

The reproductive stress hypothesis

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Abstract

In this paper, we propose the reproductive stress hypothesis that describes the pregnant females response to reproductive events based upon the activation of the hypothalamic–pituitary–adrenal axis and sympathetic adrenomedullary system. The main components of the reproductive stress hypothesis can be summarized as follows: (1) events unique to reproduction including emphysema, pregnancy, parturition and lactation cause non-specific responses in females, called active reproductive stress; (2) the fetus is a special stressor for pregnant females where endocrine hormones, including corticotropin-releasing hormones and fetal glucocorticoids secreted by the fetus and placenta, enter the maternal circulatory system, leading to another stress response referred to as passive reproductive stress and (3) response to uterine tension and intrauterine infection is the third type of stress, called fetal intrauterine stress. Appropriate reproductive stress is a crucial prerequisite in normal reproductive processes. By contrast, excessive or inappropriate reproductive stress may result in dysfunctions of the reproductive system, such as compromised immune function, leading to susceptibility to disease. The novel insights of the reproductive stress hypothesis have important implications for deciphering the pathogenesis of certain diseases in pregnant animals, including humans, which in turn may be applied to preventing and treating their occurrence.

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Introduction

The concept of stress was first introduced to the field of medicine and biology by the pioneer Hans Selye in 1936, where it was defined as ‘the non-specific response of the body to any demand’. Stress is a bodily, psychological or emotional factor that causes physical or mental tension. Any stimulation including external (environmental, psychological or social) or internal (disease or medical procedures) can induce stress. During times of heightened stress, the body activates the hypothalamic–pituitary–adrenal (HPA) axis (Smith & Vale 2006) and sympathetic adrenomedullary system (SAS) (Carter *et al.* 2015) in response to either real or perceived threats. This results in a cascade of hormone releases including adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH), cortisol, epinephrine (E) and norepinephrine (NE) (Chrousos 2000). Once the stress response is activated, behavioral and physiological changes adjust homeostasis to increase the chances of survival (Van de Kar & Blair 1999). In general, reproduction is a physiological process in mammals and regarded as a special stressor. At the symposium on the Internal

Medicine of Domestic Animals of the Chinese Association of Animal Husbandry and Veterinary Medicine in 2006, we put forward the first iteration of a reproductive cycle hypothesis. For over 10 years, we have supplemented and improved this hypothesis and its application which are reviewed herein.

Theoretical basis of the reproductive stress hypothesis

As a Chinese saying goes, ‘It is a matter of life or death when a mother faces delivering a baby after ten months of pregnancy’. Indeed, the reproduction process is life or death for the mother. Reproduction is a special stressor that overcomes the effect of routine external forces, activating a stress response that we refer to as reproductive stress. Herein, we define reproductive stress as the non-specific response of the body to reproductive activities including the estrous cycle, pregnancy, parturition and lactation. According to our hypothesis, reproductive stress includes active reproductive stress, passive reproductive stress and fetal intrauterine stress (Fig. 1).



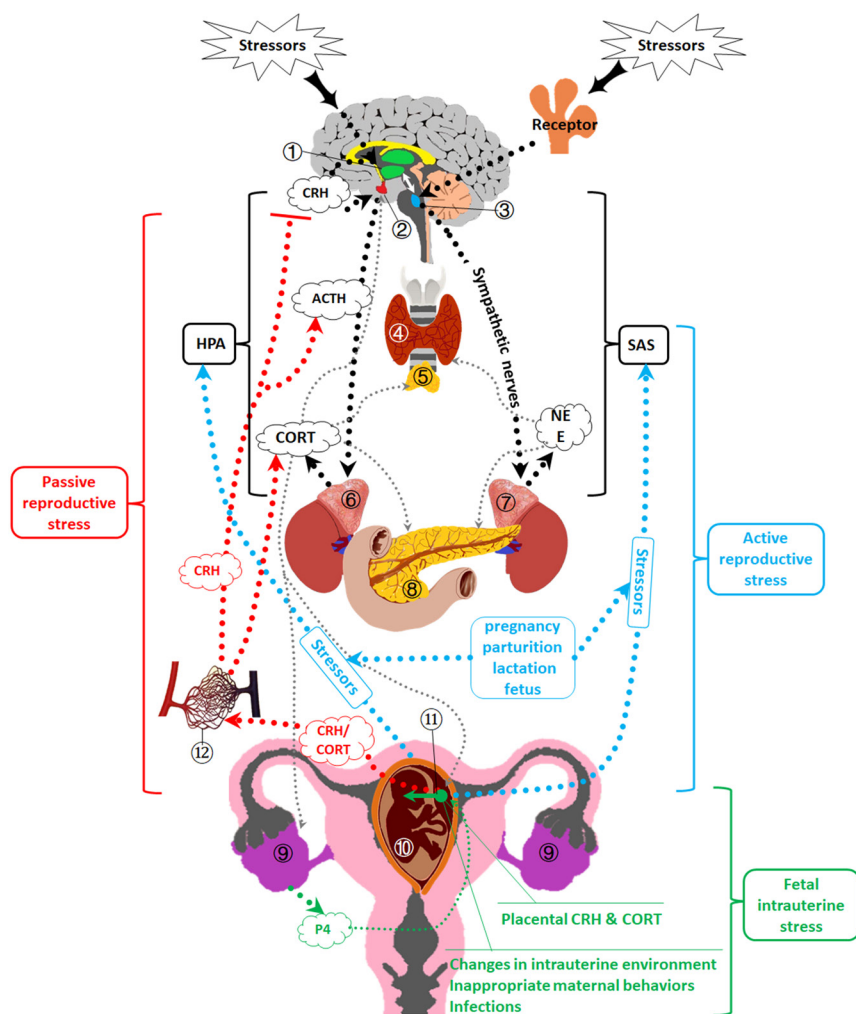


Figure 1 Mechanisms of regular stress and reproductive stress. ① Hypothalamus; ② pituitary; ③ locus coeruleus; ④ thyroid; ⑤ thymus; ⑥ adrenal cortex; ⑦ adrenal medulla; ⑧ islet; ⑨ ovary; ⑩ fetus; ⑪ placental barrier and ⑫ maternal circulatory system. Regular stress includes hypothalamic–pituitary–adrenal (HPA) axis and sympathetic adrenomedullary system (SAS), as illustrated with black symbols. Reproductive stress includes active reproductive stress, passive reproductive stress and fetal intrauterine stress. Active reproductive stress: the fetus and the processes of pregnancy, parturition and lactation act as stressors, triggering the HPA axis and the SAS, as illustrated with blue symbols. Passive reproductive stress: fetal and placental corticotropin-releasing hormone (CRH) and corticosterone (CORT) are secreted into the maternal circulatory system, the CRH inhibits the hypothalamus-secreted CRH and stimulates the secretion of adrenocorticotropic hormone (ACTH). The free CORT immediately acts on target organs through the maternal circulatory system, as illustrated with red symbols. Fetal intrauterine stress: during pregnancy, the placental CRH/CORT, infections, changes in intrauterine environment, as well as inappropriate maternal behaviors are stressors for the fetus, as illustrated with green symbols.

Active reproductive stress

The reproductive stress that activates the maternal HPA axis and SAS is designated as active reproductive stress in our hypothesis. Basal HPA activity varies with the fluctuation of the estrous cycle (Viau & Meaney 1991, Atkinson & Waddell 1997) and is highest at the end of the follicular phase or at the beginning of the luteal phase in human beings (Altemus *et al.* 2001). This is because both ACTH and cortisol as well as hypothalamic CRH content are increasing (Atkinson & Waddell 1997). Additionally, during proestrus, catecholamines increase rapidly before ovulation. This suggests that estrous can be a stressor. The enhanced HPA activity during proestrus may serve as a protective mechanism for successful reproductive activity during estrous phases (Viau & Meaney 1991).

To provide an appropriate intrauterine environment for the developing fetus, the maternal HPA system undergoes crucial alterations (Oyola & Handa 2017, Gilles *et al.* 2018). Although some studies have reported a plateau in total plasma cortisol concentrations and alleviation in HPA axis stress responses during late pregnancy (Russell *et al.* 2008), other studies have

demonstrated that the HPA axis and SAS are continually activated during pregnancy and parturition (Jung *et al.* 2011, Gilles *et al.* 2018). The maternal serum cortisol concentrations increase to 3-times the nonpregnant level throughout pregnancy in parallel to the rise in plasma corticosteroid-binding globulin (CBG) (Jung *et al.* 2011). The elevation of glucocorticoids and CRH in maternal and fetal plasma is closely associated with parturition (McLean *et al.* 1995), an indicator that parturition is an important event that leads to reproductive stress in pregnant females. Moreover, plasma levels of several components of the rennin-angiotensin-aldosterone system are increased during normal pregnancy (August *et al.* 1995). Notably, placental production of CRH, which is stress sensitive (Christian 2012), can influence the timing of parturition, namely preterm, normal term or post-term labor (McLean *et al.* 1995, Mastorakos & Ilias 2000, Hobel *et al.* 2008).

In formulating the reproductive stress hypothesis, we consulted a large body of work to compare changes in maternal hormones related to general stress and reproductive stress (mainly pregnancy and childbirth) (Table 1). The results show that the changes in stress

Table 1 Comparison of predominant hormones between regular stress and reproductive stress.

Hormones	Regular stress	Pregnancy or parturition	References
E/NE	Increase	Increase	Hydbring <i>et al.</i> 1999, Chrousos 2000, Gilles <i>et al.</i> 2018
CRH-ACTH-Glucocorticoid	Increase	Increase	McLean & Smith 1999, Mastorakos & Ilias 2003, Jung <i>et al.</i> 2011, Valsamakis <i>et al.</i> 2019
Renin-Angiotensin-Aldosterone	Increase	Increase	August <i>et al.</i> 1995, Lumbers & Pringle 2014, Verdonk <i>et al.</i> 2014
Dopamine	Increase	Increase	Ben-Jonathan & Maxson 1978, Tombeau Cost <i>et al.</i> 2017
Prolactin	Increase	Increase	Baan <i>et al.</i> 2008, Wagenmaker & Moenter 2017
Prostaglandin	Increase	Increase	Challis <i>et al.</i> 1997, Wagenmaker & Moenter 2017
Glucagon	Increase	Increase	Saudek <i>et al.</i> 1975, Harp <i>et al.</i> 2016
Insulin	Decrease	Increase with insulin resistance	Saudek <i>et al.</i> 1975, Kamba <i>et al.</i> 2016, Valsamakis <i>et al.</i> 2017
Testosterone	Decrease	Decrease	Carlsen <i>et al.</i> 2003, Oyola & Handa 2017
LH	Decrease	Decrease	Baan <i>et al.</i> 2008, Wagenmaker & Moenter 2017
GnRH	Decrease	Decrease	Sorem <i>et al.</i> 1996, Raftogianni <i>et al.</i> 2018
Progesteration	Decrease	Decrease or functional withdraw	Mitchell & Taggart 2009, Oyola & Handa 2017

ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone; E, epinephrine; GnRH, gonadotropin-releasing; NE, norepinephrine.

hormone levels during reproductive stress are consistent with those during general stress, where the levels of E, NE, CRH, ACTH and glucocorticoids in plasma are increased. The changes in other major hormones, inflammatory mediators and C-reactive proteins in the body are also similar. However, reproductive stress is different from general stress when considering certain hormones. For example, levels of both insulin and glucagon rise in late gestation (Saudek *et al.* 1975), but a reduction of insulin sensitivity is observed in normal pregnancy (Valsamakis *et al.* 2017).

This accumulating evidence indicates that reproductive activities, especially estrus, pregnancy and parturition are important stressors that can lead to a state of active reproductive stress.

Passive reproductive stress

The fetoplacental unit is an essential, special stressor that causes the secretion of endocrine hormones including CRH and glucocorticoids. During gestation, CRH production in the placenta (mainly in humans and other anthropoid primates), decidua and fetal membranes are responsible for the dramatic rise in circulating maternal immunoreactive CRH from the first trimester of pregnancy (Mastorakos & Ilias 2003), keeping pace with the maturing fetus during the second and third trimesters. In addition to the maternal sources, the mature fetus can also produce CRH, which causes the maternal CRH to peak during labor (Chen *et al.* 2010). The responsiveness of the mother to the fetus is termed passive reproductive stress in our hypothesis. It is distinct from active reproductive stress that involves maternal activation of the HPA axis and SAS. CRH acts on the fetal pituitary through CRH receptors, which can activate the fetal HPA axis. This leads to the release of ACTH, which acts on fetal adrenal glands and produces large amounts of cortisol and DHEAS (Ravanos *et al.*

2015). High cortisol concentration promotes fetal lung maturation and gene expression of CRH, prostaglandin and oxytocin in the placenta. Moreover, fetal CRH is regulated by fetal CRH-binding protein (CRH-BP) and glucocorticoids. CRH-BP can prevent placental CRH from overstimulating the pituitary gland, which may be one of the reasons for the mild elevation of ACTH levels in maternal blood (Thomson 1998).

Fetal intrauterine stress

Within the uterus, the fetus is vulnerable and exposed to many forms of stressors, including uterine tension, oligohydramnios, and potential intrauterine infection derived from disease, smoking or alcohol in the bloodstream. The responsiveness of the fetus to these stressors is called fetal intrauterine stress. Activation of the HPA axis is the main adaptive response of fetal intrauterine stress (Maršál 2018). However, the feedback of CRH by cortisol in intrauterine tissue is significantly different from that of the adult HPA axis (Menon *et al.* 2016). The former is a positive feedback loop, which produces exponential glucocorticoids before parturition, synchronizing with delivery and fetal organ maturation. However, premature birth occurs if the intrauterine environment is too extreme for fetal survival (McLean & Smith 1999).

The sequence of events between mother and fetus that trigger parturition in humans has not been fully elucidated. The promulgated theories include fetal membrane senescence (Menon *et al.* 2016), progesterone withdrawal, maternal CRH release, fetal HPA axis activation, inflammatory and mechanical factors (Ravanos *et al.* 2015). Our hypothesis posits that fetal intrauterine stress is the prime instigator of normal labor. According to the hypothesis, it is therefore predictable that multiple gestations will result in premature birth with the risk in triplets higher than for twins. Indeed, numerous reports confirm this response. In pregnant

marmoset models, scientists have showed that maternal peak and mean values for circulating CRH are correlated with fetal number. For example, pregnant females with triplets have higher CRH values than those with twins and those carrying a single fetus have the lowest value (Power *et al.* 2006). At present, premature birth risk is predicted by measuring plasma CRH concentrations. An overwhelming amount of data have demonstrated that the preterm delivery rate for multiple gestations is several times higher than for singletons (Heino *et al.* 2016, Vogel *et al.* 2018). One-third of triplets are delivered before 32 weeks of pregnancy (Papageorghiou *et al.* 2006). One study reported that the risk of preterm birth was nine-fold higher in multiple births than in singletons (Heino *et al.* 2016). An analysis of national data from 19 European countries (2004–2008) found that the increased prematurity rates in most countries was driven by higher rates of multiple births, as well as higher rates of prematurity among multiple births (Zeitlin *et al.* 2013). In some instances, these risks have resulted in selective reduction, called multifetal pregnancy reduction (from three to two fetuses in the case of triplets), in order to reduce the risk of severe preterm birth and high risk of miscarriage (Papageorghiou *et al.* 2006). In addition, the timing of parturition was significantly disrupted in experimental anencephaly (functional hypophysectomy) of the rhesus fetus, resulting in 30% preterm and 40% post-term delivery (Novy 1977), which strongly supports the importance of fetal intrauterine stress on initiation of parturition. In addition, fetal adrenal glands are large relative to adult adrenals (Mastorakos & Ilias 2003, Bronstein *et al.* 2015), providing a powerful engine for childbirth.

Physiological consequences of reproductive stress

Obviously, reproductive stress plays a significant role in human and animal reproduction processes. It exerts a wide array of physiological consequences in maternal hematologic, metabolic, endocrine and immune systems and plays a key role in events underlying fetal organ development. Maintenance of elevated serum aldosterone and cortisol concentrations during pregnancy is essential for the normal gestational increase in uterine blood flow (Jensen *et al.* 2005, Charkoudian *et al.* 2017). Physiologically, plasma volume increases by 10–15% at 6–12 weeks of gestation and then increases rapidly until 30–34 weeks (Whittaker *et al.* 1996, Jwa *et al.* 2015). It is believed that this is an adaptive mechanism to expand the plasma volume allowing for appropriate utero-placental perfusion and indirectly supports fetal arterial oxygen tension, blood pressure and development of the HPA axis (Jensen *et al.* 2002). Thus, reduction in maternal aldosterone and cortisol levels can disrupt both maternal and fetal homeostasis (Jensen *et al.* 2002). This may result in a compromised maternal state of intrauterine growth

restriction (West *et al.* 2014) and contribute to premature birth and neonatal morbidity (Schneiderman *et al.* 2017, Brue *et al.* 2018). Glucocorticoids are the determinants of cell proliferation inhibition, terminal differentiation stimulation and a basic switch for fetal organ maturation (Miranda & Sousa 2018). The most well-known function is to stimulate differentiation and functional development of the lungs (Busada & Cidowski 2017), the primary adaptive feature of aerobic life (Wood & Walker 2015). Mothers showing signs of premature labor are widely administered antenatal glucocorticoids to accelerate fetal lung development and prevent respiratory distress syndrome in preterm infants (Brownfoot *et al.* 2013, Busada & Cidowski 2017). Historically, maternal tolerance of a semiallogeneic fetus was thought to be achieved through immunosuppression (Racicot *et al.* 2014). It is now well recognized that the maternal immune system not only adapts during pregnancy, but also actively participates in all stages of the reproductive process. While glucocorticoids have been suggested to regulate reproductive function through gonadotropin (Gore *et al.* 2006) and glucocorticoid receptors (GRs) (Whirledge *et al.* 2015), recent studies have shown that female mice lacking GRs specifically in the uterus are subfertile, exhibiting defects in embryo implantation and subsequent decidualization related to inadequate remodeling of the endometrial stroma (Whirledge *et al.* 2015). In addition to their effect on lung development and the reproductive system, glucocorticoids play an essential role in accelerating the development of several other organ systems, such as the fetal cardiovascular system (Unno *et al.* 1999, Rog-Zielinska *et al.* 2014), gastrointestinal tract (Lebenthal *et al.* 1999), liver (Fowden *et al.* 2011) and brain (Buss *et al.* 2012) for the transition to extrauterine life. Late fetal glucocorticoids also regulate metabolic functions, including thyroid hormone secretion, glycometabolic enzyme activity in the liver and fat reserve mobilization for the brain and liver during the first postnatal days (Wood & Walker 2015).

Reproductive stress syndrome

However, reproductive stress is a sustained and prolonged process for pregnant females, potentially resulting in alteration of neuroendocrine events, changes in metabolism (Parisi *et al.* 2019), impairment of immune function and possible dysfunction of the reproductive system, which we designate as reproductive stress syndrome. Its clinical symptoms are complex and particular to reproductive activities but can be summarized into three categories.

First, an important clinical manifestation of reproductive stress syndrome is the abnormality of bone metabolism, which may result in osteoporosis over time. This can happen when maternal nutrition supply is insufficient or reproductive tasks are aggravated,

especially during the third trimester when the rate of fetal bone accretion is increasing. The maternal stress mechanism mobilizes the body to store nutrients to ensure the needs of offspring (Hacker *et al.* 2012). To ensure fetal growth and lactation, mobilization of body reserves is needed to accelerate the loss of nutrients such as calcium (Eisman 1998, Kovacs & Ralston 2015). On the other hand, excess glucocorticoids have harmful effects on the proliferation and differentiation of osteoblasts as well as the survival of osteoblasts and osteocytes, leading to the acceleration of the apoptosis and/or autophagy of osteoblasts (Komori 2016). Meanwhile, large amounts of endogenous glucocorticoids decrease bone strength via interconnected decrements in bone angiogenesis, vasculature volume and osteocyte–lacunar–canalicular fluid in osteoblasts and osteocytes (Weinstein *et al.* 2010).

A second clinical symptom of reproductive stress syndrome is reproductive disorders including sexual dysfunction in postpartum women (Khajehei *et al.* 2015) and the delay or absence of estrus. During the prepartum period, the reproductive stress mechanism is characterized by HPA axis activation and hypothalamic–pituitary–gonadal axis suppression (Mitchell *et al.* 2005, Grachev *et al.* 2014). High levels of CRH or arginine vasopressin secreted by the hypothalamus suppresses gonadotropin-releasing hormone and/or luteinizing hormone secretion (Dobson *et al.* 2003, Ciechanowska *et al.* 2018). Moreover, undernutrition or a large amount of body reserve loss results in the body's negative energy balance, which induces persistently low levels of insulin (Lucy 2008) and decreases the expression of growth hormone receptors in the liver and the secretion of insulin-like growth factor-1 (IGF-1). This negatively impacts reproduction as insulin and IGF-1 are unable to synergize with the gonadotrophins on ovarian cells, preventing the dominant follicle from ovulating and delaying the resumption of the estrous cycle, thereby inhibiting reproductive function (Walsh *et al.* 2011).

A third clinical aspect of reproductive stress syndrome is the potential decrease in immune function resulting in increased disease during pregnancy and parturition. Pregnancy and the postpartum period are marked by high glucocorticoids levels, as the end products of reproductive stress, and may result in autoimmunity, chronic infections, major depression or atherosclerosis through a dysregulation of the pro/anti-inflammatory and T helper (Th) 1/Th2 cytokine balance (Calcagni & Elenkov 2006). Free glucocorticoids and catecholamines systemically induce an inhibition of cytokines produced by antigen-presenting cells and Th1 cells, like interleukin (IL)-12, interferon (IFN)- γ , IFN- α and tumor necrosis factor (TNF)- α and to an upregulation of cytokines produced by Th2 cells, such as IL-4, IL-10 and IL-13 (Elenkov & Chrousos 1999, Elenkov 2003). Moreover, high maternal cortisol levels can suppress T-cell proliferation and reduce lymphocyte sensitivity to

glucocorticoids via binding on GRs (Vianna *et al.* 2011). These changes negatively affect the immune system and anti-inflammation effects throughout the process of reproductive stress.

The important application of reproductive stress hypothesis

Novel insights into human diseases from the reproductive stress hypothesis perspective

The reproductive stress hypothesis can be used to predict the risk of emerging maternal diseases and pathogenesis of commonly seen diseases, such as pregnancy-induced hypertension syndrome (PIH) and gestational diabetes mellitus (GDM).

Cushing's syndrome during pregnancy

Prolonged hypersecretion of free cortisol can induce Cushing's syndrome (Bronstein *et al.* 2015, Caimari *et al.* 2017). The presence of free cortisol can explain some of the maternal phenotypic changes associated with pregnancy such as light concentric obesity, moon face, fluid retention, supraclavicular fat pads (Wallace *et al.* 1996), feeling nervous and agitated, as well as antenatal and postpartum depression (Kammerer *et al.* 2006). Appreciation for this potential relationship emphasizes the importance of proper maternal care for successful health outcomes, especially for multiple pregnancies.

Various causes of CBG deficiency can aggravate Cushing's syndrome during pregnancy. The level of CBG is regulated by several relevant hormones, such as estrogen, and CBG decreases in the case of hyperthyroidism (Agbaht *et al.* 2014). Thus, there is ample reason to suspect that hyperthyroidism and impaired liver function pose an increased risk of Cushing's syndrome onset.

Maternal postnatal adrenocortical hypofunction syndrome, the significance of natural labor and the risk of cesarean

Fetal CRH and cortisol, exogenous hormones for the mother, are transferred to the maternal circulatory system and induce passive reproductive stress. Because of the negative feedback loop, high levels of free cortisol inhibit the secretion of CRH and ACTH, which may result in hypothalamic–pituitary–adrenocortical hypofunction. A sudden withdraw of the exogenous hormones during labor may cause hypoadrenalism and may cause serious adrenal crisis in the pregnant woman. The stimulation of labor pain reactivates the HPA axis, which may be important for preventing the adrenal crisis and may also reduce the incidence of postpartum depression. Thus, spontaneous labor among women and animals has important clinical consequences.

Currently, cesarean section (CS) is prevalent worldwide and it is a global concern. China stands out as one of the countries with the highest rates with about 50.0% of deliveries (Lumbiganon *et al.* 2010, Wang *et al.* 2017). Concomitantly, the number and rate of multiple births have dramatically risen, mainly attributable to reproductive technology such as *in vitro* fertilization. The CS rate for multiple pregnancies has also increased, largely due to the perception that CS can improve neonatal outcomes. Based on the reproductive stress hypothesis, at least two risks associated with CS can be predicted and prevented. The first is that CS may increase the risk of postpartum depression. Secondly, multiple gestations result in severe reproductive stress, particularly passive reproductive stress, which may lead to severe hypofunction of HPA that presents as shock, coma and/or death.

PIH and GDM

PIH and GDM are the main contributors to adverse maternal and fetal outcomes worldwide, especially maternal and fetal death. Indeed, PIH and GDM, both important components of metabolic syndrome (Veerbeek *et al.* 2015), are driven by similar determinants (Guariguata *et al.* 2014) including biological and genetic history, depression, short stature, older maternal age and obesity or undernutrition (Werner *et al.* 2015, Dolin & Kominiarek 2018, Mizushiri *et al.* 2018). Hypertensive pregnancy disorders, particularly GDM, are closely (Leng *et al.* 2015), and possibly directly, linked with subsequent cardiovascular morbidity (Lykke *et al.* 2009). A survey of women delivering in Denmark from 1978 to 2007 showed that mothers with PIH have a 3.12-fold greater risk of type 2 diabetes (Lykke *et al.* 2009). Another study reported the PIH-related morbidity among pregnant women in Simao City, Yunnan Province of China, was 3.6%, while the morbidity among impoverished immigrant women was 57.5% due to malnutrition (Li *et al.* 2006 in Chinese). Similar results were found for women with GDM. According to the global prevalence data of GDM (aged 20–49 years) in 2013, the highest prevalence was found in Southeast Asia (25.0%) compared with 10.4% in North America and the Caribbean (Guariguata *et al.* 2014). It is estimated that about 90% of cases of GDM occur in low- and middle-income countries (Guariguata *et al.* 2014, Goldenberg *et al.* 2016).

The pathogenesis of PIH and GDM is not very clear, but the reproductive stress hypothesis may provide an explanation. Incremental levels of free CRH and cortisol can cause severe passive stress, resulting in elevated blood pressure and blood sugar during pregnancy. The passive reproductive stress is regulated by CRH-BP and fetal free cortisol. Approximately 90% of the cortisol in circulation is bound to proteins (CBG and albumin) that are inactivated (Lewis *et al.* 2005) and the remaining

unbound fraction is biologically active. If the CBG is low or has impaired function and albumin is low, the free cortisol increases markedly, thereafter affecting the HPA axis (Lewis *et al.* 2005). Theoretically, factors that can lower immunoreactive CBG and albumin as well as increase free CRH and cortisol levels, such as malnutrition, negative nitrogen balance, liver diseases and kidney dysfunction during pregnancy, may lead to PIH and GDM. Consequently, the activated HPA axis and SAS should be considered as a fundamental cause of PIH and GDM, inducing the increased risk for elevated blood pressure and diabetes (O'Keeffe & St-Onge 2013, Hayase *et al.* 2014).

Numerous studies have confirmed this hypothesis. With PIH for example, maternal malnutrition, encompassing being overweight, obesity and undernutrition (especially protein restriction), affects the HPA axis by reducing the function of placental 11 β -hydroxysteroid dehydrogenase type 2 enzyme (11 β -HSD2). 11 β -HSD2 is the fetoplacental barrier to maternal glucocorticoids, which oxidizes bioactive cortisol into bio-inactive cortisone (Salvante *et al.* 2017). This in turn increases fetal exposure to maternal cortisol, suggesting that maternal malnutrition may have an impact not only on nutritional programming, but also on fetal stress response (Micali & Treasure 2009), thus resulting in passive reproductive stress. Studies have shown that changes in 11 β -HSD2 protein activity, which is expressed in the kidney, significantly affects blood pressure levels in healthy adults (Ferrari *et al.* 2001). Hypermethylation of the 11 β -HSD2 promoter leads to higher levels of cortisol relative to cortisone through decreasing 11 β -HSD2 synthesis, eventually facilitating the hypertensive phenotype (Ferrari *et al.* 2001, Argentieri *et al.* 2017). Meanwhile, high levels of free cortisol can affect the regulation of the kidney's sodium uptake, alongside aldosterone, and can therefore have a direct impact on salt-induced hypertension (Hunter *et al.* 2014). Accordingly, it is acceptable to presume supplementation of albumin and CRH-BP, nutritional enhancement or reducing the levels of free cortisol may prevent PIH and GDM.

Malnutrition is a broad term that includes many different manifestations of nutritional deficiencies, including undernutrition and obesity. Its main characteristic is unbalanced energy intake and consumption. It is said that many low- and middle-income countries bear the double burden of malnutrition, with stunted growth, lack of essential nutrition, along with obesity in the national population and families (Black *et al.* 2013). In the past 10 years, the nutritional health of pregnant women in China has been greatly improved, and undernutrition has been reduced, but the prevalence of relative malnutrition in pregnant women has increased. The fetus is developing rapidly over time and needs a lot of nutrients in the third trimester and may result in relative undernutrition. To meet the needs of the fetus, mothers mobilize their

nutritional storage (such as calcium), which easily leads to negative nitrogen balance and aggravated stress. This may subsequently induce HIP, GDM and other complications. Especially in China in 2015, following the implementation of the two-child policy, the situation became serious because of the increasing number of advanced-age pregnant females.

Prevention of reproductive stress syndrome

To reduce the negative effects of reproductive stress syndrome, certain measures may be taken to (1) ensure maternal nutrition supply is sufficient, especially balanced protein-energy supplementation to avoid the negative nitrogen balance during pregnancy and parturition; (2) modulate the level of CRH and free cortisol to avoid excessive stress; (3) improve the immune ability of the pregnant female and take preventative measures for osteoporosis; (4) ensure that all pregnant women have access to skilled care, including mental health services, during pregnancy, childbirth and the postpartum period; (5) use glucocorticoids with caution in the treatment of reproductive stress syndrome because of side effects that lower maternal immunity, or even worse, restrict the fetal development and growth as evidenced by reduced birth weight and impaired neuronal development reported for these fetuses (Newnham *et al.* 1999). However, a replacement of glucocorticoids may be recommended for therapy of hypoadrenalism after parturition.

Conclusions

In summary, we presented the reproductive stress hypothesis describing the physiological responses to stress in pregnant females during reproductive events. Reproductive stress is a double-edged sword. On the one hand, appropriate reproductive stress is a prerequisite for performing successful reproductive processes. On the other hand, inadequate or excessive reproductive stress may impair reproductive functions and result in a number of complications. The reproductive stress hypothesis is helpful to account for the onset of parturition and to predict some diseases using a novel framework. Necessary interventions should be taken for preventing the negative consequences of reproductive stress syndrome.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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