Changes in the Maternal Hypothalamic-Pituitary-Adrenal Axis in Pregnancy and Postpartum: Influences on Maternal and Fetal Outcomes

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Abstract
Overexposure of the developing fetus to glucocorticoids is hypothesised to be one of the key mechanisms linking early life development with later life disease. The maternal hypothalamic-pituitary-adrenal (HPA) axis undergoes dramatic changes during pregnancy and postpartum. Although cortisol levels rise threefold by the third trimester, the fetus is partially protected from high cortisol by activity of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2). Maternal HPA axis activity and activity of HSD11B2 may be modified by maternal stress and disease allowing greater transfer of glucocorticoids from mother to fetus. Here we review emerging data from human studies linking dysregulation of the maternal HPA axis to outcomes in both the mother and her offspring. For the offspring, greater glucocorticoid exposure is associated with lower birth weight and shorter gestation at delivery. In addition, evidence supports longer term consequences for the offspring including re-setting of the HPA axis and susceptibility to neurodevelopmental problems and cardiometabolic disease. For the mother, the changes in the HPA axis, particularly in the postpartum period, may increase vulnerability to mood disturbances. Further understanding of the changes in the HPA axis during pregnancy and the impact of these changes may ultimately allow early identification of those most at risk of future disease.

Introduction
There is increasing epidemiological evidence supporting the hypothesis that adult vulnerability to disease is ‘programmed’ in fetal life, and therefore shaped by the intrauterine environment as originally postulated in the Barker hypothesis [1–7]. Overexposure of the developing fetus to excess glucocorticoids is thought to be one of the key mechanisms underlying early life programming of disease [8, 9]. It is proposed that dysregulation of the maternal hypothalamic-pituitary-adrenal (HPA) axis determines fetal exposure to stress hormones influencing development and birth outcomes and also programming the fetal HPA axis, thus determining responses to stress and susceptibility to physical and mental illness in later life. This hypothesis is supported by animal studies showing that maternal glucocorticoid overexposure leads to adverse outcomes in the offspring including metabolic disorders and behavioural/anxiety phenotypes [10–19].
In humans, fetal glucocorticoid overexposure has been linked to development of cardiometabolic disease [20, 21] and there is a growing interest in the role of stress and glucocorticoid excess on offspring neurodevelopment and subsequent vulnerability to mental illness [22–34]. This is important as childhood neurodevelopmental problems and mental health disorders are major public health issues, so understanding the origins of these disorders may ultimately guide preventative strategies. In this mini-review we examine emerging evidence from human studies linking changes in the maternal HPA axis during pregnancy and postpartum with maternal and fetal outcomes with particular focus on the potential role of 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2).

The Maternal HPA Axis

The HPA axis mediates the stress response of glucocorticoids. Corticotrophin-releasing hormone (CRH) is released from the paraventricular nucleus in the hypothalamus in response to stressors and stimulates the release of adrenocorticotrophin hormone (ACTH) from the pituitary gland. In turn, ACTH stimulates the adrenal cortex to secrete cortisol into the bloodstream. Cortisol feeds back to glucocorticoid and mineralocorticoid receptors in the pituitary and hypothalamus to regulate its own secretion. During pregnancy, the regulation of the maternal HPA axis undergoes dramatic changes (fig. 1). Circulating cortisol levels rise markedly to around threefold non-pregnant levels by the third trimester [35]. This rise in cortisol is partly due to oestrogen stimulation of corticosteroid-binding globulin with a rise in free (or bioavailable) cortisol levels [36, 37]. In addition, the placenta secretes large quantities of CRH into the maternal bloodstream during the second and third trimesters of pregnancy [38–40]. Placental CRH stimulates the maternal pituitary gland, thus further increasing both ACTH and consequently cortisol levels. In turn, maternal cortisol stimulates placental CRH synthesis creating a positive feed-forward drive with resultant higher cortisol levels [41, 42]. Despite the increasing circulating levels of corti-
infection, the diurnal secretion of cortisol is maintained throughout pregnancy [43]. However, as pregnancy progresses, the increased circulating cortisol downregulates hypothalamic production of CRH and thus the responsiveness of the HPA axis to both physiological and psychological stress is attenuated during late pregnancy [44–46].

The fetus is protected from high levels of maternal glucocorticoids by the action of the placent enzyme HSD11B2. This enzyme converts active glucocorticoids (cortisol) into inactive glucocorticoids (cortisone), thus protecting the fetus from excessive glucocorticoid exposure [47–49]. Although a substantial proportion of cortisol (80–90%) is metabolised by the placenta during gestation, excess cortisol may reach the fetus [50] and the ‘barrier’ can be further weakened by maternal anxiety [51–55], infection [56] and inflammation [57] allowing increased transfer of glucocorticoids from mother to fetus. As maternal cortisol levels are so much higher than fetal levels, even modest variations in placental HSD11B2 can significantly alter fetal glucocorticoid exposure. In human pregnancy where it is difficult to measure HSD11B2 activity or fetal glucocorticoid exposure, measurements of cortisol in amniotic fluid (which is mainly fetally derived) are often used as a proxy for fetal glucocorticoid exposure. Maternal cortisol and amniotic fluid cortisol concentrations are positively correlated [54, 58, 59].

In the postpartum period, maternal plasma cortisol levels fall and the function of the HPA axis gradually returns to its pre-pregnant state. Following delivery of the placenta, there is a sharp drop in placental CRH levels. The HPA axis is relatively hyperresponsive with lack of cortisol suppression to dexamethasone for up to 3 weeks postpartum [60] and dynamic tests showing recovery of CRH secretion by 12 weeks postpartum [61]. ACTH levels also fall transiently immediately after delivery, rising again 3–4 days postpartum [62]. Cortisol levels remain normal during the postpartum period due to elevated corticosteroid-binding globulin and the adrenal gland hypertrophy that occurred during pregnancy.

Factors Influencing HPA Axis Activity during Pregnancy

Longitudinal studies with repeated cortisol measurements suggest individual variability in cortisol levels is relatively stable across pregnancy [63, 64]. So what are the pathways leading to interindividual variations in HPA axis activity in pregnancy? This has mostly been studied in the context of maternal ‘stress’ due to the documented association between a variety of different stressors ranging from chronic anxiety/depressive symptoms, to acute stressors such as bereavement or exposure to natural disasters, and poorer obstetric outcomes including reduction in gestational length, preterm delivery, and low birth weight (reviewed by Talge et al. [65]). Although many of these studies have not included measurements of maternal cortisol, it has been suggested that dysregulation of the HPA axis may underlie these associations. However, several studies show that stress and anxiety levels assessed by questionnaire do not necessarily correlate with maternal cortisol levels [64, 66]. This may be related to limitations in the approaches used to assess stress and cortisol concentrations [67] as there is a higher correlation for ambulatory assessment of maternal stress and cortisol concentrations than single assessments carried out in a research laboratory [43]. Indeed there is some evidence that positive life events lower cortisol levels during pregnancy [68]. In contrast, a history of prior major stress (child abuse) increases the cortisol awakening response during pregnancy [69] whilst experience of chronic stressful life events during early pregnancy blunts peak salivary cortisol levels in the morning [70] suggesting different stressors have differing effects on HPA axis responses. Certain circumstances may increase a woman’s vulnerability as exemplified by a recent study among US pregnant women of Mexican descent showing an association between increased ‘acculturation’, defined as members of one cultural group adapting to the beliefs and norms of another cultural group, and flatter diurnal slope of cortisol secretion in late pregnancy, the latter mediating the association between increased acculturation and lower birth weight [71]. Low socio-economic status is also associated with altered placental mRNA levels of genes important in glucocorticoid metabolism and action [72] and high maternal anxiety is associated with decreased placental HSD11B2 [51] and with higher levels of cortisol in amniotic fluid [54, 59]. These studies suggest that even if circulating maternal cortisol levels do not change in association with maternal stressors, such stressors can still lead to increased glucocorticoid transfer to the fetus by the placenta.

Less well studied is whether the maternal HPA axis function alters in association with pathophysiological changes associated with pregnancy. There is some evidence of changes in cortisol levels [73] and of altered placental HSD11B2 expression [74] in association with pre-eclampsia, though whether these changes are cause or consequence of the disease is not clear. Whether the HPA axis changes in response to gestational hypertension, dia-
Maternal HPA Axis and Offspring Outcomes

In animal models ranging from studies in rodents to non-human primates, maternal treatment with glucocorticoids and manipulations that increase endogenous glucocorticoids or reduce HSD11B2 activity lowers offspring birth weight [79–81]. In some human studies the use of exogenous glucocorticoids administered to women at threat of preterm labour also lowers birth weight [82, 83]. This does not hold true in all studies though which may reflect the importance of timing of steroid exposure [84]. There are now a number of studies showing that high endogenous cortisol levels in pregnant women, measured in blood, saliva, urine, or amniotic fluid negatively predict infant birth weight (table 1). The findings appear dependent on timing of sample collec-

| Table 1. Maternal HPA axis and fetal growth |
|----------------|----------------|----------------|----------------|----------------|----------------|
| Fetal growth   | Cortisol measurement | Timing of measurement | n  | Findings                                                                 |
| Diego et al. 2006 [85] | Maternal urinary cortisol | 16–29 weeks’ gestation | 98 | Higher maternal urine cortisol associated with below average estimated fetal weight measured by ultrasound OR 12.8 (95% CI 4.81–34.09) |
| Li et al. 2012 [86] | Maternal blood cortisol | Late gestation | 432 | Maternal serum total cortisol was significantly negative correlated with ultrasound parameters describing the fetal brain: late biparietal diameter ($R^2 = 0.512, p = 0.009$), late head circumference ($R^2 = 0.498, p = 0.001$), middle biparietal diameter ($R^2 = 0.819, p = 0.013$), middle cerebellum transverse diameter ($R^2 = 0.76, p = 0.014$) and early biparietal diameter ($R^2 = 0.819, p = 0.013$) |
| Birth size     | Cortisol measurement | Timing of measurement | n  | Findings                                                                 |
| Goedhart et al. 2010 [87] | Maternal serum cortisol | Early second trimester | 2,810 | Higher cortisol associated with lower birth weight ($B = −0.35 (95\% CI −0.53, −0.18)$, $p < 0.001$) and with small for gestational age OR = 1.00 (1.0–1.0), $p = 0.027$. However, findings no longer significant after adjustment for covariates (gestational age, infant gender, ethnicity, maternal age, parity, BMI, and smoking). Post hoc analysis revealed a moderation effect by time of day; only in those women who provided a blood sample ≤09:00 h ($n = 94$), higher maternal cortisol levels were independently related to lower birth weight ($B = −0.94, p = 0.025$) and a higher SGA risk (OR = 1.01, $p = 0.032$) |
| Bolten et al. 2011 [88] | Maternal salivary cortisol awakening response (CAR) | 13–18 (early) and 35–37 (late) weeks’ gestation | 70 | Lower birth weight associated with higher CAR in early ($β = −0.29, p < 0.05$) and late ($β = −0.30, p < 0.01$) pregnancy, with overall CAR explaining 19.8% of birth weight variance. Overall CAR also explained 9% of variance in birth length |
| Hompes et al. 2012 [89] | Diurnal salivary cortisol profile | Mid-pregnancy | 91 | Basal cortisol predicted variance in birth weight (proportion of variance in growth variable explained (PVE) = 11.6%) and body mass index at birth (PVE = 6.8%) |
| D’Anna-Hernandez et al. 2012 [71] | Maternal diurnal salivary cortisol slope | 15–18 weeks (early), 26–32 weeks (mid) and >32 weeks (late) gestation | 55 | Blunted maternal cortisol slope during late pregnancy associated with low birth weight ($r = −0.29, p = 0.05$) No significant correlations in early or mid-pregnancy |
| Baibazarova et al. 2012 [59] | Amniotic fluid cortisol | Second trimester | 158 | Higher amniotic fluid cortisol associated with lower birth weight ($r = −0.25, p < 0.01$) |

betes or obesity has not been studied, though dietary manipulations in animal studies can alter maternal stress responses [75, 76], and specific dietary supplementation with the methyl donor choline in the third trimester alters the methylation profiles of genes in fetal derived tissues and in genes that regulate fetal glucocorticoid metabolism [77]. The above factors suggest that some fetuses will be more susceptible to changes in the maternal HPA axis than others, but there is also evidence that the fetus can itself respond to adverse conditions, for example signaling to the placenta to increase production of placental CRH, allowing greater mobilisation of maternal glucose, when fetal metabolic demands increase [78]. Further work is needed to understand the cross-talk between fetus, placenta and mother and how this regulates glucocorticoid exposure to the fetus.
 tion, gestation at assessment and whether total cortisol or free (bioavailable) cortisol is measured. Likewise, measurements of cortisol and CRH in blood, saliva, amniotic fluid and hair have been linked to altered length of gestation (table 2). The changes in cortisol are modest yet have major influences on outcome; for example a 2.6% increase in cortisol levels at awakening was associated with a 1-week shortening of pregnancy duration [43]. These findings suggest that high maternal cortisol levels can overcome the protective HSD11B2 barrier and pass across the placenta, slowing fetal growth and altering gestational length. In support of this concept, observational studies show that women who consume large amounts of liquorice which contains glycyrrhizin, an HSD11B2 inhibitor, during pregnancy have a shorter gestation [95]. Likewise, lower placental HSD11B2 activity is correlated with lower birth weight [96, 97] and babies homozygous for deleterious mutations of the HSD11B2 gene are of lower birth weight, averaging 1.2 kg less than their heterozygote siblings [98]. Together these studies suggest increased exposure to cortisol is a critical factor regulating growth and gestation.

In addition to slowing fetal growth, excessive glucocorticoid exposure alters the set-point of the offspring HPA axis. Maternal and fetal/newborn cortisol levels are correlated [50, 99] and maternal cortisol levels are associated with reactivity of the newborn HPA axis as demonstrated in a recent study showing correlations between higher maternal cortisol levels in mid-late gestation and increased cortisol response in the newborn to the stress of a heel prick test [100]. The changes in offspring HPA

Table 2. Maternal HPA axis and gestation at delivery

<table>
<thead>
<tr>
<th>Gestation at delivery</th>
<th>HPA axis measurement</th>
<th>Timing of measurement</th>
<th>n</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hobel et al. 1999 [90]</td>
<td>Maternal plasma cortisol, CRH and ACTH</td>
<td>18–20, 28–30, and 35–36 weeks’ gestation</td>
<td>18 pre-term and 18 controls</td>
<td>Patients who had preterm delivery had significantly higher plasma CRH levels (p &lt; 0.0001) and ACTH levels (p &lt; 0.001) than did control subjects at all 3 gestational ages and significantly elevated cortisol levels at 18–20 weeks’ gestation and 28–30 weeks’ gestation (p &lt; 0.001)</td>
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<tr>
<td>Mancuso et al. 2004 [91]</td>
<td>Maternal plasma CRH</td>
<td>18–20 and 28–30 weeks’ gestation</td>
<td>282</td>
<td>Women who delivered preterm had significantly higher rates of CRH at both 18–20 weeks’ gestation and 28–30 weeks’ gestation (r = –0.37, p &lt; 0.01 and r = –0.41, p &lt; 0.01 respectively) compared with women who delivered term</td>
</tr>
<tr>
<td>Sandman et al. 2006 [92]</td>
<td>Maternal plasma cortisol and CRH</td>
<td>15, 19, 25 and 31 weeks’ gestation</td>
<td>203</td>
<td>CRH levels only at 31 weeks predicted preterm birth (F1,201 = 5.53, p = 0.02); levels of cortisol were higher in women who delivered preterm at 15 weeks’ gestation (F1,201 = 4.45, p = 0.03) with a similar trend at 19 weeks’ gestation</td>
</tr>
<tr>
<td>Buss et al. 2009 [93]</td>
<td>Maternal cortisol awakening response (CAR)</td>
<td>16.8 (SD 1.4) and 31.4 (1.3) weeks’ gestation</td>
<td>101</td>
<td>A larger CAR in late pregnancy and reduced attenuation of the CAR from early to late gestation were associated significantly with shorter gestational length</td>
</tr>
<tr>
<td>Kramer et al. 2009 [94]</td>
<td>Plasma CRH and (in a subset) hair cortisol</td>
<td>24–26 weeks’ gestation</td>
<td>204 preterm and 444 controls; subset n = 31 cases and 86 controls</td>
<td>Maternal plasma CRH was significantly higher in cases than in control in crude analyses but not after adjustment (for concentrations above the median, adjusted odds ratio = 1/1 (95% CI 0.8–1.6)) In the subset, hair cortisol levels were positively associated with gestational age. Concentrations were higher in the hair of women who delivered at term than in those who delivered at &lt;34 weeks’ gestation (190.6 SD 99 vs. 148.6 SD 39.2 ng/g, p &lt; 0.05)</td>
</tr>
<tr>
<td>Entringer et al. 2011 [43]</td>
<td>Diurnal salivary cortisol profile</td>
<td>23.4 (SD 9.1) weeks’ gestation</td>
<td>25</td>
<td>Higher salivary cortisol concentrations at awakening and throughout the day (p = 0.001), as well as a flatter cortisol response to awakening (p = 0.005), were associated with shorter length of gestation</td>
</tr>
<tr>
<td>Baibazarova et al. 2012 [59]</td>
<td>Amniotic fluid cortisol</td>
<td>Second trimester</td>
<td>158</td>
<td>Higher amniotic fluid cortisol associated with shorter gestational age (r = –0.18, p &lt; 0.05)</td>
</tr>
</tbody>
</table>
axis activity associated with glucocorticoid overexposure in utero may persist into adult life as low birth weight is associated with higher fasting cortisol levels [101–103] and with activation of the HPA axis [104, 105]. Likewise, increased cortisol reactivity has been demonstrated in 6- to 11-year-olds born at term who had prenatal glucocorticoid treatment [82].

Follow-up studies of infants exposed to antenatal glucocorticoids in utero suggest an increased risk of adverse neurodevelopmental outcomes. Though data are difficult to interpret as the babies are often born premature, studies have shown associations between antenatal glucocorticoid exposure and reduced head circumference at birth and an increase in distractibility and inattention in teenage offspring [106]. There is also some evidence that endogenous maternal HPA axis activity influences fetal neurodevelopment. For example, fetuses of mothers with higher CRH levels showed less habituation of the fetal heart rate to repeated vibroacoustic stimulation compared to those of mothers with low CRH levels [22]. This finding is thought to suggest impaired neurodevelopment as fetal heart rate habituation is known to correlate with later infant development at 18 months and 3 years of age [107]. There is inconsistency in the literature linking maternal cortisol to offspring temperament and emotional reactivity. Studies have shown higher maternal cortisol levels linked to offspring temperament, only cortisol measurements in the third trimester associating with infant emotional reactivity [20] or mental and motor development [108] while others have reported no associations between maternal cortisol measurements or amniotic fluid cortisol and these outcomes [59, 109].

Higher levels of amniotic cortisol have also been associated with lower cognitive scores in the infant at 17 months [110]. Regulation of cortisol exposure through activity of HSD11B2 appears critical as the offspring of women who consumed large quantities of liquorice had significantly impaired cognitive and behavioural development [111, 112]. A recent study has attempted to dissect the mechanisms underlying the altered infant neurodevelopment showing higher maternal cortisol levels measured in earlier but not later gestation were associated with a larger right amygdala volume measured by MRI in girls at age 7 years [113]. The amygdala is important for emotional memory processing and regulates a variety of emotions including fear, depression and anxiety. The higher maternal cortisol levels in early gestation were associated with more affective problems in girls, and this association was mediated in part by amygdala volume.

Intriguingly a prospective study of 6- to 9-year-olds also reported that pregnancy anxiety at 16 weeks, but not later in gestation, was associated with altered brain structure detected by MRI scans [114].

Exposure to exogenous glucocorticoids in utero is associated with adverse metabolic outcomes including higher blood pressure at age 14 years [21] and higher insulin levels at age 30 years [115]. Increased exposure to endogenous glucocorticoids, estimated from measurements of cord blood cortisol and cortisone, is also associated with higher blood pressure aged 3 years [116]. Maternal cortisol levels during pregnancy are also associated with changes in offspring body composition at 5 years, with higher maternal cortisol being independently associated with higher fat mass index in girls and lower fat mass index in boys, suggesting gender differences in offspring vulnerability [117].

Overall, these results support the hypothesis that over-exposure to glucocorticoids increase the risk of development of both mental and physical illness in later life. Crucially, the timing of excess glucocorticoid exposure appears key to determining outcome suggesting there are critical windows of development during which different fetal organs and systems are vulnerable to glucocorticoids. For example, it is thought that cortisol early in pregnancy may prime the ‘placental clock’ predetermining the CRH surge and hence timing of delivery from very early in gestation [118]. Any insult occurring in early pregnancy may disrupt this exquisitely sensitive system. Other studies have shown different windows of susceptibility. For example, higher maternal cortisol in late pregnancy but not early pregnancy has been associated with more advanced physical and neuromuscular maturation in the neonate and mental development scores on the Bayley Scales at 12 months [63, 119] which is in keeping with the rapid development of the neural system which occurs between 28 and 32 weeks. Another potential explanation is that although the circulating levels of cortisol, ACTH and placental CRH rise as pregnancy progresses, the responsiveness of the HPA axis is blunted and this may protect mother and fetus to effects of stress in the later stages of pregnancy.

**Maternal Consequences of Stress and Altered HPA Axis Activity in Pregnancy**

Changes in maternal HPA axis activity influence timing of labour but are there any longer term consequences of dysregulation of the HPA axis during pregnancy for
women? The observation that women who develop a physical illness in pregnancy such as pre-eclampsia are at later risk of hypertension and cardiovascular disease [120], suggests that pregnancy is itself a physiological stressor, and an adverse metabolic response to pregnancy predicts later disease susceptibility. Similarly, follow-up of women exposed to extreme stress in pregnancy indicate these women are at increased risk of adverse mental health [121]. In the non-pregnant state, activation of the HPA axis increases the risk of metabolic and psychiatric disease [8, 122–130]. Preliminary evidence that altered HPA responses to pregnancy may influence later maternal mental health comes from a small study showing that increased cortisol responses to a standardized psychosocial stress test during healthy pregnancy predict postpartum depressive symptoms [131]. Further, higher mid-pregnancy CRH levels are associated with increased postpartum depressive symptoms [132]. In addition, dysregulation of the normal recuperation of the HPA axis in the postpartum period has been implicated in mood disorders occurring in that time period. For example, women who develop the postpartum ‘blues’ have been reported to have higher postpartum cortisol levels [133, 134], higher ACTH levels, a greater fall in CRH levels [62] and blunted responses to CRH testing [61]. In another study, patients with postpartum thoughts of harming the infant had higher levels of ACTH in the immediate postpartum period compared to women without these intrusive thoughts [135].

Conclusions

The challenges of measuring the dynamic and changing HPA axis in pregnancy have limited the translation of the numerous animal studies linking glucocorticoid overexposure to later disease into human studies. Nevertheless, evidence is accumulating showing changes in the maternal HPA axis leading to lower birth weight and gestation and long-term adverse health outcomes for the offspring. We currently do not know whether interventions during pregnancy to modulate HPA axis activity would be beneficial, though there is some evidence that use of simple stress reduction instructions can reduce maternal perceived stress as well as morning cortisol levels [136]. The early postpartum period may also be critical, as in animal studies postnatal care also effects offspring HPA axis function. Increased maternal care has been associated with enhanced negative feedback sensitivity of the axis, reduced CRH and reduced stress response, which consequently reduces fear behaviour in offspring [137, 138]. Cross-fostering studies with rats with high and low maternal care can reverse the phenotype of offspring [139]. These elegant studies suggest that a postnatal intervention may allow modification of some programmed changes. Therefore, early detection of, and preventative measures could have a huge impact on childhood neurodevelopment and adult mental health.

Given the difficulties in assessing the HPA axis in pregnancy, attention is turning to use of the placenta for biomarkers of future disease. One such biomarker is epigenetic markers, i.e. changes in gene expression such as DNA methylation, histone modification and chromatin packaging, which do not involve changes in DNA sequence. There is now preliminary evidence in humans that methylation levels of genes involved in glucocorticoid pathways are altered by the early life environment. Methylation of the HSD11B2 promoter is associated with reduced transcription [140] and a recent study has shown that increased DNA methylation of the HSD11B2 promoter in the placenta associates with lower birth weight and with altered newborn behaviour with poorer infant quality of movement, a marker of adverse neurobehavioural outcomes [141]. While these data are preliminary, they do suggest that it may be possible to identify at birth those most at risk of later disease.

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References

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