Pregnancy Complications and the Risk of Metabolic Syndrome for the Offspring

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Abstract

Metabolic syndrome is a growing problem globally, and is a contributor to non-communicable diseases such as type II diabetes and cardiovascular disease. The risk of developing specific components of the metabolic syndrome such as obesity, hyperlipidemia, hypertension, and elevated fasting blood sugar has been largely attributed to environmental stressors including poor nutrition, lack of exercise, and smoking. However, large epidemiologic cohorts and experimental animal models support the "developmental origins of adult disease" hypothesis, which posits that a significant portion of the risk for adult metabolic conditions is determined by exposures occurring in the perinatal period. Maternal obesity and the rate of complications during pregnancy such as preterm birth, preeclampsia, and gestational diabetes continue to rise. As our ability to reduce perinatal morbidity and mortality improves the long-term metabolic consequences remain uncertain, pointing to the need for further research in this area.

Keywords

Maternal obesity; Gestational diabetes; Preeclampsia; Metabolic syndrome; Hypertension; Hyperlipidemia; Type II diabetes; Cardiovascular disease; Pregnancy complications

Introduction

Metabolic syndrome is defined as the presence of at least 3 of the following metabolic risk factors: abdominal obesity, high triglycerides, low high-density lipoprotein cholesterol, high blood pressure, and elevated fasting blood sugar [1]. Metabolic syndrome is a growing global health issue and is a risk factor for incident diabetes and cardiovascular disease

(CVD). There is a substantial body of evidence demonstrating that environmental exposures in adolescence and adulthood such as poor nutrition, a sedentary lifestyle, and smoking contribute significantly to the risk of metabolic syndrome. In addition to childhood and adulthood environmental exposures, there is growing evidence that in utero exposures also contribute to metabolic syndrome. Therefore, the identification of metabolic syndrome in children and young adults may facilitate primary prevention efforts, before the onset of overt CVD and type 2 diabetes mellitus (T2DM).

"Developmental programming" also referred to as "fetal origins of adult disease" or the "Barker Hypothesis", is the basis for the observation that low birth weight is not only associated with immediate morbidities for the neonate but also leads to later risk for adult diseases [2–4]. The theory posits that there are critical time periods during fetal and postnatal development, when an individual is sensitive to environmental stressors. During these early periods of "plasticity", changes to an individual's metabolism can remain permanent. The adaptations that occur during critical periods of fetal and postnatal development promote survival in an inadequate environment (ie, poor nutrition or growth restriction). In these surviving individuals, however, later-in-life exposure to nutritional abundance and growth can cause metabolic disturbances that promote the development of diseases such as hypertension, obesity, and diabetes.

Another possible explanation for the associations between *in utero* exposures and adult disease is that there are shared genetic risk factors that impact both early and later-life outcomes. This explanation is well supported by the "fetal insulin hypothesis", which posits that the same genetic factors that predispose to decreased fetal insulin secretion in utero may also affect insulin resistance in adulthood [5]. Evidence from animal models also suggests that the intrauterine milieu influences not only the development of the fetus but also the reproductive fitness of that fetus such that subsequent generations may continue to be affected [6•, 7, 8]. This observation is described as "intergenerational programming." For example, female rodents (F0) fed a low protein diet give birth to offspring (F1) with low birth weight, reduced insulin sensitivity, and high cholesterol [9, 10]. The F1 females also give birth to offspring (F2) with metabolic conditions, despite being fed a normal diet [9, 10]. The presence of metabolic conditions in the F2 generation indicates that even in the absence of the original environmental stressor (poor nutrition), these offspring remain susceptible to metabolic conditions through "intergenerational programming." One possible mechanism for the transmission of chronic diseases between generations is epigenetic changes that are inherited to the subsequent generations; however, more research in this area is needed.

In the following review, we examine the evidence from human studies focused on the relationship between maternal complications of pregnancy and the subsequent risks for metabolic syndrome later in life for both the affected mothers and their offspring.

Birth Weight, Intrauterine Environment, and Metabolic Syndrome

The associations between birth weight and conditions that comprise "metabolic syndrome" ie, hypertension, glucose intolerance, and obesity are observed in studies across the world, and are well supported by large meta-analyses (Table 1). Other conditions in both childhood and adulthood that are associated with birth weight include bone health, chronic kidney disease, asthma, type 1 diabetes, cancer, and a host of other conditions [20–28]. While the focus has largely been on the relationship of low birth weight (LBW) and later-life metabolic disease, there is strong evidence that the association of birth weight is "U"-shaped, meaning both high birth weight (macrosomia) and LBW carry significant risk for later-life conditions [29••].

While many studies show birth weight is independently associated with risk for later-life disorders, others suggest it is not the cause but rather a surrogate marker of risk for adulthood metabolic syndrome [29••]. Specifically, it is argued that over-nutrition and accelerated "catch-up growth" increase the long-term risks for metabolic syndrome in individuals born LBW. Infants born LBW can be described as appropriately grown for gestational age, but born early (preterm delivery at 32 weeks, for example) or as growth restricted and/or small for gestational age (SGA). SGA is most often defined as a birth weight below the 10th percentile based on growth curves standardized to gestational age and infant gender. SGA can represent infants that are constitutionally small due to genetic or environmental causes or infants that are small due to intrauterine growth restriction (IUGR). IUGR suggests that there is growth restriction or that the fetus' growth potential is not being met. IUGR is often accompanied by oligohydramnios and abnormal umbilical artery Doppler flow. LBW and SGA likely have distinct etiologies in their contributions to adult metabolic syndrome.

Maternal conditions such as obesity, gestational diabetes (GDM), and preeclampsia may contribute to the development of in utero stress that is responsible for adverse birth outcomes such as LBW or macrosomia; and through developmental programming, these maternal conditions may also increase susceptibility to adult metabolic disease in the offspring [30, 31]. While the underlying biological and etiologic mechanisms for these various hypotheses are poorly understood, it is clear that the predisposition to adult disease lies in key areas of fetal and postnatal development where there is a complex network of genetic, epigenetic, metabolic, and environmental influences contributing to future disease risk.

Maternal Obesity

Obesity is a significant global health problem; with one-third of adults in the United States classified as overweight (BMI 25–29.9 mg/kg^2) and another third classified as obese (BMI >30 mg/kg^2) [32]. Current estimates by the World Health Organization predict that by 2015, 2.3 billion adults will be overweight and 700 million will be obese [32]. Even more concerning is that childhood obesity is also on the rise with 12.5 million (17 %) children classified as obese in the United States [33]. In addition to the environment, fetal exposure to maternal obesity in utero plays a significant role in the risk of childhood obesity [34]. Obesity and T2DM, which often coexist, are common metabolic disorders encountered by women during their pregnancies, with an estimated one-third of all pregnancies complicated by maternal obesity [35]. Obese women are at an increased risk for maternal complications including GDM, preeclampsia, and thromboembolic events [36, 37]; and obstetric complications such as fetal macrosomia, stillbirth, shoulder dystocia, cesarean delivery, and preterm delivery [36–38].

Maternal obesity exerts a "U" shaped influence on birth weight in that this condition confers risk for high birth weight as well as LBW, which is partly due to the increased risk for preterm birth in obese women [39–41]. Macrosomic infants have increased amounts of adipose tissue and are therefore at heightened risk for childhood obesity and diabetes later in life [34]. LBW infants have periods of rapid catch-up growth, which is thought to program them for a higher risk of obesity and metabolic syndrome [42•]. However, a systematic review by Harder et al. shows that most published studies examining birth weight and adulthood obesity demonstrate a linear relationship, whereby higher birth weight predisposes to obesity in adulthood [29••, 43]. No studies report an inverse relationship and only a small portion (8 %) show a "U" shaped distribution between birth weight and later-life obesity [29••, 43]. In addition, several studies observe that high maternal pre-pregnancy BMI and excessive weight gain during pregnancy are better predictors for adulthood

metabolic syndrome and obesity in the offspring than birth weight (high or low) alone [42•, 44–46].

Gestational Diabetes

GDM, like maternal obesity, is a growing concern within the obstetrics field. It is estimated that at least 7 % of all pregnancies are complicated with GDM, which is believed to be underdiagnosed [47]. A recent study of 25,000 non-diabetic pregnancies collected from 9 countries observe that GDM is present in approximately 18 % of the studied pregnancies when careful diagnostic criteria are employed [48]. Maternal obesity often coexists with GDM, with up to 25 % of obese women having concurrent GDM [49]. This combination of maternal disease adds additional risk and complexity to evaluating both the immediate and long-term outcomes for the mother and offspring.

GDM is a significant problem with lasting long-term metabolic consequences for both the mother and offspring. Among women diagnosed with GDM, approximately 5 %–10 % are found to have diabetes (most often type II) immediately after pregnancy [47]. Additionally, women with GDM are at a 35 %–65 % increased risk of developing diabetes later-in-life, and their offspring are more likely to develop obesity and T2DM in childhood and adulthood [47]. Several studies observe that children born to diabetic mothers have a higher BMI than children born to mothers without GDM; this effect appears to be more pronounced in older (9–14 years) rather than younger (5–8 years) children [30, 50•, 51]. In a study that compared children 6–11 years according with maternal GDM status, those born large for gestational age to mothers with GDM were at higher risk of metabolic syndrome than infants that were born to mothers who were neither obese or had GDM [40]. Another study found that children (10–16 years) born to mothers with GDM had higher systolic blood pressure, BMI, and 2-hour glucose and insulin levels than control children [52]. This risk appears to carry well into adulthood with findings that young adults (19–27 years) born to mothers with GDM are at an 8-fold increased risk for T2DM [53].

Preeclampsia

Preeclampsia is a serious multi-system disorder of pregnancy that is defined as hypertension occurring after the 20th week of pregnancy in the presence of proteinuria. The prevalence of preeclampsia is between 2 % and 10 % worldwide with ~8.5 million women affected each year [54, 55]. Preeclampsia results in ~18 % of maternal deaths each year and a significant portion of fetal morbidity and mortality, which is generally related to iatrogenic delivery preterm due to severe preeclampsia [55]. The cause of preeclampsia remains uncertain and the only established cure for preeclampsia is delivery of the fetus. A minority of women (1 out of ~3000 pregnancies per year) with severe preeclampsia will develop eclampsia, characterized by the occurrence of generalized convulsions or seizures. Severe preeclampsia, remote from delivery, presents a complicated medical scenario posing significant risks to both the mother with continuing the pregnancy and the fetus with preterm delivery. More so, reduced placental blood flow often accompanies preeclampsia and can result in fetal hypoxia and intrauterine growth restriction (IUGR) [55]. Women who have had preeclampsia are at a 4-fold increased risk for chronic hypertension and a 2-fold increased risk for ischaemic heart disease and stroke within 10–15 years after their affected pregnancy [56].

In addition to increased maternal risk for CVD and metabolic syndrome after a preeclamptic pregnancy, the offspring also carries additional metabolic risks. A large study of the Helsinki Birth Cohort population found that offspring born to preeclamptic mothers were at approximately a 2-fold increased risk for stroke; however, there was no evidence of an increased risk for coronary heart disease [31]. A systematic review and meta-analysis of

cardiovascular risk factors in children and young adults born to preeclamptic mothers revealed that children and young adults aged 4–30 years old born to preeclamptic mothers have higher systolic (2.39 mm Hg increase) and diastolic (1.35 mm Hg increase) blood pressures than their counterparts born to non-preeclamptic mothers [57••]. The long-term clinical significance of this increase is unclear. A modest yet significant increase in BMI was observed among children born to preeclamptic mothers, even among term, normal weight infants. Few studies have examined the risks of preeclampsia and adult offspring cholesterol and glucose metabolism; therefore, no concrete conclusions could be drawn from the meta-analysis on these factors [57••].

Genetic and Epigenetic Mechanisms

Most of the biology and etiology underlying the connections between the intrauterine environment, fetal growth, and later-life metabolic disease is unknown; however, emerging evidence suggests that shared genetic risk factors mediate these effects [58••]. Genome-wide association studies and large meta-analyses have examined genetic associations with birth weight and the risk of developing later-life metabolic disorders, such as T2DM [59–64]. A recent systematic review described significant overlap in genes that are related to both birth weight and T2DM (Table 2) [58••]. Genotypes in the ADCY5, CDKAL1, and HHEX-IDE genes are associated with low birth weight as well as later-life high fasting plasma glucose levels and T2DM [64]. Maternal genetic variants in GCK and TCF7L2 are associated with high infant birth weight and T2DM [62]. These associations likely arise due to the link between GCK and TCF7L2 and maternal glucose levels throughout pregnancy. Because maternal glucose crosses the placenta, increased levels can result in an increase in fetal insulin secretion, which in turn, can lead to an increase in birth weight [65].

Epigenetic changes, or those that affect gene expression through mechanisms other than those mediated by the underlying DNA, comprise another mechanism that may mediate the link between the intrauterine environment and later-life disease [67••]. Specific epigenetic changes include DNA methylation and histone modifications. A recent study demonstrated that epigenetic profiles measured at birth are associated with childhood adiposity [68]. This epigenetic mechanism explained ~25 % of the variation in fat mass. Evidence also suggests that epigenetic changes occurring during a time of developmental 'plasticity', such as during periods of fetal growth, can be passed on from one generation to the next [69]. Studies are also demonstrating that maternal nutrition is not only directly important for fetal growth but also influences adulthood diseases through epigenetic mechanisms [70–72].

Conclusions

The growing body of epidemiologic evidence presented here, and experimental evidence in animal models reviewed elsewhere [29••], indicates that pregnancy complications and adverse birth outcomes strongly predispose both mother and offspring of affected pregnancies to metabolic syndrome, CVD, and T2DM later in life. These reproductive factors, however, are rarely taken into consideration when evaluating an individual's risk for metabolic diseases. Approximately 1 in 12 infants are born LBW each year in the United States and an even greater proportion is exposed to adverse pregnancy conditions such as gestational diabetes, preeclampsia, or maternal obesity. As our ability improves to reduce the immediate morbidity and mortality of these infants, many more persons with low and high birth weight are surviving to adulthood, and are therefore at an increased risk for later-life morbidity and mortality. In addition to increasing the offspring's risk for metabolic syndrome, pregnancy complications also increase the mother's risk for developing CVD later in life. More research is needed to understand the biological etiology underlying these relationships, including genetic and epigenetic mechanisms. However, with an increasing

body of evidence indicating that the intrauterine environment influences an offspring's risk for metabolic syndrome in adulthood, further clinical consideration is warranted through increased monitoring, risk stratification, and follow-up of individuals with such adverse reproductive histories.

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Table 1

Meta-analyses of significant associations between birth weight and components/correlates of metabolic syndrome

Study	N	Exposure	Birth Weight Reference Group	Outcome	Effect OR [95 % CI]
Silveira et al. 2008 [11]	5867	LBW (<2.5 kg)	>3.4 kg	Metabolic syndrome	2.53 [1.57, 4.08]
Harder et al. 2007 [12]	132,180	HBW (>4 kg)	2.5–4 kg	T2DM	1.36 [1.07, 1.73]
		LBW (<2.5 kg)	2.5–4 kg	T2DM	1.47 [1.26, 1.72]
Whincup et al. 2008 [13]	152,084	BW continuous	per 1–kg rise	T2DM	0.80 [0.72, 0.89]
Mu et al. 2012 [14]	39,641	LBW (<2.5 kg)	>2.5 kg	hypertension	1.21 [1.13, 1.30]
	32,951	HBW (>4 kg)	<4 kg	hypertension	0.78 [0.71, 0.86]
	32,351	LBW (<2.5 kg)	>2.5 kg	SBP	2.58 [1.51, 3.64]
	28,144	HBW (>4 kg)	<4 kg	SBP	−2.08 [−2.98, −1.17]
de Jong et al. 2012 [15]	3080	preterm or VLBW	term	SBP	2.50 [1.67, 3.32]
Gamborg et al. 2007 [16]	197,954	BW continuous	per 1–kg rise	SBP in females	−2.80 [−3.85, −1.76]
				SBP in males	−1.52 [−2.27, −0.77]
Zhao et al. 2012 [17]	211,457	HBW (>4 kg)	2.5–4 kg	BMI>25	1.46 [1.27, 1.68]
Yu et al. 2011 [18]	39,216	HBW (>4 kg)	<4 kg	BMI>30	2.07 [1.91, 2.24]
Owen et al. 2003 [19]	23,247	BW continuous	per 1–kg rise	Total cholesterol	−0.05 [−0.08, −0.02]

HBW high birth weight, *LBW* low birth weight, *SBP* systolic blood pressure, *T2DM* type 2 diabetes mellitus

Table 2

Shared significant ($P<10^{-3}$) genetic associations with birth weight and T2DM

Gene	SNP	Risk allele	Fetal or Maternal	Obs. for BW meta-analysis[a]	Effect size for BW [95 % CI][b]	P-value	Effect for T2DM OR [95 % CI]	P value	References
ADCY5	rs9883204	C	Fetal	38,214	−30 [−38, −23]	7×10^{-15}	[c]1.12 [1.09, 1.15]	1×10^{-20}	[58••, 59, 63]
CDKAL1	rs7754840	C	Fetal	24,885	−20 [−29, −11]	5×10^{-6}	1.16 [1.12, 1.20]	5×10^{-19}	[58••, 61, 64]
HHEX-IDE	rs1111875	C	Fetal	25,164	−16 [−24, −8]	8×10^{-5}	1.16 [1.13, 1.20]	$<5.0\times10^{-4}$	[58••, 64, 66]
GCK	rs1799884	T	Maternal	12,643	30 [15, 44]	5×10^{-5}	[c]1.08 [1.04, 1.11]	2×10^{-6}	[58••, 61, 62]
TCF7L2	rs7903146	T	Maternal	13,406	23 [11,35]	3×10^{-4}	1.44 [1.40, 1.49]	1×10^{-109}	[58••, 61, 62]

[a]Most recent meta-analysis reported

[b]Change in BW per fetal risk allele in grams

[c]SNP for T2DM risk is rs11708067 for ADCY5 and rs1990458 for GCK