The Effects of Chronic Stress on Female Fertility- a Brief Review of Definitions, Physiological Models of Interaction and Newest Evidence

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Introduction

Chronic stress is known to impact our health. Several models of interaction of how chronic stress can affect fertility have been proposed. These were mainly based on animal and cell studies. So far, the effect of chronic stress on fertility in populations based studies left inconclusive results while it had been easier to demonstrate that fertility treatments are associated with higher stress levels and reduced quality of life. In this brief review the definition of stress, the definition of infertility and sterility, common causes of infertility and the possible models of interaction between chronic stress and female fertility will be discussed with an insight into newest available evidence.

Definition, Classification and Measures of Stress

According to WHO (2021) *stress is defined as any type of change that causes physiological, emotional or physical strain and is considered the body's response to anything that requires attention or action*. Others define it as a state of real or perceived threat to homeostasis that may challenge an organism's well-being while the restoration of homeostatic conditions is mediated by complex endocrine, immune and nervous systems – the so-called stress response. Not everyone responds to stress in the same way (Smith and Vale, 2006; Joseph and Whirledge, 2017).

According to Palomba et al. (2018) stress can be divided into different sub-categories: acute time-limited such as public speaking; brief naturalistic such as seen in an academic examination; it can be seen in sequences; it can be chronic or distant (e.g. linked to a past traumatic experience). In a state of chronic stress the person experiences a sense of feeling overwhelmed and pressured over a long period of time. The Vienna-born scientist Hans Selye was the first one in 1949 to describe the three stages of adaptation a person goes through when experiencing chronic stress. The model is known as the *general adaptation syndrome*, a three-stage process that the body goes through when exposed to prolonged stress involving a phase of alarm reaction, one of resistance and a final stage of exhaustion (Selye, 1950; Burgess, 2017).

Causes for chronic stress can be extremely variated and can be for example of psychosocial, financial, infectious, lifestyle, nutritional or environmental nature (Burgess, 2017; Yale Medicine, 2022).

Psychological Measures of Stress:

Several questionnaires for assessing stress can be found. A valid and reliable assessment tool for personal stress is the Perceived Stress Scale (PSS). For more questionnaires please visit: https://humanstress.ca/researchers/measure-stress/questionnaires/

Physiological Measures of Stress:

The measurement of chronic stress is not simple. Newest evidence suggests that most reliable biomarker for stress is cortisol as well as adenocorticotropic hormone (ACTH). Hair cortisol measurement appears to the best biomarker for chronic stress providing a reliable evaluation of hypothalamic-pituitary-adrenal (HPA)- axis activity (Noushad et al., 2021). This study did however not consider salivary alpha-amylase which was proposed as a potential biomarker of noradrenergic activity and is used in several studies as a surrogate marker of stress (Lupien, 2013).

Definition of Infertility and Sterility

Definitions of infertility and sterility can vary depending on language. In the English language following definitions are used: according to WHO (2021) infertility is defined as a disease that affects the female or male reproductive system causing failure to achieve pregnancy after 12 months of unprotected regular intercourse. It can be primary or secondary, the first being defined as a pregnancy that has never been achieved and the latter as a pregnancy that is not achieved after at least one prior pregnancy (WHO, 2021). In medical usage sterility is generally defined as the inability to produce a live child either due to infertility, deliberately induced by surgical procedures or due to contraception (Oxford Reference, 2023).

In German language sterility and infertility are often defined as follow:
Sterility is defined as the failure to achieve pregnancy despite regular unprotected intercourse while infertility is defined as the inability to carry out a pregnancy after conception (Goerke and Valet, 2020). It is frequently seen that sterility and infertility are used interchangeably.
How are infertility and sterility defined in French language?

Infertility Rate in Switzerland

In Switzerland, approximately one in five couples is unable to conceive. Primary female causes are found in about 30% of cases, primary male causes also in about 30% and in about 20% of cases the inability to conceive is due to female and male causes. In the remaining 20% causes remain unknown (USZ, n.d.).

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Causes for Female Infertility

Female infertility can be caused by a series of abnormalities of the ovaries, fallopian tubes, uterus or the endocrine system.
Structural causes involve tubal disorders (caused for example by Chlamydia infection or abdominal/pelvic surgeries, postpartum sepsis or consequences of unsafe abortion), uterine disorders of congenital (e.g. uterus subseptus) inflammatory (e.g. adenomyosis, endometriosis) or of benign nature (e.g. uterine fibroids).
Disorders of the endocrine system are often the cause for hormonal imbalances of the reproductive hormones (WHO, 2020). Typical disorders include PCO-syndrome, adiposity, dysfunctions of the thyroid gland, diabetes, hyperprolactinemia. In particular higher age when starting family planning is often related to lower ovarian reserve. Further factors influencing fertility are lifestyle factors including long-term physical or emotional stress, use of medication, unhealthy diet, smoking, alcohol or drug abuse, environmental toxins, etc. (Goerke and Valet, 2020; WHO, 2020; USZ n.d.).

The Endocrine Feedback Loop of the Female Reproductive System

In normal circumstances and under the influence of the pulsatile secretion of gonadotropin-releasing-hormone (GnRH) secreted by the hypothalamus, the pituitary releases follicle stimulating (FSH) and luteinising hormone (LH). It must be mentioned that the pulsatile release of GnRH is of fundamental importance to the regulation of the menstrual cycle. It is driven by the hypothalamic neuronal networks. The exact mechanism of the pulse generator remains however inconclusive (Voliostis et al., 2019).
FSH and LH act on the ovary to regulate the maturation of the oocyte, ovulation as well as the production of steroid hormones. On the other hand, oestradiol, progesterone, activins and inhibins produced by the ovary regulate the secretion of gonadotropins by feeding backwards (Ehlert and Roland von Känel, 2010; Joseph and Whirledge, 2017).

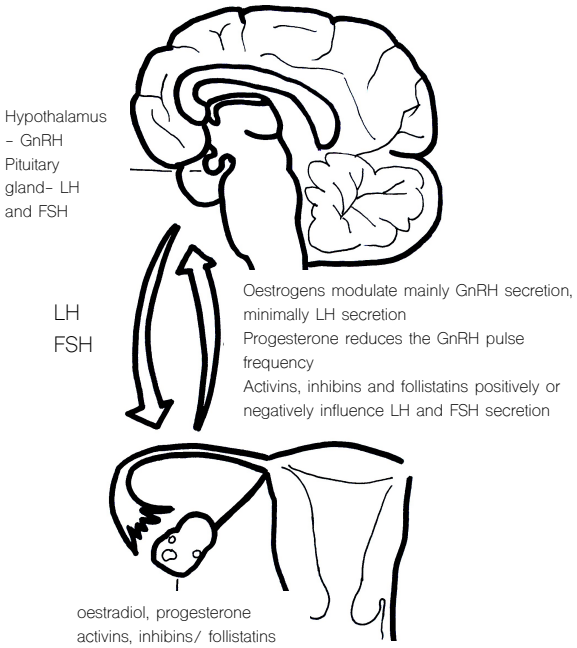

Figure 1 The endocrine feedback loop of the female reproductive system (R.J. Ramsauer, 2023)

Physiology of Stress on the Gonadal Axis

Most models of interaction are based on animal or cell culture studies. It has been observed that stress

factors can cause a change in the homeostatic regulation of different hormonal axes in particular of the HPA axis as well as the sympathetic-adrenal-medullary (SAM) axis causing hormonal dysregulation by mediating the functions of the hypothalamic-pituitary-gonadal (HPG) axis (Ehlert and Roland von Känel, 2010; Joseph and Whirledge, 2017; Palomba et al. 2018). Corticotropic-hormone (CTH) produced by the paraventricular nucleus of the hypothalamus was found to have an inhibitory effect on the kisspeptid hormone production leading to reduced GnRH levels. Similarly, high levels of glucocorticoids have an inhibitory effect on the GnRH neurons, the FSH and LH released by the pituitary as well as the gonads by reducing oestrogen production (Ehlert and Roland von Känel, 2010; Joseph and Whirledge, 2017). Besides the effects on the HPA and SAM axes, stress appears to independently act on female fertility by reducing endometrial receptivity (Kondoh et al., 2008). This study was however again an animal based study. The cross-sectional study by Pal, Bevilacqua and Santoro (2010) found that chronic lifetime psychosocial stressors are predictive of higher FSH levels as well as increased likelihood for a reduced ovarian reserve.
Stressful events appear therefore to affect ovulatory function, fertilisation and implantation.

Chronic Stress and Infertility

For many years the relationship between chronic stress and infertility has been discussed with somewhat inconclusive results while is has been easier to demonstrate that infertility as well as infertility treatments can cause stress (Rooney and Domar, 2018).
Evidence suggests that lifestyle factors have a major effect on female fertility. According to Ehlert and Roland von Känel (2010), physical stress seen for example in athletes has an impact on the female cycle leading to an amenorrhoea rate of more than 25%. Eating disorders such as anorexia nervosa (generally associated with a reduction in leptin levels) or depression can also lead to an amenorrhoea, affecting fertility. Studies analysing the effect of depression on the female cycle found an up to three-fold higher rate of amenorrhoea in women who had suffered of depression once during their lives. Depression significantly correlates with anxiety and elevated cortisol levels.
Interesting are the results seen in studies where reduced fertility outcomes were observed in couples going through assisted reproduction exposed to higher stress levels, fear or negative attitude towards life circumstances (Ehlert and Roland von Känel, 2010).
Already in 2014, the prospective cohort study by Lynch et al. found an association between stress and infertility. The recently published review of Palomba et al. (2018) evaluated the relationship between stress, quality of life and female fertility. The researchers concluded that the alteration of the HPA and HPG axes are the more likely mechanism of female fertility modulation as already seen in animal studies. Certain habits of modern life appear to significantly interfere with female reproductive health while on the other hand infertility, preconception stress and treatments for infertility appear to be a major stressor worsening quality of life and fertility outcome, thus creating a vicious circle.
Instead, psychological interventions such as mindfulness based stress reduction, relaxation training, cognitive behavioural therapy appear relevant in decreasing chronic stress and anxiety leading potentially to higher pregnancy rates (Rooney and Domar, 2018).

Conclusion

One in five couples is unable to conceive in Switzerland, female causes alone accounting for about 30% of cases. Numerous causes for infertility exists. In this short review, the effect of chronic stress on female fertility was evaluated. Interaction models explain how chronic stress influences the female reproductive system leading to fertility problems most likely mainly by affecting our HHA and SAM axes which then affect our HPG axis in turn. Human studies appear to support these models of interaction. Infertility and assisted reproduction treatments themselves are sources of stress and reduced quality of life. Various therapeutic approaches aiming at reducing stress levels can however be a useful treatment interventions in such circumstances.

Think about:
From an osteopathic perspective how could you try to influence the HPA/SAM and HPG axes? What techniques could you use and why? Are there any other hormonal axes you would consider assessing and treating when evaluating a female patient with infertility issues? What other treatment approaches would you consider and why?

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