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Impact of stress and stress physiology during pregnancy on child metabolic function and obesity risk

Sonja Entringer
Department of Pediatrics, University of California, Irvine, California, USA

Abstract

Purpose of review—To summarize recent conceptual frameworks and empirical findings addressing the role of prenatal stress and stress biology in the context of fetal programming of metabolic function and obesity risk.

Recent findings—The link between stress exposure and adverse health outcomes is well established. Growing evidence from animal and human studies now suggests that the experience of severe stress or perturbations in stress-related immune and endocrine processes during pregnancy may also impact the developing fetus to produce increased susceptibility for childhood and adult obesity, and dysregulated glycemic control.

Summary—Because endocrine and immune ligands commonly associated with stress play an essential role during intrauterine development in cellular growth and differentiation perturbations in these systems during pregnancy are likely to produce alterations of structure and function of the brain and peripheral physiological systems in the offspring. To systematically study the effects of intrauterine stress exposure on child metabolic function and obesity risk, a multilevel approach is required that includes molecular and cellular studies, the use of animal models, and human observational and interventional studies. Such studies will set the stage for translational research to inform the subsequent development of diagnostic and primary or secondary intervention strategies in at-risk individuals.

Keywords

developmental programming; metabolic function; obesity risk; prenatal stress

INTRODUCTION

Substantial evidence in humans and animals suggests that conditions during intrauterine life play a major role in shaping not only all aspects of fetal development and birth outcomes but also subsequent newborn, child, and adult health outcomes and susceptibility for many of the complex, common disorders that confer the major burden of disease in society (i.e., the concept of fetal, or developmental, origins of health and disease risk) [1,2]. This concept is rapidly gaining acceptance as a more comprehensive approach than that of genetic causation alone in understanding the cause of many complex common disorders, including obesity and its comorbidities. Several intrauterine conditions have been identified as risk factors for obesity and metabolic dysfunction in the offspring, including maternal obstetric

Correspondence to Sonja Entringer, PhD, UC Irvine Development, Health and Disease Research Program, University of California, Irvine, 333 The City Blvd. W, Suite 1200 Orange, CA 92868, USA. Tel: +1 714 940 1924; fax: +1 714 940 1939; sentring@uci.edu.

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complications (diabetes, hyperglycemia), maternal undernutrition or overnutrition, and unhealthy maternal behaviors such as smoking. This paper advances a framework and reviews empirical evidence from animal and human studies that highlights the role of intrauterine stress and stress biology in this context. We discuss putative stress-related maternal–placental–fetal endocrine and immune/inflammatory candidate mechanisms that may mediate the effects of several different clinical or behavioral risk factors during pregnancy on the developing human embryo and fetus, with a specific focus on body composition, metabolic function, and obesity risk.

ROLE OF INTRAUTERINE STRESS IN THE CONTEXT OF FETAL PROGRAMMING

The rationale for considering a role for stress and stress biology in fetal programming of child and adult obesity and metabolic dysfunction derives, in part, from concepts in evolutionary biology, particularly developmental plasticity, life history theory and maternal–fetal conflict theory [3]. Based on the consideration that key environmental conditions that have shaped natural selection and provide cues for developmental plasticity include not only variation in energy substrate availability (i.e., nutrition) but also challenges that have the potential to impact the structural or functional integrity and survival of the organism (i.e., stress), it is likely and plausible that prenatal stress represents an important aspect of the intrauterine environment that would be expected to influence many, if not all, developmental outcomes [3,4]. Moreover, we submit the application of a prenatal stress framework offers an excellent model system for the study of intrauterine development and associated developmental, birth, and subsequent health-related phenotypes because it is increasingly apparent that the developing fetus acquires and incorporates information about the nature of its environment in part via the same biological systems that in an already-developed individual mediate adaptation and central and peripheral responses to endogenous and exogenous stress (i.e., the maternal–placental–fetal neuroendocrine and immune systems [3]).

Obesity and metabolic dysfunction are complex, multifactorial outcomes. Major risk categories include sociodemographic, genetic, obstetric, nutritional, behavioral, psychosocial, and other environmental factors. Studies of the effects of stress and stress-related processes on these outcomes generally treat other risk factors as potential confounding variables and attempt to adjust for their putative effects by either study design (subject selection criteria) or statistical adjustment. However, it is probable that causation of complex disorders does not reside in any single factor or in the additive effects of numerous factors, but lies at the interface between multiple risk factors (interaction, or multiplicative effects [5]). We have previously illustrated this in the context of the potential interactive effects between stress and nutrition [3]. For example, several experimental studies in humans support the notion that acute stress (e.g., exposure to laboratory-based stressors or endocrine stress analogues) affects both food choice and food intake behavior [6,7,8▪▪]. In the context of depression (a stress-related disorder) it has been suggested that cortisol and insulin may stimulate ingestion of energy-dense comfort food, which then protects the hypothalamic–pituitary–adrenal axis from stress-induced dysfunction and associated symptoms of anxiety and discomfort (i.e., ‘emotional eating’, reviewed in [8▪▪]). Despite the plausibility of stress–nutrition interaction effects in the context of human pregnancy we are not aware of human studies to date that have examined these potential interactive effects during pregnancy on offspring body composition and metabolic function.

STRESS-RELATED MATERNAL–PLACENTAL–FETAL ENDOCRINE AND IMMUNE PROCESSES AS POTENTIAL MEDIATORS OF FETAL PROGRAMMING OF HEALTH AND DISEASE

The fetal programming hypothesis has led to the search for underlying mechanisms by which disparate intrauterine insults exert a multitude of effects on different physiological systems in the offspring. We suggest that stress-related maternal–placental–fetal endocrine and immune processes in gestation constitute an attractive underlying common candidate mechanism because they act as a sensor, transducer as well as effector of stress. They are responsive to many classes of intrauterine perturbations (sensor); they act as a conduit of cues about the stress-related milieu between the maternal and fetal compartments (transducer); and they act directly on multiple targets of fetal programming in the brain and peripheral systems (effector) [1,3]. Unlike exposure to toxins and teratogens, it is important to appreciate the fact that maternal–placental–fetal hormones and cytokines play an essential role in orchestrating key events underlying cellular growth, replication, and differentiation in the brain and peripheral tissues [3]. Thus, perturbations in the level and/or time of exposure of these biological effectors are likely to produce alterations of normal structure and function.

As previously described, stress biology refers to the set of biological adaptations in response to challenges or demands that threaten the stability of the internal milieu of the organism [1,3]. The nervous, endocrine, immune, and vascular systems play a major role in adaptations to stress. A critical goal and end result of these adaptations is to redistribute the allocation and utilization of energy substrate across different tissues and organ systems. Pregnancy produces major alterations in neuroendocrine and immune function that are crucial in providing a favorable environment within the uterus and fetal compartment for growth, differentiation, maturation and conveying signals when the fetus is ready for extrauterine life. Glucocorticoid physiology (cortisol in humans) has received extensive and well placed consideration as a critical endocrine mediator of fetal programming, with an emphasis on not only hormone production but also maternal–fetal transfer mediated by the activity of the placental enzyme 11β-hydroxysteriod dehydrogenase [9▪]. Less well recognized is the perhaps equally important role of the peptide corticotrophin-releasing hormone (CRH). In primates, but not other mammals, the placenta synthesizes and releases CRH in large amounts into the fetal and maternal circulations, with actions on central and multiple peripheral target systems in both compartments (reviewed in [4]). With respect to the immune axis, a major endeavor of pregnancy-related alterations in immune function is to achieve and maintain the optimal balance between tolerating the fetal semi-allograft while not suppressing maternal immune responses to an extent that increases maternal or fetal susceptibility to infection. Thus, a generalized reduction of maternal immune responsiveness occurs during pregnancy, mediated by hormonal changes, trophoblast expression of key immunomodulatory molecules, and a progressive switch from a TH_1/TH_2 balance to a predominantly T-helper 2-type pattern of cytokines [10].

Studies by our research group and by others have shown that despite the large pregnancy-associated changes in maternal physiology, the system is responsive to maternal psychosocial states (such as high stress and low social support), that maternal psychophysiological stress responses are progressively attenuated with advancing gestation, and that after accounting for the effects of other established risk factors, the degree of attenuation is a significant predictor of shortened length of gestation and earlier delivery (reviewed in [4]). Studies by other groups have reported that elevated psychosocial stress and depressive symptoms in pregnant women are associated with changes in immune and inflammatory markers (in-vivo and in-vitro evidence, summarized in [4]). In addition to

psychosocial stress, substantial in-vitro and in-vivo evidence indicates that maternal–placental–fetal endocrine and immune processes during pregnancy respond to a variety of other maternal and intrauterine perturbations, including biological effectors of stress, obstetric risk conditions such as preeclampsia, pregnancy-induced hypertension, gestational diabetes, infection, reduced uteroplacental blood flow, and behavioral factors such as the constituents of maternal diet, overnutrition and undernutrition, and smoking (reviewed in [1]). Thus, based on these observations, it is apparent that measures of maternal–fetal endocrine and immune/inflammatory stress markers capture physiological responses to a wide range of intrauterine perturbations including but not limited to prenatal stress.

PRENATAL STRESS AND PROGRAMMING OF BODY COMPOSITION, METABOLIC FUNCTION, AND OBESITY RISK

At the individual level, obesity results when energy intake exceeds energy expenditure. However, there is wide variation among children or adults at identical levels of excess energy intake in their propensity to gain weight and accrue fat mass. This variation across individuals defines susceptibility for developing obesity/adiposity. Once an individual becomes obese it is difficult to lose weight, and even more difficult to sustain weight loss, because of the remarkable efficiency of energy balance homeostasis mechanisms [11]. For these reasons, it is important to gain a better understanding of the origins of individual differences in the susceptibility for weight and fat mass gain, in order to predict obesity risk and develop strategies for primary prevention.

In this section we review evidence from animal and human studies that adverse circumstances during pregnancy (physiological as well as psychological stressors, conceptualized here as ‘prenatal stress’) that have the potential to induce changes in maternal–placental–fetal stress biology are associated with a higher risk for overweight, obesity and metabolic dysfunction of the offspring (Tables 1 and 2). The increase in stress hormones and proinflammatory cytokines in the fetal compartment during sensitive or critical developmental windows can impact the structure and function of the brain and peripheral targets that are related to body composition, energy balance homeostasis, and metabolic function (i.e., adipose tissue, pancreas, and liver).

As depicted in Table 1a and b, the induction of stress during pregnancy in an animal paradigm or the experience of severe psychological stress during pregnancy in humans is associated with a higher risk for obesity and metabolic dysfunction in the offspring. Several animal studies that induced stress in the pregnant female found that the offspring were heavier and exhibited greater adiposity (particularly when exposed to a high-caloric diet [13,14▪▪,15▪,16]), impaired glycemic control [12,13,15▪,16], and increased food intake [12,14▪▪]. A recent study in rodents [14▪▪] examined gene expression and DNA methylation profiles in response to exposure to a prenatal stress paradigm and reported that the increased susceptibility to obesity in prenatally stressed animals was related to transcriptomic and epigenetic changes in the hypothalamus, a brain region involved in the regulation of appetite and food intake.

To date, only a few human studies have examined the relationship between maternal psychosocial stress exposure during pregnancy and offspring obesity risk and metabolic function (summarized in Table 1b). As a first step to addressing this question, we conducted a retrospective case–control study in a sample of healthy young adults born to mothers with healthy pregnancies and normal birth outcomes. One half of the study population of young adults was born to mothers who had experienced a major stressful life event during the index pregnancy (prenatal stress group), whereas the other half was a sociodemographically matched population with no history of maternal exposure to prenatal stress (comparison

group). The potential effects of established obstetric, newborn, and childhood risk factors on adult health were controlled using a stringent set of exclusionary criteria. Our results indicated that the young adults exposed during intrauterine life to maternal psychosocial stress consistently exhibited significant dysregulation in key physiological parameters, thereby placing them at increased risk for developing complex common disorders (summarized in [3]). Specifically in the context of programming of obesity and metabolic function individuals in the prenatal stress group exhibited higher BMI and percentage body fat, primary insulin resistance, and a lipid profile consistent with the metabolic syndrome [17]. The results of this retrospective study were recently confirmed in a larger epidemiological study that found an association between maternal bereavement from death of someone close during pregnancy and an increased risk of overweight and type 2 diabetes in the offspring in later childhood [19,20▪▪]. Another study [21] reported that maternal depression during pregnancy was a significant predictor of obesity risk in early childhood among different racial/ethnic groups, and in yet another study [22] perceived maternal stress assessed either during pregnancy (in the majority of cases) or during the first 12 months of the child's life was related to higher risk of overweight in the infants. Flory *et al.* [18▪▪] examined the offspring of Holocaust survivors and found that those adults whose mothers were exposed to the Holocaust had a higher risk for having two or more metabolic syndrome conditions (e.g., hypertension, dyslipidemia, type 2 diabetes, and overweight) compared to nonexposed individuals. In this study, maternal Holocaust exposure was not restricted to the period of pregnancy, supporting a life course perspective of the effects of maternal stress on offspring health outcomes. The life course perspective suggests that offspring birth and later health outcomes are the product of not only the 9 months of pregnancy, but of the entire life course of the mother from her own conception onward (or even before her own conception), and leading up to the index pregnancy [4].

Table 2a and b summarizes the available animal and human literature on the relationship between intrauterine exposure to stress-related endocrine and immune biomarkers and offspring obesity risk and metabolic function. Administration of glucocorticoids to the pregnant mother has been consistently shown to produce impaired glucose tolerance and hyperinsulinemia in the offspring across several independent studies [24,25,33]. Blood glucose levels are also elevated in the offspring if the mother is administered a 11β-hydroxysteroid dehydrogenase inhibitor during pregnancy, which protects the fetus from maternal glucocorticoid overexposure [34]. Exposure to maternal glucocorticoids are also reported to induce structural changes in the pancreas (reduced pancreatic β-cell number [25]) and functional alterations in hepatic tissue (increased phosphoenolpyruvate carboxykinase expression [33]) that may underlie the alterations in glycemic control observed in these animals. In addition, maternal exposure to proinflammatory cytokines and an immune challenge during pregnancy are associated with increased body weight, adipose tissue mass [23,27], elevated food intake, and increased circulating leptin levels [27] in the offspring.

In humans, placental CRH concentrations in pregnancy have been shown to significantly predict the rate of fetal growth and size at birth [32], which, in turn, is a significant predictor of childhood and adult adiposity. Other studies have reported a positive association between CRH levels in pregnancy and increased central adiposity [30], and alterations in adiponectin levels in 3-year-old children [29]. Yet others have reported a positive association between maternal levels of interleukin-6 in pregnancy and neonatal adiposity [31]. A study that followed up individuals whose mothers participated in a double-blinded, placebo-controlled and randomized trial of antenatal betamethasone administration found increased insulin resistance in the exposed compared to non-exposed adults [28].

A recent study that used both in-vitro and in-vivo methodology supports a role for glucocorticoid exposure in adipogenesis [35▪▪], a process that in humans occurs primarily during late fetal and early postnatal life. In this study, in-vitro exposure to glucocorticoids induced an increase in the differentiation of preadipocytes to adipocytes in a concentration-dependent manner. Moreover, rats implanted with corticosterone pellets exhibited more visceral adiposity [35▪▪].

CONCLUSION

Based on the conceptual framework and empirical findings presented here we suggest it is important to consider the potential role of intrauterine stress and stress biology in arriving at a better understanding of the developmental programming of susceptibility for obesity risk and metabolic diseases. In the context of human research, opportunities are limited for experimental manipulations of prenatal stress and the intrauterine environment, and for access to many of the target tissues of interest, particularly in fetal life. Thus, to systematically study the effects of prenatal stress on offspring disease susceptibility and the underlying programming mechanisms, a multilevel approach is required that includes molecular and cellular studies, the use of appropriate animal models, and well designed human studies (see also [1,3] for overviews of proposed research designs in this context). It is apparent that current approaches to the prevention and management of obesity and associated metabolic disorders have yielded only very limited success. It is therefore critical to adopt a developmental framework in order to arrive at a better understanding of the origins of individual differences in the propensity for weight and fat mass gain, and to develop and test hypotheses that set the stage for translational research to inform the subsequent development of primary intervention strategies before an individual becomes overweight or obese, or secondary interventions to increase the likelihood of a favorable and more sustained response to weight-loss strategies.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

1. Entringer S, Buss C, Wadhwa PD. Prenatal stress and developmental programming of human health and disease risk: concepts and integration of empirical findings. Curr Opin Endocrinol Diabetes Obes. 2010; 17:507–516. [PubMed: 20962631]
2. Barouki R, Gluckman PD, Grandjean P, et al. Developmental origins of noncommunicable disease: implications for research and public health. Environ Health. 2012; 11:42. [PubMed: 22715989]
3. Entringer S, Buss C, Swanson JM, et al. Fetal programming of body composition, obesity, and metabolic function: the role of intrauterine stress and stress biology. J Nutr Metab. 2012; 2012:632548. [PubMed: 22655178]
4. Wadhwa PD, Entringer S, Buss C. The contribution of maternal stress to preterm birth: Issues and considerations. Clin Perinatol. 2011; 38:351–384. [PubMed: 21890014]

5. Laland KN, Sterelny K, Odling-Smee J, et al. Cause and effect in biology revisited: is Mayr's proximate-ultimate dichotomy still useful? Science. 2011; 334:1512–1516. [PubMed: 22174243]
6. Hitze B, Hubold C, van Dyken R, et al. How the selfish brain organizes its supply and demand. Front Neuroenergetics. 2010; 2:7. [PubMed: 20616886]
7. George SA, Khan S, Briggs H, Abelson JL. CRH-stimulated cortisol release and food intake in healthy, nonobese adults. Psychoneuroendocrinology. 2010; 35:607–612. [PubMed: 19828258]
8■■. Gibson EL. The psychobiology of comfort eating: implications for neuropharmacological interventions. Behav Pharmacol. 2012; 23:442–460. An important, comprehensive review on the psychobiological mechanisms underlying 'comfort eating' (eating induced by negative affect). [PubMed: 22854304]
9■. Harris A, Seckl J. Glucocorticoids, prenatal stress and the programming of disease. Horm Behav. 2011; 59:279–289. A review of animal and human studies on glucocorticoid programming, with an emphasis on molecular mechanisms and effects on the brain. [PubMed: 20591431]
10. Weetman AP. Immunity, thyroid function and pregnancy: molecular mechanisms. Nat Rev Endocrinol. 2010; 6:311–318. [PubMed: 20421883]
11. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med. 2011; 365:1597–1604. [PubMed: 22029981]
12. Lesage J, Del-Favero F, Leonhardt M, et al. Prenatal stress induces intrauterine growth restriction and programmes glucose intolerance and feeding behaviour disturbances in the aged rat. J Endocrinol. 2004; 181:291–296. [PubMed: 15128277]
13. Mueller BR, Bale TL. Impact of prenatal stress on long term body weight is dependent on timing and maternal sensitivity. Physiol Behav. 2006; 88:605–614. [PubMed: 16828814]
14■■. Paternain L, Batlle MA, De la Garza AL, et al. Transcriptomic and epigenetic changes in the hypothalamus are involved in an increased susceptibility to a high-fat-sucrose diet in prenatally stressed female rats. Neuroendocrinology. 2012; 96:249–260. This study is the first to investigate gene expression and epigentic profiles in hypothalamic tissue that underlie the prenatal stress-induced obesity risk of the offspring. [PubMed: 22986707]
15■. Paternain L, de la Garza AL, Batlle MA, et al. Prenatal stress increases the obesogenic effects of a high-fat-sucrose diet in adult rats in a sex-specific manner. Stress. 2012 [Epub ahead of print] This study systematically investigates how prenatal stress exposure in combination with a high-fat diet in the offspring enhances predispostion for obesity risk and metabolic disorders.
16. Tamashiro KL, Terrillion CE, Hyun J, et al. Prenatal stress or high-fat diet increases susceptibility to diet-induced obesity in rat offspring. Diabetes. 2009; 58:1116–1125. [PubMed: 19188431]
17. Entringer S, Wust S, Kumsta R, et al. Prenatal psychosocial stress exposure is associated with insulin resistance in young adults. Am J Obstet Gynecol. 2008; 199:498e1–498e7. [PubMed: 18448080]
18■■. Flory JD, Bierer LM, Yehuda R. Maternal exposure to the holocaust and health complaints in offspring. Disease Markers. 2011; 30:133–139. This study shows that maternal exposure to severe stress even before pregnancy increases offspring risk for metabolic syndrome conditions, supporting a life course perspective of the effects of maternal stress on offspring health outcomes. [PubMed: 21508517]
19. Li J, Olsen J, Vestergaard M, et al. Prenatal stress exposure related to maternal bereavement and risk of childhood overweight. PLoS One. 2010; 5:e11896. [PubMed: 20689593]
20■■. Li J, Olsen J, Vestergaard M, et al. Prenatal exposure to bereavement and type-2 diabetes: a Danish longitudinal population based study. PLoS One. 2012; 7:e43508. A large population based cohort study that shows that severe stress in the preconception and the prenatal period may increase the risk for developing type 2 diabetes in childhood and young adulthood. [PubMed: 22952698]
21. Taveras EM, Gillman MW, Kleinman K, et al. Racial/ethnic differences in early-life risk factors for childhood obesity. Pediatrics. 2010; 125:686–695. [PubMed: 20194284]
22. Watt TT, Appel L, Roberts K, et al. Sugar, Stress, and the Supplemental Nutrition Assistance Program: Early childhood obesity risks among a clinic-based sample of low-income Hispanics. J Community Health. 2012 Epub ahead of print.

23. Dahlgren J, Nilsson C, Jennische E, et al. Prenatal cytokine exposure results in obesity and gender-specific programming. Am J Physiol Endocrinol Metab. 2001; 281:E326–E334. [PubMed: 11440909]
24. De Blasio MJ, Dodic M, Jefferies AJ, et al. Maternal exposure to dexamethasone or cortisol in early pregnancy differentially alters insulin secretion and glucose homeostasis in adult male sheep offspring. Am J Physiol Endocrinol Metab. 2007; 293:E75–E82. [PubMed: 17356009]
25. de Vries A, Holmes MC, Heijnis A, et al. Prenatal dexamethasone exposure induces changes in nonhuman primate offspring cardiometabolic and hypothalamic-pituitary-adrenal axis function. J Clin Invest. 2007; 117:1058–1067. [PubMed: 17380204]
26. Lindsay RS, Lindsay RM, Waddell BJ, Seckl JR. Prenatal glucocorticoid exposure leads to offspring hyperglycaemia in the rat: studies with the 11 beta-hydroxysteroid dehydrogenase inhibitor carbenoxolone. Diabetologia. 1996; 39:1299–1305. [PubMed: 8932995]
27. Nilsson C, Larsson BM, Jennische E, et al. Maternal endotoxemia results in obesity and insulin resistance in adult male offspring. Endocrinology. 2001; 142:2622–2630. [PubMed: 11356713]
28. Dalziel SR, Walker NK, Parag V, et al. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. Lancet. 2005; 365:1856–1862. [PubMed: 15924982]
29. Fasting MH, Oken E, Mantzoros CS, et al. Maternal levels of corticotropin-releasing hormone during pregnancy in relation to adiponectin and leptin in early childhood. J Clin Endocrinol Metab. 2009; 94:1409–1415. [PubMed: 19190112]
30. Gillman MW, Rich-Edwards JW, Huh S, et al. Maternal corticotropin-releasing hormone levels during pregnancy and offspring adiposity. Obesity (Silver Spring, MD). 2006; 14:1647–1653.
31. Radaelli T, Uvena-Celebrezze J, Minium J, et al. Maternal interleukin-6: marker of fetal growth and adiposity. J Soc Gynecol Investig. 2006; 13:53–57.
32. Wadhwa PD, Garite TJ, Porto M, et al. Placental corticotropin-releasing hormone (CRH), spontaneous preterm birth, and fetal growth restriction: a prospective investigation. Am J Obstet Gynecol. 2004; 191:1063–1069. [PubMed: 15507922]
33. Nyirenda MJ, Lindsay RS, Kenyon CJ, et al. Glucocorticoid exposure in late gestation permanently programs rat hepatic phosphoenolpyruvate carboxykinase and glucocorticoid receptor expression and causes glucose intolerance in adult offspring. J Clin Invest. 1998; 101:2174–2181. [PubMed: 9593773]
34. Lindsay RS, Lindsay RM, Edwards CR, Seckl JR. Inhibition of 11-beta-hydroxysteroid dehydrogenase in pregnant rats and the programming of blood pressure in the offspring. Hypertension. 1996; 27:1200–1204. [PubMed: 8641724]
35■■. Campbell JE, Peckett AJ, D'Souza AM, et al. Adipogenic and lipolytic effects of chronic glucocorticoid exposure. Am J Physiol Cell Physiol. 2011; 300:C198–C209. This study investigates the effects of chronic glucocorticoid exposure on lipolysis and adipogenesis and demonstrates that glucococorticoids affect adipogenesis through increased preadipocyte differentiation. [PubMed: 20943959]

KEY POINTS

- Recent evidence suggests that severe stress experience during pregnancy may impact the developing fetus to produce increased susceptibility for childhood and adult obesity, and alterations in metabolic function.
- Therefore, to prevent complex common health disorders, more emphasis should be placed on the well-being of women of reproductive age prior to conception and across gestation, in order to more effectively address health-related and disease-risk-related issues in their offspring.
- More research is needed on the effects of intrauterine stress exposure on child metabolic function and obesity risk, using a multilevel approach, to develop specific diagnostic and primary or secondary intervention strategies in this area.

Table 1

Exposure to stress and related states during pregnancy and offspring metabolic function and body composition/risk for overweight

Author	Species	Prenatal predictor	Outcome studied in the offspring	Age of offspring	Effect
(a) Animal studies					
Lesage *et al.* [12]	Rats	Chronic stressor during late pregnancy	Glycemic control, weight, food intake behavior	Adulthood	Hyperglycemia, increased food intake after fasting
Mueller and Bale [13]	Mice	Chronic variable stress early mid or late in gestation	Body weight, glucose and leptin levels	Adulthood	Increased body weight, glucose and leptin levels; interaction effects with timing of stressor during gestation and maternal stress sensitivity
Paternain *et al.* [14▪▪]	Rats	Chronic mild stress during the third week of gestation	Adiposity, glycemic control	Adulthood	Higher adiposity and insulin resistance when exposed to high-fat-sucrose diet; increased energy intake
Paternain *et al.* [15▪]	Rats	Chronic mild stress during the third week of gestation (induced 'depressive-like state')	Adiposity	Adulthood	Higher adiposity when exposed to high-fat sucrose diet
Tamashiro *et al.* [16]	Rats	Novel variable stress paradigm during the third week of gestation	Body weight, body composition, glucose tolerance, and endocrine parameters	Birth through early adulthood	Higher body weight. In early adulthood, when exposed to high-fat diet, impaired glucose tolerance

Author	Prenatal predictor	Outcome studied in the offspring	Age of offspring	Effect
(b) Human studies				
Entringer *et al.* [17]	Maternal negative life events during pregnancy	Glycemic control, BMI, percentage of body fat, leptin	Young adults	Associated with reduced insulin sensitivity, higher BMI and percentage of body fat and higher leptin levels
Flory *et al.* [18▪▪]	Maternal exposure to Holocaust	Metabolic syndrome conditions	Adulthood	Associated with higher risk for having two or more metabolic syndrome conditions (e.g., hypertension, dyslipidemia, type 2 diabetes, and overweight)
Li *et al.* [19]	Maternal bereavement (loss of elder child, husband, or parent) in period 1 year before conception until birth	Overweight	Children (7–13 years)	Associated with higher risk
Li *et al.* [20▪▪]	Maternal bereavement (loss of elder child, husband, or parent) in period 1 year before conception until birth	Type 2 diabetes	Children	Associated with higher risk
Taveras *et al.* [21]	Maternal depression during pregnancy	Obesity	Children (3 years)	Associated with higher risk
Watt *et al.* [22]	Maternal perceived stress (assessed either during pregnancy or up to 12 months postnatally)	Overweight	Infants (2–12 months)	Associated with higher risk

Table 2

Biological stress ligands during pregnancy and offspring metabolic function and body composition/risk for overweight

Author	Species	Prenatal predictor	Outcome studied in the offspring	Age offspring studied	Effect
(a) Animal studies					
Dahlgren *et al.* [23]	Rats	Prenatal administration of dexamethasone or IL-6 or TNF-α	Adiposity	Adulthood	All exposures associated with increased body weight and adipose tissue mass
De Blasio *et al.* [24]	Sheep	Maternal glucocorticoid administration during pregnancy	Glycemic control	Adulthood	Hyperinsulinemia
de Vries *et al.* [25]	Nonhuman primates	Maternal dexamethasone administration during pregnancy	Glycemic control	Young adulthood	Impaired glucose tolerance and hyperinsulinemia, with reduced pancreatic b-cell number at 12 months
Lindsay *et al.* [26]	Rats	Glucocorticoid exposure (11β-hydroxysteroid dehydrogenase type 2 inhibitor)	Glycemic control	Adulthood	Hyperglycemia
Nilsson *et al.* [27]	Rats	Maternal exposure to immune challenge during pregnancy	Adiposity, food intake, leptin levels, glycemic control	Adulthood	Associated with increased adipose tissue weights, elevated food intake, increased circulating leptin, reduced insulin sensitivity

Author	Prenatal predictor	Outcome studied in the offspring	Age of offspring	Effect
(b) Human studies				
Dalziel *et al.* [28]	Betamethasone administration during pregnancy (randomized–controlled trial)	Glucose tolerance	Young adulthood	Increased insulin resistance
Fasting *et al.* [29]	Second trimester placental CRH levels	Adiponectine and leptin concentrations	3 years	No association with leptin; associated with higher concentrations of adiponectin
Gillman *et al.* [30]	Second trimester placental CRH levels	Adiposity	3 years	Associated with an overall decrease in body size, but an increase in central adiposity
Radaelli *et al.* [31]	Maternal IL-6 levels at delivery	Body composition	Newborns	Associated with increased fat mass
Wadhwa *et al.* [32]	Placental CRH levels at 33 weeks gestation	Fetal growth restriction	Newborns	Associated with higher risk

CRH, corticotrophin-releasing hormone; IL, interleukin; TNF, tumor necrosis factor.