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Review

Prenatal maternal stress: effects on pregnancy and the (unborn) child

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Abstract

Background: Animal experiments have convincingly demonstrated that prenatal maternal stress affects pregnancy outcome and results in early programming of brain functions with permanent changes in neuroendocrine regulation and behaviour in offspring. *Aim*: To evaluate the existing evidence of comparable effects of prenatal stress on human pregnancy and child development. *Study design*: Data sources used included a computerized literature search of PUBMED (1966–2001); Psychlit (1987–2001); and manual search of bibliographies of pertinent articles. *Results*: Recent well-controlled human studies indicate that pregnant women with high stress and anxiety levels are at increased risk for spontaneous abortion and preterm labour and for having a malformed or growth-retarded baby (reduced head circumference in particular). Evidence of long-term functional disorders after prenatal exposure to stress is limited, but retrospective studies and two prospective studies support the possibility of such effects. A comprehensive model of putative interrelationships between maternal, placental, and fetal factors is presented. *Conclusions*: Apart from the well-known negative effects of biomedical risks, maternal psychological factors may significantly contribute to pregnancy complications and unfavourable development of the (unborn) child. These problems might be

Abbreviations: ACTH, adrenocorticotropin-releasing hormone; CRH, corticotropin-releasing hormone; pCRH, placental CRH; CRH-BP, CRH binding protein; GR, glucocorticoid receptors; PG, prostaglandins; Oxyt, oxytocin; DHEA-S, dehydro-epiandrosterone-sulphate; 11β-HSD, 11β-hydroxysteroid-dehydrogenase.

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reduced by specific stress reduction in high anxious pregnant women, although much more research is needed.

Keywords: Prenatal stress; Maternal anxiety; Pregnancy; Child development; Pregnancy complications; Stress regulation

1. Introduction

'To begin my life with the beginning of my life, I record that I was born'. This is the first sentence in the chronicles of David Copperfield [1]. According to Ch. Dickens, human development does not start until after birth, and most scientists until the mid-20th century have also ignored the importance of life in the womb [2]. However, today we know that normal growth and development of the unborn child can be negatively influenced by a number of factors, including complications of pregnancy, infections, and teratogens.

Intrauterine exposure to medicinal and social drugs (alcohol, cocaine, tobacco) may cause structural and/or functional developmental deficits that often result in life-long physical or mental handicaps. Moreover, epidemiologic and experimental animal studies have demonstrated strong evidence that fetal exposure to an overall nutritional deficiency or a shortage of specific nutrients during a critical period may lead to permanent alterations in the development and function of a particular organ system [3,4]. This early programming is related to the emergence of a number of diseases in later life, including cardiovascular and allergic diseases, hypertension, diabetes, and schizophrenia.

Little is known about possibly deleterious and/or programming effects on the unborn child of maternal psychologic influences or stress during pregnancy. For a long time, people thought that maternal psychic impressions would induce a structural fetal abnormality ('maternal imagination'). For instance, it was believed that sudden fright because of a leaping hare would result in a child with a harelip. Another example of association of ideas is a child affected with ichthyosis born to a mother who has done her washing regularly in a river where fish were abundant [5]. Although these cases have to be ascribed to popular superstition, recent animal experiments have yielded sound proof that prenatal maternal stress affects the fetus resulting in life-long effects [6–8]. The aim of this review is to evaluate whether the effects of stress on the course of pregnancy and the offspring as found in many animal experiments also apply to the human situation.

2. Stress and pregnancy

In daily life, humans and animals are often confronted with situations that demand adaptation. There is stress if adaptation is with great difficulty or impossible. The physiologic and behavioural responses to stressors are generally well known, though

mainly for male adults [9]. Stressors may vary from life events (e.g. divorce, serious illness or death of a relative or friend) to daily hassles (e.g. domestic affairs, financial or relational problems, and queuing). During exposure to a stressor, the whole system of stress regulation, that is, the hypothalamus–pituitary–adrenal cortex system (HPA axis) and the sympathetic nervous system–adrenal medulla system, is activated. Various hormones, including corticotropin-releasing hormone (CRH), adrenocorticotropin-releasing hormone (ACTH), cortisol, and (nor)adrenaline, are released in large quantities to the blood. However, individuals may respond differently to an identical stressful stimulus. The degree of stress response depends also on genetic factors, personality characteristics, previous experience, support from the social environment, and the way of coping with stress. This applies to pregnant women as well. However, they are also confronted with other possible stress factors, such as physical alterations, hormonal changes (often associated with rapid changes in mood), and pregnancy-specific anxiety, for example, fear of child integrity and fear of pain during delivery [8,10]. Moreover, young age, poor education, low socioeconomic status, sexual abuse, unwanted pregnancy, having no partner, poor preparation for pregnancy or delivery, and depressive symptoms and a psychiatric history are known to negatively influence psychic well-being of the pregnant woman, while other factors (adequate social support, older age, and having a paid job) contribute positively to this [11]. The interaction between all these factors renders stress research in pregnant women to be complicated and requires a multidimensional concept of stress involving psychologic, social, and physiologic components. However, researchers of prenatal stress have generally confined themselves to only one aspect of stress or anxiety, such as the effects of life events, work load, or general stress that were evaluated by using self-administered inventories. Physiologic and hormonal responses to stress in pregnancy or the effects of pregnancy-specific anxieties have only sporadically been investigated to date [2,8,12].

3. Prenatal stress and complications of pregnancy

The HPA axis and the reproductive system show a complex relationship in both pregnant and non-pregnant women. The hormones of the HPA axis have strong, mainly inhibiting, effects on the HPG(onads) axis [9]. Moreover, CRH and cortisol receptors are abundant in the endometrium, myometrium, and the ovaries. It is therefore not surprising that psychologic (and physical) stress may disturb the sexual and reproductive capacities. Anovulation, oligomenorrhea, and reduced libido are often seen under these circumstances.

In vitro-fertilisation (IVF) patients with functional disorders of the HPG axis often have higher stress-scores than women who are infertile on the basis of anatomic problems (tuba obstruction, malformations of the cervix or uterus) [13]. Some IVF studies, but not all, have also demonstrated that the chance to conceive and to bring the pregnancy to a good end is smaller if the patient reports more stress or anxiety at the onset of therapy [14,15].

Animal experiments have shown that exposure of the pregnant dam to stressful conditions (capture, noise, immobilisation, introduction of a strange male, crowding,

etc.) often results in a smaller litter size (embryo resorption), structural malformations, growth retardation, lower birth weight of the puppies, and even a shift in the sex ratio [16]. Recent well-controlled studies in humans also suggest a direct relationship between prenatal maternal stress and a number of pregnancy complications.

3.1. Spontaneous abortion

An increased risk of spontaneous abortion has been found for a recent life event (death of a relative or being victim of criminality) [17], and for stress in the work place [18].

3.2. Structural malformations

A strong relationship has been found between the (unexpected) death of an older child during early pregnancy and the occurrence of craniofacial malformations and heart defects [19]. A number of studies have shown that structural malformations can also emerge in the context of increased psychosocial problems, especially for quarrels with the partner or members of the family [20].

3.3. Preeclampsia

Depression and anxiety [21] and also some forms of work stress [22] that are experienced during the first trimester seem to be associated with an increased risk for developing preeclampsia in a later phase of pregnancy. Patients who eventually develop preeclampsia often have increased serum concentrations of placental CRH (pCRH) from 18 to 20 weeks of gestation onwards (see below) [23,24].

3.4. Preterm delivery

The relationship between stressful experiences during pregnancy and an increased risk of preterm delivery has been a consistent finding of independent studies for several decades [25,26]. It has been suggested that preterm uterine activity and shortened length of pregnancy result from stress during the third trimester. Remarkably, serum concentrations of placental CRH are already raised at 15–20 weeks of pregnancy in women who deliver preterm [23,27].

3.5. Birth weight

Recent well-controlled research has documented that high levels of anxiety and depression result in reduced birth weight and smaller head size (a measure of brain development). This effect of prenatal stress is of the same magnitude as the effect of smoking [25]. The chance of delivering a low birth weight baby is higher if exposure to stress, daily hassles in particular, occurs during the first 3 months of pregnancy [28]. This may explain why others found a normal birth weight in infants of women whose husband died after the fourth month of pregnancy [29].

4. Prenatal stress and development of the central nervous system: animal experiments

Animal experiments in which the mother (rat, monkey) was exposed to various stressors during pregnancy (electric foot shock, immobilisation, unexpected loud noises, etc.) have demonstrated that this treatment results in various permanent changes in the offspring. Prenatally stressed animals show delayed motor development and exhibit, at adult age, reduced exploration and adaptive behaviour, more emotional and anxious reactions in an unfamiliar environment, impaired cognitive functions (attention, learning), and alterations in social and sexual behaviour (e.g. feminisation of masculine behaviour) [6–8,30]. Studies in the rhesus monkey have demonstrated that these postnatal effects are largest in animals of which the mothers were exposed to stress during early pregnancy [7].

In later life, prenatally stressed animals also have higher basal blood glucocorticoid levels and a reduced number of glucocorticoid receptors (GR) (down-regulation) in the hippocampus. When exposed to a stressful stimulus, their hormonal response not only is more rapid and stronger, but prolonged as well. These findings of hyperactivation and dysregulation indicate that the normal negative feed-back mechanism of the HPA axis is heavily impaired [6–8]. Besides, alterations have been found in almost all known regulatory and neurotransmitter systems in the brain, including the opioid, cholinergic, serotonergic, dopaminergic, GABA-ergic, and noradrenergic systems [6,8].

Many of the changes induced by prenatal maternal stress can also be brought about by maternal administration of natural or synthetic corticosteroids [31–33]. This treatment can result in growth retardation [31], structural malformations (especially in the craniofacial region) [31], neurotoxic effects (the hippocampus in particular) [34], delayed motor development [33], and aberrations in neuroendocrine responses to stressful events in offspring [6,8]. These findings illustrate that the maternal HPA axis is involved in early neuroendocrine programming of her offspring [32].

5. Prenatal stress and development of the central nervous system: observations in the human

It is presently unclear if prenatal programming of brain functions also occurs in the human. We do know that exposure to an increased maternal stress level influences fetal brain growth (reduced head circumference) and that prenatally stressed infants have lower scores at neonatal neurologic examination [25].

During ultrasound observation, fetuses of high anxious women have been found to be more active than those of low anxious women [35]. This is in line with the observation of dramatically increased fetal movements during acute maternal panic caused by an earthquake [36]. This finding illustrates that a maternal stress signal reaches the fetus and that he or she responds to it.

Some studies performed within 2–3 days after birth have demonstrated that newborn infants cry more and are difficult to sooth if their mothers were more anxious, had more depressive symptoms, or were classified as a type-A mother (flurried, impatient, and competitive) [37]. These studies suggest that the differences in neonatal behaviour

emerged before birth (either due to prenatal stress or genetically determined), as they were unlikely caused by environmental influences in the short period thereafter. However, the mode of delivery may have played a role. Recently, it was found that infants born after assisted delivery (forceps or ventouse) showed a greater stress response to inoculation at 8 weeks (they cried more and for longer periods, and had higher cortisol secretion) than infants born vaginally or by caesarean section [38].

Retrospective studies have related problems at child age to maternal psychologic stress during pregnancy resulting from, for instance, aircraft noise, family or relational problems, or death of the partner [6,39]. Remarkably, many of the problems at child age resemble those seen in well-controlled animal experiments, such as delayed motor development, and cognitive and behavioural disorders. In psychiatric literature, exposure to prenatal maternal stress is often regarded an important factor underlying several forms of psychopathology, including attention deficit hyperactivity disorder (ADHD), schizophrenia, and depression [40–42]. Increased concentrations of cortisol (blood) and CRH (cerebrospinal fluid), and a hyperresponsive HPA axis which is difficult to influence with the dexamethasone-suppression test, are characteristic for adult depressive patients. Attention deficits as seen with ADHD are also known to occur in prenatally stressed animals. So, also in the human, early neuroendocrine disturbances may predispose for psychic and/or other disorders in later life [43], but only prospective longitudinal studies with multiple measurements of prenatal stress and thorough follow-up of the children may answer this question. At present, only two such studies have made a start and are still in progress.

Huizink [8] performed a study in 170 healthy nulliparous women. Levels of maternal stress and anxiety were determined three times during pregnancy. High amounts of stress and anxiety during the first trimester of pregnancy appeared to be associated with low psychomotor scores on the Bayley developmental test and poor adaptation to a new environment, and with more problematic behaviour when the infants were 8 months of age. The strongest effects on infant development and behaviour were found for pregnancy-specific anxieties, such as fear of health and integrity of the unborn baby and fear of (pain during) delivery.

Van den Bergh [10] and Van den Bergh et al. [12] followed-up 70 mother–infant pairs from the first trimester of pregnancy to the age of 9 years. Observations of fetal behaviour at 36 weeks' gestational age (using ultrasound) and of neonatal behaviour showed that infants of high anxious women had more bodily activity than infants of low anxious women. During the first 7 months after birth, the former infants exhibited the following behavioural characteristics more frequently: crying, irritability, irregularity of biological functions, gripes, and difficult temperament. At 9 years of age, these children (boys in particular) were still more active. Moreover, they showed more attention deficits, had more problems with inhibition of difficult behaviour, and were more aggressive. These relationships were established on the basis of independent behavioural assessments by the investigator, the mother, and teachers [12].

The design of such human studies does not allow to estimate the relative contributions of genetic versus environmental factors or their interaction effects. Genetic vulnerability factors in the mother, passed on to her child, as well as chronic environmental stressors may have influenced both maternal stress and the long-term outcome variables. Genetic-sensitive designs involving twins are necessary to address this issue.

Future research also has to reveal whether or not the effects of prenatal exposure to stress will be persistent into adulthood. Like in prenatally stressed animals, further development of these children may change for the better under the positive influence of particular environmental factors, but may also deteriorate further. Longitudinal studies from the Czech Republic, Finland, and Sweden have provided evidence that children of women who had faced unwanted pregnancies which they had to bring to an end as they were refused to undergo an abortion, had more developmental disorders at the age of 20 years [44]. The adolescents, men in particular, showed more often than a control group behavioural disorders, learning problems, and emotional problems in engaging lasting friendships or relations. These problems generally worsened over time, but ameliorated in some cases when there had been social support.

6. Regulation of the maternal HPA axis

CRH is produced and secreted by the hypothalamus. It plays a central role within the HPA axis and is involved in the physiologic response to stress. CRH stimulates ACTH

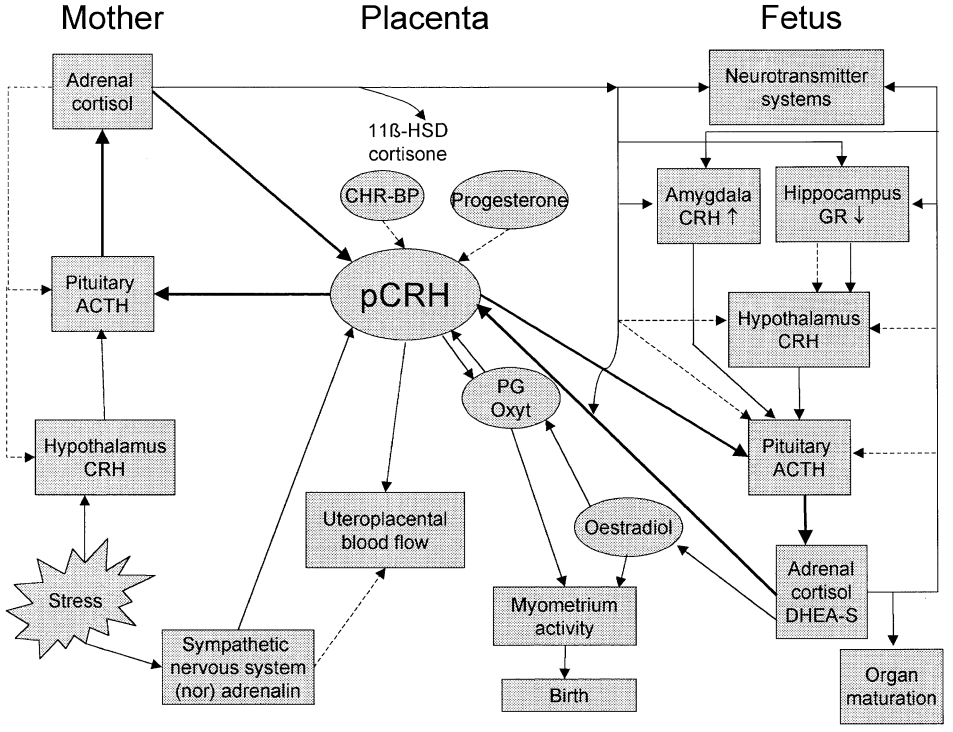

Fig. 1. Effects of maternal stress on uteroplacental blood flow and hormonal regulation in the mother, placenta, and fetus, and on fetal development and the duration of pregnancy. Activating influences are indicated by solid lines; inhibitory effects, including negative feed-back, by dotted lines. The presence of feed-forward mechanisms at either side of the placenta is represented by thick lines.

production and secretion by the pituitary. In turn, ACTH stimulates the production and secretion of cortisol by the adrenal cortex. Regulation of these hormones is achieved by a negative feed-back mechanism [9]. This occurs in pregnant and non-pregnant women alike, although important changes take place in the course of pregnancy [45,46]. From about 8–10 weeks' gestation, CRH is also produced by the placenta. This placental CRH has the same biological activity as hypothalamic CRH and is secreted to both the maternal and fetal compartments (Fig. 1). Moreover, it is known that cortisol stimulates synthesis and release of pCRH, which is opposite to the inhibitory effect of cortisol on the CRH-producing cells of the hypothalamus. In the mother, pCRH is inactivated to a large extent by a CRH binding protein (CRH-BP) under normal conditions, except for the last 2–4 weeks of pregnancy. In this period, there is a rapid increase in free pCRH. The mentioned alterations result in a shift from normal negative feed-back regulation of the maternal HPA axis to a positive feed-back, or better feed-forward, mechanism through the effect of peripherally produced pCRH. In the course of pregnancy, blood concentrations of CRH, ACTH, and cortisol increase gradually, but during the few weeks before parturition, they rise rapidly [46]. Under abnormal circumstances (preeclampsia, threatened preterm delivery, maternal stress), these alterations may be initiated prematurely (see above).

7. Transmission of maternal stress to the unborn baby

The question of how signals of maternal stress may reach the fetus has not been dealt with so far. It seems most logic that this occurs through (stress) hormones. Three mechanisms may be distinguished, which may operate simultaneously and may amplify each other's effects. The possible mechanisms involve: (a) reduction in blood flow to the uterus and fetus at increased levels of maternal stress; (b) transplacental transport of maternal hormones; (c) stress-induced release of placental CRH to the intrauterine environment (Fig. 1).

7.1. Reduced uteroplacental blood flow

Corticosteroids and catecholamines are known to exert strong effects on the tone of peripheral blood vessels. Besides, the placenta is abundant of receptors for these hormones. Activation of the sympathetic nervous system by stress may lead to reduced blood flow to the uterus and fetus, and may contribute to fetal growth restriction. Indeed, Doppler blood flow studies have shown increased resistance of the uterine artery in women with high anxiety scores at about 32 weeks of gestation [47].

7.2. Transplacental transport of maternal stress hormones

Corticosteroids pass the placenta readily in many animal species. In contrast, the human fetus is relatively (so not completely) protected against direct exposure to high cortisol concentrations. In the placenta, 50–90% of maternal cortisol is converted to cortisone by the enzyme 11β-hydroxysteroid-dehydrogenase (11β-HSD-2). Cortisone is biologically inactive [4]. The activity of 11β-HSD-2 increases near the end of pregnancy just at the

time that hypercortisolaemia develops in the mother, and thus seems to be of adaptive significance [46].

On the other hand, maternal cortisol levels have been found to be linearly related with the (much lower) fetal cortisol levels at antenatal umbilical cord blood sampling (cordocentesis), a very stressful event to the mother [48]. This means that a small increase in maternal cortisol may cause a substantial increase in fetal cortisol. It is, therefore, conceivable that cortisol reaches the human fetus under certain circumstances. This may happen normally, since maternal cortisol is not completely inactivated in the placenta, or under specific conditions, for example, if the maternal cortisol concentration is very high, if the activity of 11β-HSD-2 is reduced (interindividual differences; polymorphisms ?) or impaired, when the placenta is immature (early pregnancy), or when placental function is poor as with some pregnancy complications.

7.3. Secretion of placental CRH to the fetus

Fetal cortisol is important for the maturation of virtually all fetal organ systems. The fetal HPA axis is regulated through negative feed-back from early in gestation onward. In a later stage of pregnancy, placental CRH enters the fetal circulation via the umbilical vein [46]. Since CRH-BP is absent in the fetus, pCRH stimulates the fetal HPA axis to produce and secrete ACTH, cortisol, and androgens (dehydro-epiandrosterone-sulphate; DHEA-S). Subsequently, fetal cortisol enters the placental circulation via the umbilical arteries and further stimulates the production of pCRH. This way, the fetal HPA axis is also regulated by a feed-forward mechanism at the end of pregnancy. On the one hand, this results in a large increase in cortisol by which maturation of the fetal organs is enhanced. On the other hand, pCRH initiates, through an increase in DHEA-S (the precursor of oestrogens), a cascade of events which may lead to increased uterine activity and eventually delivery [45,46].

At the end of normal pregnancy, the simultaneous stimulation of organ maturation and initiation of parturition constitute a positive effect of a feed-forward mechanism. However, premature activation of either or both in the placenta coupled feed-forward systems may result in preterm labour and delivery (Fig. 1). This is evidenced by the earlier mentioned association between prematurely raised blood pCRH (and decreased CRH-BP) levels in pregnant women who were confronted with preterm delivery [23,27] and preeclampsia [24] only in a later stage of pregnancy.

Diminished supply of nutrients and oxygen (hypoxaemia) may cause a stress response in the fetus. This involves increased secretion of pCRH that, in turn, contributes to the feed-forward mechanisms at either side of the placenta [45].

Fig. 1 also shows how maternal stress might affect development of the fetal brain and HPA-axis activity. Maternal cortisol that has escaped from inactivation by 11β-HSD in the placenta may participate in the feed-forward loop between the placenta and the fetal pituitary–adrenal axis. Overproduction and hypersecretion of fetal cortisol thus may arise from maternal cortisol in the fetal compartment and/or from pCRH secretion. Increased fetal cortisol (of maternal or fetal origin) may inhibit growth and differentiation of the developing nervous system, may damage the brain, and may have a programming or organizing effect on the fetal neuroendocrine system resulting in the permanent disorders mentioned earlier.

8. Outlook

Known biomedical risk factors, such as maternal diseases, teratogenic agents, complications of pregnancy, and nutritional deficiencies and infections, explain about half of the number of cases of low birth weight and prematurity and their associated problems after birth [49]. Prenatal maternal stress and anxiety may be responsible for an important proportion of the other (unexplained) cases. This appears from recent well-performed studies that took into account medical and obstetric histories, life style (smoking and drinking behaviour), socioeconomic status, and the course of pregnancy and delivery. These studies have demonstrated that exposure to prenatal stress not only affects physical development of the infants (birth weight, head size, and structural malformations), but also their functional development, evidenced by poor psychomotor performance and more difficult behaviour during the first 10 years of life. Whether these problems will be long-lasting and permanent and will eventually lead to psychopathology has to be revealed by continuation of the existing follow-up studies and by other independent studies.

In the past, several attempts have been made to reduce the amount of stress in pregnant women, to diminish its negative effects on the outcome of pregnancy [49,50]. By repeated telephone calls or home visits by a social worker, extensive information was given about a healthy life style during pregnancy. One has also attempted to provide direct psychologic support and to optimize support from the social environment. The results of such intervention programs have appeared to be disappointing. However, the possibility exists that the offered help in these studies has not been intensive or specific enough.

Huizink [8] has demonstrated that maternal stress in the first half of pregnancy is an important predictor of problematic infant behaviour. This was found especially for pregnancy-specific anxieties, such as fear of the baby's health and fear of (pain during) delivery. This finding may be the clue to come to early detection of high stressed or anxious pregnant women. By filling out a short inventory in early pregnancy, information can easily be obtained about the intensity of pregnancy-specific anxieties. Pregnant women at increased risk may then be invited to participate in a program aiming at stress reduction by providing specific information, education, or relaxation methods.

Many animal experiments and a number of retrospective and prospective human studies (the latter with a limited follow-up period) indicate that it is very important to further investigate possible ways of preventing and reducing prenatal maternal stress. This the more so given the still increasing experience of stress by (pregnant) women in modern society. In addition, more information has to be acquired about stress regulation in pregnant women and about mechanisms by which maternal stress influences the course of pregnancy and development of the unborn baby. Changes in the levels of specific maternal hormones (ACTH, pCRH, CRH-BP, prolactin, or oxytocin) may be early indicators of a raised stress level in the intrauterine environment.

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