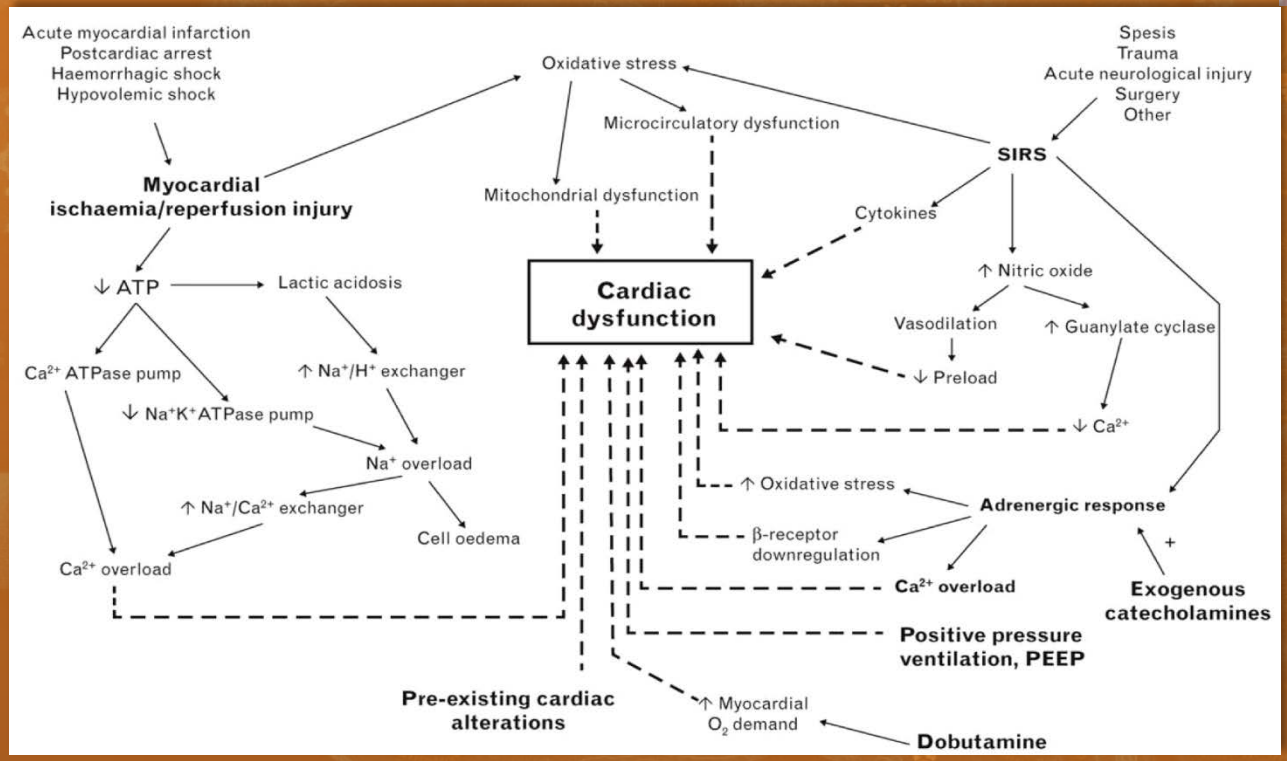
Заболевания сердца на сегодняшний день –
наиболее частая косвенная причина смертности вообще
и материнской смертности в частности.

Заболевание сердца и беременность

Lewis G., ed. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer-2003–2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. London: CEMACH, 2007.

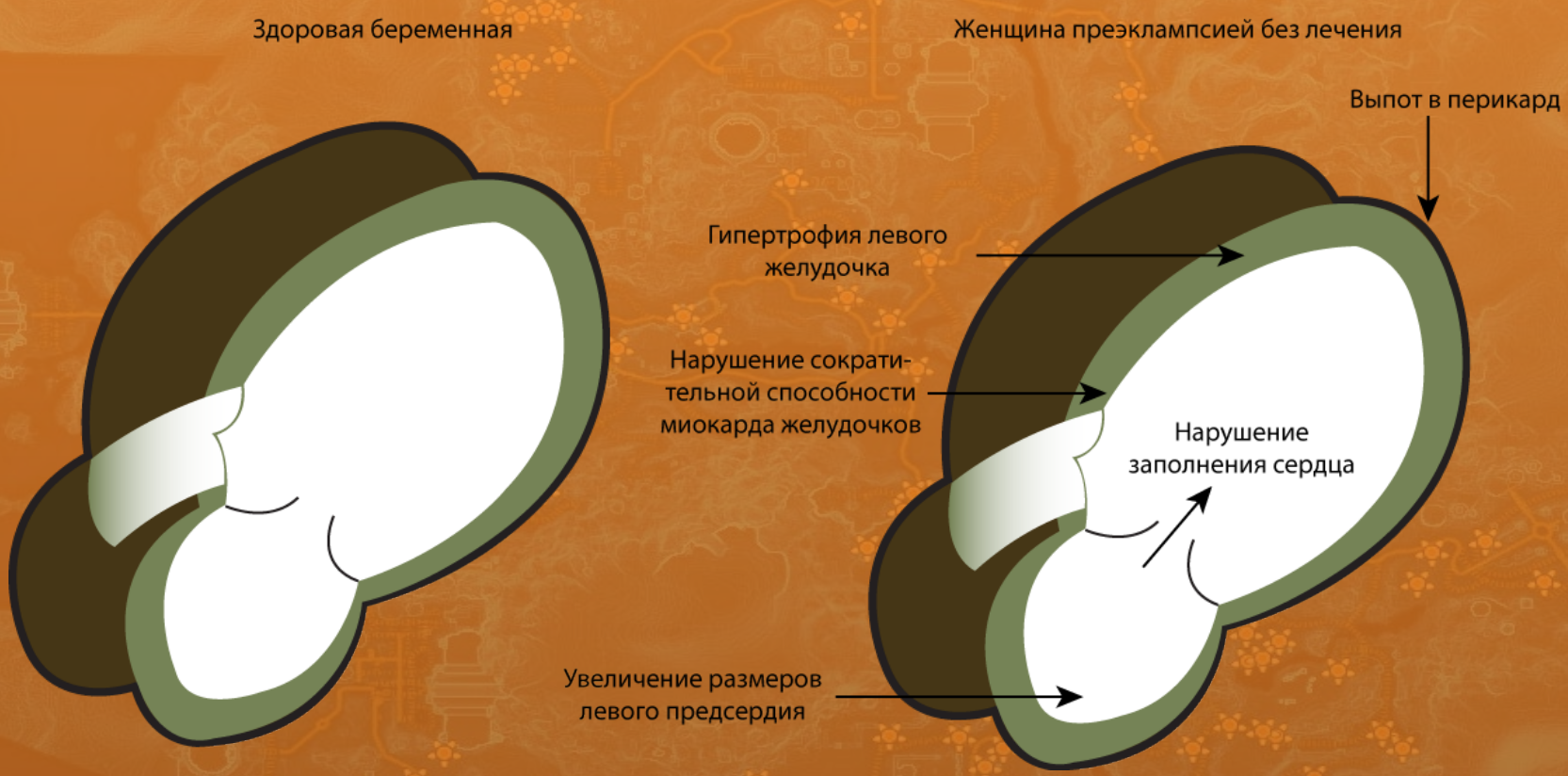
Основные определяющие факторы нарушений функции миокарда у больных в критическом состоянии





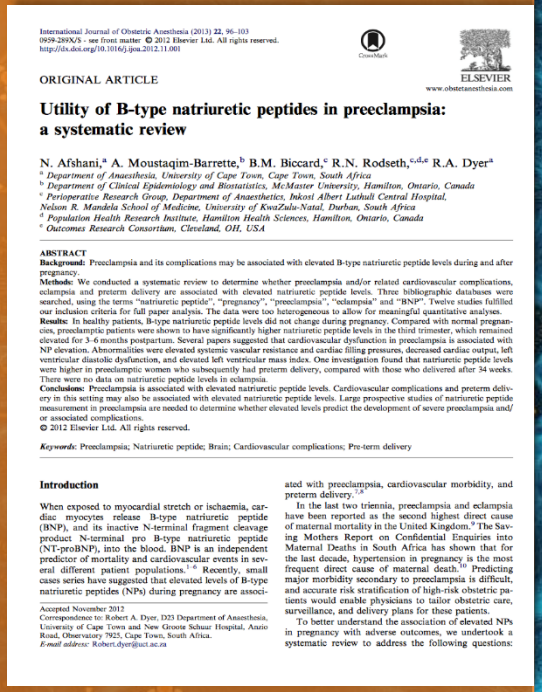
Donati A., Carsetti A., Damiani E. The role of cardiac disfunction in multiorgan disfunction Current Opinion in Anesthesiology 29(2):172-177, April 2016

Диастолические и структурные изменения



Сердечно-сосудистые осложнения при преэклампсии и повышенные уровни натрий-уретического пептида типа В

В высококачественном сравнительном исследовании (женщины с преэклампсией и здоровые беременные) несколько эхокардиографических признаков диастолической дисфункции левого желудочка **сопровождались повышением NP**



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http://dx.doi.org/10.1016/j.ijoa.2012.11.001

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ORIGINAL ARTICLE

Utility of B-type natriuretic peptides in preeclampsia: a systematic review

N. Afshani,[a] A. Moustaqim-Barrette,[b] B.M. Biccard,[c] R.N. Rodseth,[c,d,e] R.A. Dyer[a]
[a] *Department of Anaesthesia, University of Cape Town, Cape Town, South Africa*
[b] *Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada*
[c] *Perioperative Research Group, Department of Anaesthetics, Inkosi Albert Luthuli Central Hospital, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa*
[d] *Population Health Research Institute, Hamilton Health Sciences, Hamilton, Ontario, Canada*
[e] *Outcomes Research Consortium, Cleveland, OH, USA*

ABSTRACT
Background: Preeclampsia and its complications may be associated with elevated B-type natriuretic peptide levels during and after pregnancy.
Methods: We conducted a systematic review to determine whether preeclampsia and/or related cardiovascular complications, eclampsia and preterm delivery are associated with elevated natriuretic peptide levels. Three bibliographic databases were searched, using the terms "natriuretic peptide", "pregnancy", "preeclampsia", "eclampsia" and "BNP". Twelve studies fulfilled our inclusion criteria for full paper analysis. The data were too heterogeneous to allow for meaningful quantitative analyses.
Results: In healthy patients, B-type natriuretic peptide levels did not change during pregnancy. Compared with normal pregnancies, preeclamptic patients were shown to have significantly higher natriuretic peptide levels in the third trimester, which remained elevated for 3–6 months postpartum. Several papers suggested that cardiovascular dysfunction in preeclampsia is associated with NP elevation. Abnormalities were elevated systemic vascular resistance and cardiac filling pressures, decreased cardiac output, left ventricular diastolic dysfunction, and elevated left ventricular mass index. One investigation found that natriuretic peptide levels were higher in preeclamptic women who subsequently had preterm delivery, compared with those who delivered after 34 weeks. There were no data on natriuretic peptide levels in eclampsia.
Conclusions: Preeclampsia is associated with elevated natriuretic peptide levels. Cardiovascular complications and preterm delivery in this setting may also be associated with elevated natriuretic peptide levels. Large prospective studies of natriuretic peptide measurement in preeclampsia are needed to determine whether elevated levels predict the development of severe preeclampsia and/or associated complications.

Keywords: Preeclampsia; Natriuretic peptide; Brain; Cardiovascular complications; Pre-term delivery

Introduction

When exposed to myocardial stretch or ischaemia, cardiac myocytes release B-type natriuretic peptide (BNP), and its inactive N-terminal fragment cleavage product N-terminal pro B-type natriuretic peptide (NT-proBNP), into the blood. BNP is an independent predictor of mortality and cardiovascular events in several different patient populations.[1–6] Recently, small cases series have suggested that elevated levels of B-type natriuretic peptides (NPs) during pregnancy are associated with preeclampsia, cardiovascular morbidity, and preterm delivery.[7,8]

In the last two triennia, preeclampsia and eclampsia have been reported as the second highest direct cause of maternal mortality in the United Kingdom.[9] The Saving Mothers Report on Confidential Enquiries into Maternal Deaths in South Africa has shown that for the last decade, hypertension in pregnancy is the most frequent direct cause of maternal death.[10] Predicting major morbidity secondary to preeclampsia is difficult, and accurate risk stratification of high-risk obstetric patients would enable physicians to tailor obstetric care, surveillance, and delivery plans for these patients.

To better understand the association of elevated NPs in pregnancy with adverse outcomes, we undertook a systematic review to address the following questions:

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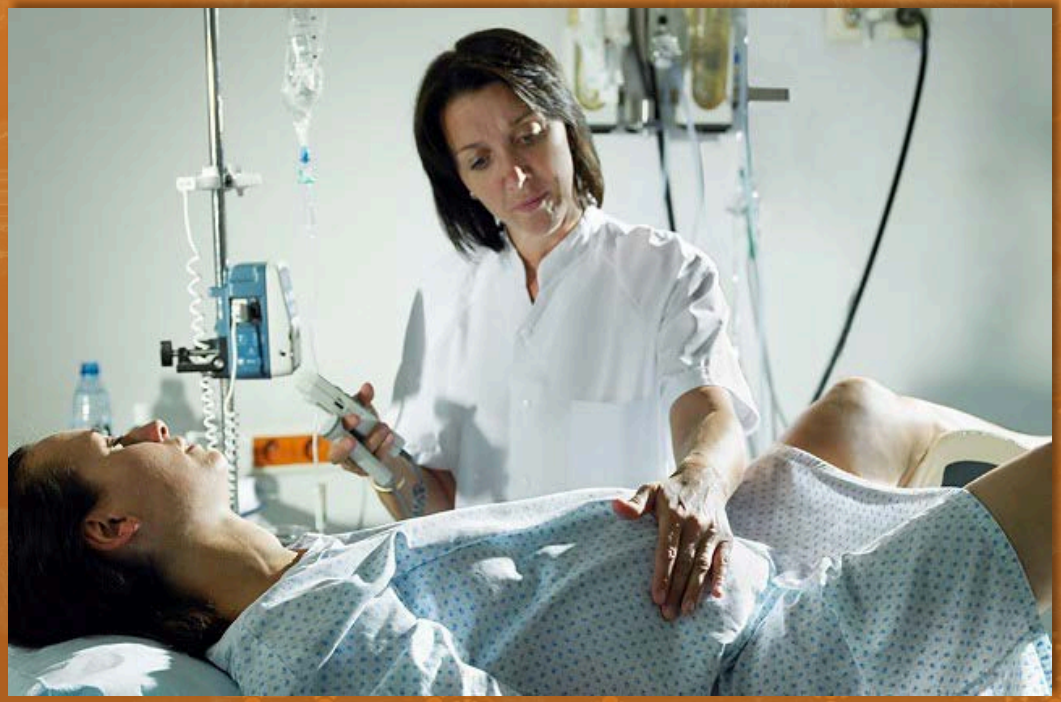
Correspondence to: Robert A. Dyer, D23 Department of Anaesthesia, University of Cape Town and New Groote Schuur Hospital, Anzio Road, Observatory 7925, Cape Town, South Africa.
E-mail address: Robert.dyer@uct.ac.za

N. Afshani, A. Moustaqim-Barrette, B.M. Biccard, R.N. Rodseth, R.A. Dyer. Utility of B-type natriuretic peptides in preeclampsia: a systematic review. International Journal of Obstetric Anesthesia (2013) 22, 96–103

У здоровых беременных уровни NP

не меняются



American Journal of Obstetrics and Gynecology (2005) 193, 450–4

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American Journal of Obstetrics & Gynecology
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Evaluation of B-type natriuretic peptide (BNP) levels in normal and preeclamptic women

Jamie L. Resnik, MD,* Christina Hong, MD, Robert Resnik, MD, Radmila Kazanegra, MD, Jennifer Beede, BA, Vikas Bhalla, MD, Alan Maisel, MD

Division of Cardiology and Endocrinology and the Department of Medicine, Veteran's Affairs Medical Center and University of California, San Diego, and Department of Reproductive Medicine, University of California, San Diego, San Diego, CA

Received for publication August 23, 2004; revised November 19, 2004; accepted December 2, 2004

KEY WORDS
Preeclampsia
B-natriuretic peptide
BNP
Pregnancy
Left ventricular dysfunction

Objective: B-type natriuretic peptide (BNP) is synthesized in cardiac ventricles in response to volume expansion. This study evaluated BNP levels to determine trends during pregnancy, and to assess BNP as a diagnostic tool in preeclampsia.
Study design: We studied 163 BNP levels in 118 pregnant women, ranging from first trimester to term. An additional 34 patients with preeclampsia were studied and compared to 25 normal control patients at term. Plasma BNP values were determined using a standard assay.
Results: The median BNP levels during the 1st, 2nd, 3rd trimester, and at term were equivalent (18.4, 17.9, 15.5, and 17.8 pg/mL, respectively, $P = .796$). The median BNP levels in normal patients, mild preeclamptics, and severe preeclamptics were 17.8, 21.1, and 101 pg/mL, respectively, with the severe group being significantly higher than the mild group ($P = .003$) and any phase of normal pregnancy ($P < .001$ in each case). A BNP cut-off of <40.6 pg/mL had a negative predictive value of 92% in excluding preeclampsia.
Conclusion: In normal pregnancies, median BNP values are <20 pg/mL, and stable throughout gestation. In severe preeclampsia BNP levels are elevated. This may reflect ventricular stress and/or subclinical cardiac dysfunction associated with preeclampsia.

Preeclampsia is one of the most common disorders of pregnancy, affecting about 5% of pregnancies, and resulting in substantial maternal and neonatal morbidity and mortality.[1,2] Untreated preeclampsia is characterized by a marked increase in peripheral vascular resistance, which, in turn, causes an increase in blood pressure.[3,4] This increase in afterload is superimposed upon the existing volume overloaded hemodynamic state of pregnancy.

B-type natriuretic peptide (BNP) is synthesized in cardiac ventricular tissue in response to volume expansion and pressure overload. It is an approved marker for the diagnosis of congestive heart failure (CHF) in patients with dyspnea in an acute care setting.[5,6] BNP levels

Principal Investigator was Jamie L. Resnik, MD (grant RCO91H-RESNIK).
Supported by an Academic Senate Grant, University of California, San Diego.
* Reprint requests: Jamie L. Resnik, MD, Department of Reproductive Medicine, 200 W Arbor Drive, Mail Code #8433, San Diego, CA 92103-8433.
E-mail: jresnik@ucsd.edu

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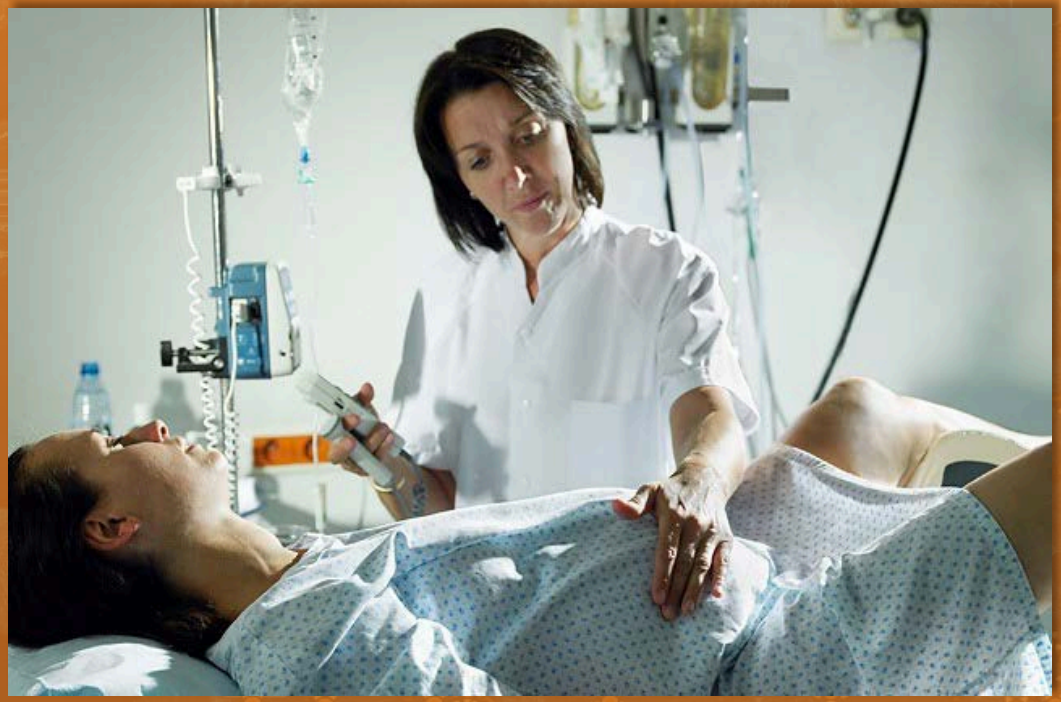
doi:10.1016/j.ajog.2004.12.006

Resnik JL, Hong C, Resnik R, et al. Evaluation of B-type natriuretic peptide (BNP) levels in normal and preeclamptic women. Am J Obstet Gynecol 2005;193:450–4.

У беременных с преэклампсией нарастание уровней NP происходит соответственно степени тяжести ПЭ



American Journal of Obstetrics and Gynecology (2005) 193, 450–4

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E-mail: jresnik@ucsd.edu

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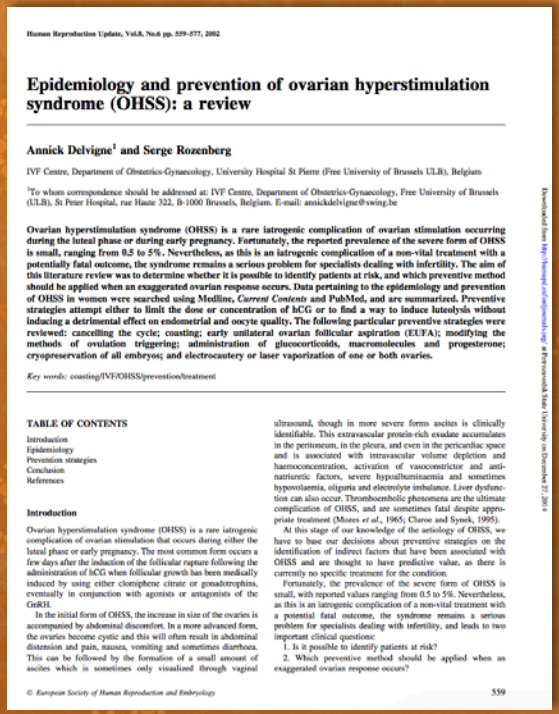
doi:10.1016/j.ajog.2004.12.006

Moghbeli N, Srinivas SK, Bastek J, et al. N-terminal pro-brain natriuretic peptide as a biomarker for hypertensive disorders of pregnancy. Am J Perinatol 2010;27:313–9.

Resnik JL, Hong C, Resnik R, et al. Evaluation of B-type natriuretic peptide (BNP) levels in normal and preeclamptic women. Am J Obstet Gynecol 2005;193:450–4.

Механизм развития риска сердечно-сосудистых осложнений при гиперстимуляции яичников

- Заметное увеличение яичников
- Скопление жидкости в интерстиции и третьем пространстве
- Выпот в перикард, плевральный и перитонеальный выпот
- Состояние гиперкоагуляции
- Прямая овариальная фолликулярная активация ренин-ангиотензин-альдостероновой системы
- Гиперконцентрация
- Увеличение проницаемости сосудов и эндотелиальная дисфункция
- Почечная недостаточность
- Гипотензия
- Легочно-сердечная недостаточность



Human Reproduction Update, Vol.8, No.6 pp. 559–577, 2002

Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review

Annick Delvigne[1] and Serge Rozenberg

IVF Centre, Department of Obstetrics-Gynaecology, University Hospital St Pierre (Free University of Brussels ULB), Belgium

[1]To whom correspondence should be addressed at: IVF Centre, Department of Obstetrics-Gynaecology, Free University of Brussels (ULB), St Peter Hospital, rue Haute 322, B-1000 Brussels, Belgium. E-mail: annickdelvigne@swing.be

Ovarian hyperstimulation syndrome (OHSS) is a rare iatrogenic complication of ovarian stimulation occurring during the luteal phase or during early pregnancy. Fortunately, the reported prevalence of the severe form of OHSS is small, ranging from 0.5 to 5%. Nevertheless, as this is an iatrogenic complication of a non-vital treatment with a potentially fatal outcome, the syndrome remains a serious problem for specialists dealing with infertility. The aim of this literature review was to determine whether it is possible to identify patients at risk, and which preventive method should be applied when an exaggerated ovarian response occurs. Data pertaining to the epidemiology and prevention of OHSS in women were searched using Medline, *Current Contents* and PubMed, and are summarized. Preventive strategies attempt either to limit the dose or concentration of hCG or to find a way to induce luteolysis without inducing a detrimental effect on endometrial and oocyte quality. The following particular preventive strategies were reviewed: cancelling the cycle; coasting; early unilateral ovarian follicular aspiration (EUFA); modifying the methods of ovulation triggering; administration of glucocorticoids, macromolecules and progesterone; cryopreservation of all embryos; and electrocautery or laser vaporization of one or both ovaries.

Key words: coasting/IVF/OHSS/prevention/treatment

TABLE OF CONTENTS

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a rare iatrogenic complication of ovarian stimulation that occurs during either the luteal phase or early pregnancy. The most common form occurs a few days after the induction of the follicular rupture following the administration of hCG when follicular growth has been medically induced by using either clomiphene citrate or gonadotrophins, eventually in conjunction with agonists or antagonists of the GnRH.

In the initial form of OHSS, the increase in size of the ovaries is accompanied by abdominal discomfort. In a more advanced form, the ovaries become cystic and this will often result in abdominal distension and pain, nausea, vomiting and sometimes diarrhoea. This can be followed by the formation of a small amount of ascites which is sometimes only visualized through vaginal ultrasound, though in more severe forms ascites is clinically identifiable. This extravascular protein-rich exudate accumulates in the peritoneum, in the pleura, and even in the pericardiac space and is associated with intravascular volume depletion and haemoconcentration, activation of vasoconstrictor and anti-natriuretic factors, severe hypoalbuminaemia and sometimes hypovolaemia, oliguria and electrolyte imbalance. Liver dysfunction can also occur. Thromboembolic phenomena are the ultimate complication of OHSS, and are sometimes fatal despite appropriate treatment (Mozes *et al.*, 1965; Charoe and Synek, 1995).

At this stage of our knowledge of the aetiology of OHSS, we have to base our decisions about preventive strategies on the identification of indirect factors that have been associated with OHSS and are thought to have predictive value, as there is currently no specific treatment for the condition.

Fortunately, the prevalence of the severe form of OHSS is small, with reported values ranging from 0.5 to 5%. Nevertheless, as this is an iatrogenic complication of a non-vital treatment with a potential fatal outcome, the syndrome remains a serious problem for specialists dealing with infertility, and leads to two important clinical questions:

1. Is it possible to identify patients at risk?
2. Which preventive method should be applied when an exaggerated ovarian response occurs?

Hum. Rep. Update 2002; 8(6):559–577

Время влияет на сепсис

- Работа группы по исследованию лактата и ее протоколы привели к снижению риска госпитальной смерти (соотношение рисков 0,61, (CI 0.43–0.87), с поправкой на предопределенные факторы риска.
- Мониторинг лактата
  - ✓ Улучшение вентиляции *(HR 0.72; 95% CI 0.5–0.98)*
  - ✓ Уменьшение потребности в инотропной поддержке *(HR 0.65; 95% CI 0.42–1.00)*
  - ✓ Ранний перевод из отделения интенсивной терапии *(HR 0.65; 95% CI 0.5–0.85)*

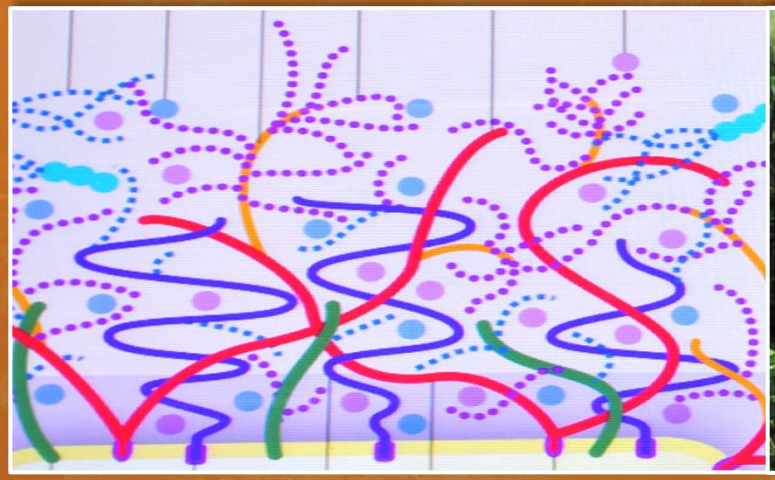

Editorials

Palliative Care for Pulmonary Patients

Am J Resp Crit Care Med 2010; 182: 752

Эндотелий – это то, о чем необходимо заботиться

Гликокаликс – затерянный в джунглях



Маркеры сепсиса

Клиническое применение

- **Выявление инфекции**
  - *Действительно ли у пациента имеется инфекция?*
    - ✓ Антибиотики, хирургическое вмешательство
- **Показатели тяжести**
  - *Относится ли пациент к группе высокого риска*
    - ✓ Прогноз, (новые) методы лечения сепсиса
- **Мониторинг ответа пациента на терапию**
  - *Улучшается ли состояние пациента?*
    - ✓ Повторная хирургическая операция, изменение режима антибактериальной терапии

Некоторые маркеры сепсиса

Resistin lactoferrin

Фибриноген

Неоптерин

Фосфолипаза

Копептин

Гелзолин

Gas6

Остеопонтин

ИЛ-13

ИЛ-10

sPLA2

СРБ

Эластаза

sCD163

TREM

Альфа амилоид

Факторы комплемента

Фосфолипаза

CD 64

ИЛ-6

Нитриты/нитраты

Рецепторы фактора некроза опухоли

Группа протеина высокой мобильности-1

sCD14

Фактор некроза опухоли

Прокальцитонин

Эндотелиальная молекула адгезии лейкоцитов-1

Миелоид, относящийся к протеину (MRP) 8 и 14

Альфа1антитрипсин

sIL-1 рецепторы

Церулоплазмин

Протеин С

Интерферон-γ

Рецепторы ИЛ-2

Эндотелин-1

Гранзим К

ИЛ-8

Е-селектин

Маркеры сепсиса


Пресепсин – самый ранний предиктор тяжести и исхода сепсиса
При развитии сепсиса повышение Пресепсина происходит через 1- 1,5 часа. (ПКТ через 14 часов)
Уменьшение ложноположительного сепсиса в 2 раза
Пресепсин имеет более высокую клиническую специфичность, чем прокальцитонин
Казань, Восстания-100, Химград,
564-65-49, 564-47-74, 564-36-31

- Рекомендации по определению уровня прокальцитонина обеспечивают уменьшение продолжительности лечения и уменьшение установленных суточных доз антибиотиков у больных в критическом состоянии с предполагаемой бактериальной инфекцией.
- Это уменьшение ассоциировалось со значительным снижением смертности. Концентрации прокальцитонина могут помочь врачу в определении истинной бактериальной инфекции, что позволяет выставить правильный диагноз и адекватное лечение – краеугольные камни антибиотикоуправляемости

Articles

Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial

Evelien de Jong, Jos A van Oers, Albertus Beishuizen, Piet Vos, Wytze J Vermeijden, Lennoke E Haas, Bart G J Loef, Tom Dormans, Gertrude C van Melsen, Yvette C Kluiters, Hans Kemperman, Maarten J van den Tweel, Jeroen A Schouten, Jörn O Stowelbank, Hans C Krabbe, Hans Kieft, Georg H Rüge, Veerle C van Dam, Joost van Felt, Laura Bormans, Martine Dekkerman-Otten, Auke C Reidinga, Henrik Endeman, Jos W Twisk, Iwoud M W van de Garde, Anne Marie G A de Smet, Josef Kesecioglu, Armand E Girbes, Maarten W Nijsten, Dylan W de Lange

Summary

Background In critically ill patients, antibiotic therapy is of great importance but long duration of treatment is associated with the development of antimicrobial resistance. Procalcitonin is a marker used to guide antibacterial therapy and reduce its duration, but data about safety of this reduction are scarce. We assessed the efficacy and safety of procalcitonin-guided antibiotic treatment in patients in intensive care units (ICUs) in a health-care system with a comparatively low use of antibiotics.

Methods We did a prospective, multicentre, randomised, controlled, open-label intervention trial in 15 hospitals in the Netherlands. Critically ill patients aged at least 18 years, admitted to the ICU, and who received their first dose of antibiotics no longer than 24 h before inclusion in the study for an assumed or proven infection were eligible to participate. Patients who received antibiotics for presumed infection were randomly assigned (1:1), using a computer-generated list, and stratified (according to treatment centre, whether infection was acquired before or during ICU stay, and dependent on severity of infection [ie, sepsis, severe sepsis, or septic shock]) to receive either procalcitonin-guided or standard-of-care antibiotic discontinuation. Both patients and investigators were aware of group assignment. In the procalcitonin-guided group, a non-binding advice to discontinue antibiotics was provided if procalcitonin concentration had decreased by 80% or more of its peak value or to 0·5 μg/L or lower. In the standard-of-care group, patients were treated according to local antibiotic protocols. Primary endpoints were antibiotic daily defined doses and duration of antibiotic treatment. All analyses were done by intention to treat. Mortality analyses were completed for all patients (intention to treat) and for patients in whom antibiotics were stopped while being on the ICU (per-protocol analysis). Safety endpoints were reinstitution of antibiotics and recurrent inflammation measured by C-reactive protein concentrations and they were measured in the population adhering to the stopping rules (per-protocol analysis). The study is registered with ClinicalTrials.gov, number NCT01139489, and was completed in August, 2014.

Findings Between Sept 18, 2009, and July 1, 2013, 1575 of the 4567 patients assessed for eligibility were randomly assigned to the procalcitonin-guided group (761) or to standard-of-care (785). In 538 patients (71%) in the procalcitonin-guided group antibiotics were discontinued in the ICU. Median consumption of antibiotics was 7·5 daily defined doses (IQR 4·0–12·7) in the procalcitonin-guided group versus 9·3 daily defined doses (5·0–16·4) in the standard-of-care group (between-group absolute difference 2·48, 95% CI 1·26–4·12, p=0·0001). Median duration of treatment was 5 days (3–8) in the procalcitonin-guided group and 7 days (4–11) in the standard-of-care group (between-group absolute difference 1·22, 0·65–1·78, p<0·0001). Mortality at 28 days was 149 (20%) of 761 patients in the procalcitonin-guided group and 196 (25%) of 785 patients in the standard-of-care group (between-group absolute difference 5·4%, 95% CI 1·2–9·5, p=0·0122) according to the intention-to-treat analysis, and 107 (20%) of 538 patients in the procalcitonin-guided group versus 121 (27%) of 457 patients in the standard-of-care group (between-group absolute difference 6·6%, 1·3–11·9, p=0·0154) in the per-protocol analysis. 1-year mortality in the per-protocol analysis was 191 (36%) of 538 patients in the procalcitonin-guided and 196 (43%) of 457 patients in the standard-of-care groups (between-group absolute difference 7·4, 1·3–13·8, p=0·0185).

Interpretation Procalcitonin guidance stimulates reduction of duration of treatment and daily defined doses in critically ill patients with a presumed bacterial infection. This reduction was associated with a significant decrease in mortality. Procalcitonin concentrations might help physicians in deciding whether or not the presumed infection is truly bacterial, leading to more adequate diagnosis and treatment, the cornerstones of antibiotic stewardship.

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Introduction

great importance in critically ill patients, but overly long antimicrobial treatment is undesirable because of increasing antibiotic resistance.[1] However, with

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Journal of Immunology Research

Важна не только абсолютная цифра, но и динамика

- *Цель*. Изучение что является лучшим индикатором инфекции у пациентов в критическом состоянии: абсолютное значение прокальцитонина или изменение показателей прокальцитонина.
- *Результаты*: Из **114** пациентов у **85** (**75%**) инфекция подтверждена.

Уровни прокальцитонина были сходными у I-группы (средний: *1.04 [0.40-3.57]* по сравнению с II-группой: *0.53 [0.16–1.68]*. Уровни прокальцитонина были значительно выше в I-группе: *4.62 [1.91–12.62]* по сравнению с *1.12 [0.30–1.66]*.

Область под кривой для прогнозирования инфекции для абсолютных значений прокальцитонина составила *0.64 [95% CI = 0.52–0.76]*; в процентном изменении: *0.77 [0.66–0.87]*; а для дельты-прокальцитонина: *0.85 [0.78–0.92]*.

Research Article

Delta Procalcitonin Is a Better Indicator of Infection Than Absolute Procalcitonin Values in Critically Ill Patients: A Prospective Observational Study

Domonkos Trásy,[1] Krisztián Tánczos,[2] Márton Németh,[1] Péter Hankovszky,[3] András Lovas,[1] András Mikor,[1] Edit Hajdú,[2] Angelika Osztroluczki,[1] János Fazakas,[4] and Zsolt Molnár[1]

Domonkos Trásy, Krisztián Tánczos, Márton Németh,1 Péter Hankovszky, András Lovas, András Mikor, Edit Hajdú, Angelika Osztroluczki, János Fazakas, Zsolt Molnár. Delta Procalcitonin Is a Better Indicator of Infection Than Absolute Procalcitonin Values in Critically Ill Patients: A Prospective Observational Study. Journal of Immunology Research Volume 2016 (2016), Article ID 3530752, 9 pages. http://dx.doi.org/10.1155/2016/3530752

Важна не только абсолютная цифра, но и динамика

- Оптимальное пороговое значение для дельты-прокальцитонина, подтверждающей инфекцию составило **0.76 нг/мл** чувствительность *80 [70–88]%*, специфичность *86 [68-96]%*.

Ни абсолютные значения, ни изменения СРБ, температуры или лейкоцитов не могут предсказать инфекцию

- *Заключение:* результаты работы позволяют предположить, что значения дельта-прокальцитонина являются лучшими по сравнению с абсолютными значениями в подтверждении инфекции у пациентов в критическом состоянии.

Research Article

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Спасибо за внимание!