

CAESAREAN SECTION AND THE RISK OF POSTPARTAL DEPRESSION: IS THERE A POSSIBLE ROLE OF HEAT SHOCK PROTEINS?

Krunoslav Šporčić¹, Marko Čačić², Krešimir Reiner³, Matko Pavlović⁴ & Slobodan Mihaljević⁵

¹Department of Anaesthesiology and Intensive Care Medicine, General Hospital Vinkovci, Vinkovci, Croatia

²Department of Cardiology, St. Antonius Hospital Kleve, Kleve, Germany

³Department of Anesthesiology and Intensive Care Medicine, Clinic for Obstetrics and Gynecology, University Clinical Hospital Centre Zagreb, Zagreb, Croatia

⁴Department of Psychiatry, General Hospital Bjelovar, Bjelovar, Croatia

⁵Department of Anaesthesiology, Reanimatology and Intensive Care Medicine, University Hospital Centre Zagreb, Zagreb, Croatia

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SUMMARY

Data on the potential connection between surgical stress during caesarean section and the role of heat shock proteins in development of postpartal depression is lacking in the literature. This is a narrative review with a goal to establish the potential role of heat shock proteins during caesarean section and development of postpartal depression. Systemic hyperinflammatory state, such as the one that occurs during surgery, may trigger protective cell reaction, which is usually called the heat shock response. Results of several researches bring strong evidence of correlation between expression of genes coding for family of heat shock proteins with the onset of depressive symptoms. Also, a recent meta-analysis established caesarean section as a risk factor for development of postpartal depression. It is obvious that heat shock proteins play a certain role in development of psychiatric disorders. However, a role of heat shock proteins in development of postpartal depression remains open for debate. We emphasise the need for a randomised control trial which would enable an answer to the mentioned issue.

Key words: heat shock proteins - caesarean section - postpartal depression

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INTRODUCTION

The rate of birth by caesarean section is in its peak in developed countries, as well as the clinical depression which is the most common mental health condition in the general population. Some data suggest that the rate of delivery by caesarean section increased for almost 50% over the past two decades. Rate of delivery by caesarean section is around 30% in most developed countries, which is attributed to maternal factors, such as increasing age and obesity, as well as the evolution in medicine which made caesarean section safer to perform regarding to maternal and fetal morbidity and mortality (Barber et al. 2011, Liston 2003). According to the World Health Organisation, globally more than 300 million people of all ages suffers from depression. Depression is also marked as a leading cause of disability worldwide. World Health Organisation has predicted that by the year 2020, depression will rank second in global disease burdens. Nowadays, worldwide prevalence of depression is estimated to be around 10% (Grace Y Lim et al. 2018). Some data confirm that more than 10% of mothers in developed countries are affected by postpartal depression (Lanes et al. 2011). Also, some data from the literature confirm that caesarean section represents a risk factor for developing postpartal depression (Xu et al. 2017). Heat shock proteins are very well recognised factor in inducing stress response

during various states, such as the stress response to surgical procedures. Further, some data also suggest the link between heat shock proteins and development of clinical depression. However, there is no data on the potential connection between surgical stress during caesarean section and the possible role of heat shock proteins in development of postpartal depression. This is a narrative review on the role of heat shock proteins in development of postpartal depression after caesarean section.

STRESS RESPONSE TO SURGERY

Surgical procedures are associated with complex local and systematic inflammatory response, characterised by neurohumoral, immune and metabolic changes. The choice of different anaesthetic techniques may alter the degree of systematic inflammatory response (Türkan et al. 2011, Marana et al. 2003, Malatinsky et al. 1986, Sacredote et al. 2000, Hamberger & Jarnberg 1983, Kelbel & Weis 2001, Guisasola et al. 2015). During operative and postoperative period, systemic response of mother and fetus is associated with oxidative stress, which is a result of an increased production of reactive oxygen species, as well as decrease in antioxidant enzymes, accompanied by the release of numerous pro and anti-inflammatory cytokines (Beilin et al. 2003, Mokart et al. 2005). This hyperinflammatory state may trigger protective cell reaction, which is usually called the „heat shock

response“, and represents a consequence of the cellular response to increased stress levels or high temperature. Within the aforementioned reaction, and proportionally to the intensity of stimulation, there is an increase in concentration of heat shock proteins within different cellular/biological compartments (Marana et al. 2003).

ROLE OF HEAT SHOCK PROTEINS IN PATHOPHYSIOLOGY OF MENTAL DISORDERS

Recent studies indicate strong connection between systemic inflammatory response followed by oxidative stress with pathophysiology underlying clinically significant episodes of affective disorders. Growing body of evidence suggest that higher expression of genes coding for family of heat shock proteins are in correlation with mood changes and anxiety levels. Nevertheless, the mechanisms of heat shock protein action and subsequent effects on psychic status, as well as its potential role in etiology of mental disorders are still unclear. Results of several researches bring strong evidence of correlation between expression of genes coding for family of heat shock proteins with the onset of depressive symptoms. A longitudinal study of neurotrophic, oxidative, and inflammatory markers in first-onset depression in mid-life women confirmed the thesis that inflammation, oxidative stress, and brain-derived neurotrophic factor are all associated with the pathophysiology of major depressive disorder. Study has shown that women suffering from major depressive disorder had higher activity of heat shock protein 70, which is important in cell protection from oxidative stress and direct inhibition of apoptosis, compared to those who did not develop major depressive disorder. Authors have also concluded that development of major depressive disorder in midlife women may be associated with a systemic cascade of pro-oxidative and pro-inflammatory events, including increased levels of heat shock protein 70 and decreased levels of brain-derived neurotrophic factor (Pasquali et al. 2017). Furthermore, heat shock proteins, among other pro-inflammatory proteins, became a new focal point in a pursuit for valid antidepressant efficacy predictors. A study conducted on one hundred and forty two patients suffering from major depressive disorder and treated with antidepressants has shown that genetic variants within the genes coding for family of heat shock protein 70 may affect the action of antidepressants and thus their therapeutic efficacy (Pae et al. 2007). A cross sectional study conducted on patients suffering from ulcerative colitis have shown that those with verified induction of heat shock protein 70 genes in polymorphonuclear cells from the affected areas of colon had significantly higher scores on psychometric scales used for evaluation of anxiety and depression, such as Zung Depression Rating Scale and Spielberg State-Trait Anxiety Inventory (Vlachos et al. 2014). Some authors also suggest that there is a connection between expression of genes coding for family

of heat shock protein 70 and levels of brain-derived neurotrophic factor. Researchers have investigated the effects of heat shock protein induction on neural structures in mice, focusing on hippocampal regions. Stressed mice were treated with geranylgeranylacetone, a known heat shock protein inducer. Results have shown evident decrease in hippocampal heat shock protein 105 expression in mice that were affected with stressful stimuli. The same mice have been treated with geranylgeranylacetone and consequently, the expression of heat shock protein 105 was increased. Authors have concluded that there is a correlation between higher heat shock protein 105 expression in hippocampus of a mouse and hippocampal cell proliferation, as well as elevation of brain-derived neurotrophic factor levels. From the clinical aspect, researches have noted improvement of depression-like behavior in mice treated with geranylgeranylacetone (Hashikawa et al. 2017).

Heat shock proteins are a group of proteins and highly conserved molecules that are present in almost all sub-cellular structures (e.g. nucleus, mitochondria, endoplasmic reticulum and cytoplasm) of all cell types, from prokaryotes to eukaryotes (Robert 2003). Traditionally, heat shock proteins have also been known as molecular chaperones because of their physiological and protective roles in the cells. They facilitate protein folding and maintenance of natural structures, as well as functions of other proteins, when cells are exposed to homeostatic challenges, such as extreme temperature, anoxia, hypoxia, prolonged exposure to heavy metals, drugs, or other chemical agents, that may induce stress or protein denaturation (Liu et al. 2012, Macario et al. 2007).

Human heat shock proteins are categorised under distinct families, based on their functions in the cells, their homologies in the primary structures, and their approximate molecular weight, which is measured in kDa (Kampinga et al. 2004). They have a dual role, depending on the intracellular or extracellular localisation. Intracellular heat shock proteins have a protective function and enable the cell to survive the deadly conditions (Bruemmer-Smith et al. 2001, Schmitt et al. 2007, Mehlen et al. 1996, Pandey et al. 2000). Extracellular, as well as the heat shock proteins localised on the cell membrane mediate immunological functions and play a key role in the stimulation of the immune system. In humans, the presence of heat shock proteins in serum is associated with the occurrence of stress factors, such as inflammation, bacterial, or viral infection. Although the heat shock proteins are protective and their endogenous increase in response to injury reduces cell damage, they can also lead to apoptosis. In other words, a paradoxical deleterious response can occur (Horváth et al. 2008, Pittet et al. 2002, Gelain et al. 2011, Heiserman et al. 2015).

Heat shock proteins play a crucial role in embryofetal development. They are involved in every stage of the reproductive process, from formation of the male and female gametes to fertilisation and post-fertilisation

development. Heat shock protein production is enhanced during in vitro embryo culture and they are among the first proteins produced during mammalian embryo growth. Furthermore, presence or absence of heat shock proteins influences various aspects of reproduction in many species. Various studies have shown that in mice, the 68–70-kDa heat shock proteins appear early in development and are primary products of the zygote (Saito et al. 2013, Morange et al. 1984).

Heat shock protein 70 is present at the blastocyst stage during differentiation of the embryonic internal cellular mass (Wittig et al. 1983). The expression of heat shock proteins appears to be a vital component of the preimplantation embryo. In mice and bovine blastocysts cultured in vitro, introduction of antibodies to the heat shock protein 60 and heat shock protein 70, as well as anti-heat shock protein 60 and anti-heat shock protein 70, respectively, significantly inhibits further embryo development (Neuer et al. 1998, Matwee et al. 2001). Role of heat shock protein 60 has been described as being similar to the role heat shock protein 70. Human anti-heat shock protein 60 and human anti-heat shock protein 70 have been detected in peripheral circulation of healthy non-pregnant individuals, as well as in pregnant women as a natural phenomenon (Ziegert et al. 2009).

CAESAREAN SECTION, HEAT SHOCK PROTEINS AND POTENTIAL LINK TO POSTPARTAL DEPRESSION

Stress response to surgery is modulated by several factors, including magnitude of the injury, type of procedure (e.g. laparoscopy vs laparotomy) and type of anaesthesia. One study showed that in the clinical setting of a low stress laparoscopic surgery, the changes associated with sevoflurane suggest a more favourable metabolic and immune response when compared to isoflurane. In addition, the type of volatile anaesthetic used significantly affected the stress response (Marana et al. 2003). One meta-analysis involving total of 28 studies with total of 532 630 participants suggests that caesarean section, as well as the emergent caesarean section, both increase the risk of developing postpartal depression. The authors concluded that adverse physiological outcomes during pregnancy, such as infection, postpartum hemorrhage, uterine rupture, chronic pelvic pain and gastrointestinal dysfunction might enhance surgical trauma and stress during caesarean section, which might increase the risk of postpartal depression (Xu et al. 2017).

It is obvious that heat shock proteins play a certain role in development of psychiatric disorders. However, the exact mechanisms of heat shock protein actions and subsequent effects on psychic status, as well as the potential role of heat shock proteins in etiology of mental disorders are still unclear. In the context of the issue mentioned above, it is also unclear what is the exact role of heat shock proteins in development of postpartal depression.

CONCLUSIONS

There is a growing incidence of delivery by caesarean section in developed countries which adds to the risk of developing postpartal depression. Heat shock proteins play a role in developing major depressive symptoms. In the context of a higher risk of developing postpartal depression after caesarean section, it is to conclude that heat shock proteins could have a potential role in developing depressive symptoms after caesarean section because they do exert an effect on central nervous system during surgical systemic stress response. It is to highlight the need for a randomised control trial which would enable a more appropriate answer on the issue of involvement of heat shock proteins in development of postpartal depression after caesarean section.

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Contribution of individual authors:

Krunoslav Šporčić & Slobodan Mihaljević: design of the study, literature searches and analyses, interpretation of data, manuscript writing, approval of the final version

Marko Čačić, Krešimir Reiner & Matko Pavlović: literature searches and analyses, manuscript writing, approval of the final version

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Correspondence:

Kresimir Reiner, MD

Department of Anesthesiology and Intensive Care Medicine,
Clinic for Obstetrics and Gynecology, University Clinical Hospital Centre Zagreb
Kišpatićeva 12, 10 000 Zagreb, Croatia
E-mail: kreso.reiner@gmail.com