Maternal Glucocorticoid Metabolism Across Pregnancy: A Potential Mechanism Underlying Fetal Glucocorticoid Exposure

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Context: Across pregnancy, maternal serum cortisol levels increase up to 3-fold. It is not known whether maternal peripheral cortisol metabolism and clearance change across pregnancy or influence fetal cortisol exposure and development.

Objectives: The primary study objective was to compare maternal urinary glucocorticoid metabolites, as markers of cortisol metabolism and clearance, between the second and third trimester of pregnancy. Secondary objectives were to test associations of total maternal urinary glucocorticoid excretion, with maternal serum cortisol levels and offspring birth weight z score.

Design, Participants, and Setting: A total of 151 women with singleton pregnancies, recruited from prenatal clinic at the Pittsburgh site of the Measurement of Maternal Stress (MOMS) study, had 24-hour urine collections during both the second and third trimesters.

Results: Between the second and third trimester, total urinary glucocorticoid excretion increased (ratio of geometric means [RGM] 1.37, 95% CI 1.22-1.52, P < .001), and there was an increase in calculated 5β-reductase compared to 5α-reductase activity (RGM 3.41, 95% CI 3.04-3.83, P < .001). During the third trimester total urinary glucocorticoid excretion and serum cortisol were negatively correlated (r = –0.179, P = .029). Mean total urinary glucocorticoid excretion across both trimesters and offspring birth weight z score were positively associated (β = 0.314, P = .001).
Glucocorticoids play a critical role in fetal maturation. Although a surge in glucocorticoid exposure toward the end of pregnancy helps prime a fetus for life outside the womb (1), excess or inappropriately timed exposure can adversely program offspring development (2, 3). There is growing evidence that circulating levels of maternal cortisol influence both fetal cortisol exposure and development. Maternal blood cortisol levels correlate with cortisol levels measured in fetal blood (4) and amniotic fluid (5). Elevated cortisol levels measured in maternal blood or saliva are associated with offspring growth restriction and adverse neurodevelopment and metabolic health (6–8).

Maternal regulation of glucocorticoids changes profoundly across pregnancy, with circulating cortisol levels rising approximately 3-fold by delivery (9). Multiple factors contribute to maternal hypercortisolism, including rising cortisol-binding globulin (10), placental secretion of corticotropin-releasing hormone (CRH) (11), and reduced sensitivity of the hypothalamic–pituitary–adrenal (HPA) axis to glucocorticoid-mediated central negative feedback (12). Altered breakdown, clearance, and regeneration of cortisol within maternal peripheral tissues could also influence maternal serum levels and fetal glucocorticoid exposure.

Relatively little intact cortisol is excreted from the body passively, with the majority instead being metabolized to compounds considered more inert before urinary excretion (13). Metabolism of cortisol to $5\beta$-tetrahydrocortisol (THF), and its derivatives $\alpha$-cortol and $\beta$-cortol, and $5\alpha$-tetrahydrocortisol ($\alpha$-THF), are reliant on the activity of A-ring reductases, $5\beta$-reductase, predominantly expressed in the liver, and $5\alpha$-reductase, expressed both in liver and fat. $11\beta$-hydroxysteroid dehydrogenase type 2 ($11\beta$-HSD2) acts in the kidney and placenta, converting cortisol to cortisone. In contrast, $11\beta$-hydroxysteroid dehydrogenase type 1 ($11\beta$-HSD1) is most highly expressed in the liver, where it regenerates active cortisol from inert cortisone. These processes are outlined in Fig. 1. Peripheral glucocorticoid metabolism varies as a function of age, sex, and obesity and in many disease states (14–16).

The sum of glucocorticoid metabolites measured in a 24-hour sample of urine represents total urinary glucocorticoid excretion. Because the majority of glucocorticoids are excreted in urine, this measurement has also been used as an estimate of glucocorticoid production by the adrenal gland (17). Additionally, comparison of the relative levels of metabolites offers insight into the activity of enzymes converting cortisol in peripheral tissues.

To date there has been limited investigation of maternal peripheral glucocorticoid metabolism and clearance in pregnancy. Longitudinal studies of maternal peripheral glucocorticoid metabolism in pregnancy have been limited by small sample size (18) or have relied on metabolites collected in spot urine or blood samples that are subject to diurnal variation (19, 20). There is growing evidence that maternal peripheral glucocorticoid metabolism and clearance are altered in preeclampsia (20–22). There are also preliminary data supporting a role for peripheral glucocorticoid metabolism influencing fetal development, with a higher plasma cortisol to cortisol ratio (representing more inert compared to active glucocorticoid) measured in mothers with psychiatric morbidity during the third trimester, being associated with higher offspring birth weight (23).

The aims of this study were to assess how maternal urinary glucocorticoid excretion, measured in 24-hour urine, changes between the second and third trimester of pregnancy, and to test the associations of total urinary glucocorticoid excretion with maternal serum cortisol levels and offspring birth weight z score. We tested the hypothesis that total urinary glucocorticoid excretion, as a marker of maternal adrenal cortisol production, increases across pregnancy, and is negatively associated with offspring birth weight z score.

**Materials and Methods**

**Participants and clinical protocol**

The Measurement of Maternal Stress (MOMS) study was a multisite prospective cohort that recruited women with singleton pregnancies from antenatal clinics in Pittsburgh, Pennsylvania; Chicago, Illinois; Schuylkill County, Pennsylvania; and San Antonio, Texas between June 2013 and May 2014. Exclusion criteria were fetal congenital abnormality, chromosomal abnormalities, progesterone use before 14 weeks’ gestation, or regular maternal corticosteroid use. All participating women gave written informed consent, and the study protocol was approved by the institutional review board of each site. A description of the cohort has been presented previously (24).
This study reports data from a subset (151 of 200) of mother-baby dyads, recruited from the Pittsburgh site, who had 24-hour urine collected for measurement of total glucocorticoids and metabolites on 2 occasions during pregnancy, between 12.7 and 22.1 weeks’ gestation (second trimester), and between 31.9 and 36.4 weeks’ gestation (third trimester).

Participants also had blood collected for measurement of serum cortisol at study visits during the second and third trimester. Maternal demographic and medical information, including body mass index (BMI), age, ethnicity, diabetes mellitus, preeclampsia, gestational hypertension, and offspring outcomes including birth weight and birth gestation, were recorded either during study visits or on review of participants’ medical records. Offspring birth weight z scores were calculated according to International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) standards (25).

**Laboratory methods**

**Serum.** Serum was obtained by centrifuging whole blood at 1000 g at 4°C for 15 minutes, then aliquoting serum into 2-mL cryovials. Cortisol was assessed by radioimmunoassay at the Development, Health and Disease Research Program’s laboratory at the University of California, Irvine. Ten percent of samples were measured in duplicate, and interassay and intra-assay coefficients of variation were less than 10%.

**Urinary glucocorticoids.** Urinary glucocorticoid metabolites were analyzed by gas chromatography–triple quadrupole mass spectrometry at the Edinburgh Clinical Research Facility Mass Spectrometry Core as previously described (26). The interassay and intra-assay coefficients of variation were less than 13%. Analytes included cortisol (F), cortisone (E), α-THF, THF, α-cortol, β-cortol, tetrahydrocortisone (THE), α-cortolone, and β-cortolone. The sum of these measured analytes is referred to as total urinary glucocorticoid excretion.

The following ratios of urinary metabolites were used as parameters to estimate peripheral glucocorticoid metabolism:

1. 11β-HSD2 activity = F/E
2. Total 11β-HSD2 activity = (THF + α-THF)/THE
3. Relative 5β-reductase and 5α-reductase activity = THF/α-THF
4. 5α-reductase activity = F/(α-THF + β-cortol)
5. 5β-reductase metabolism of F = F/(THF + α-cortol + β-cortolone)
6. 5β-reductase metabolism of E = E/(THE + α-cortolone + β-cortolone)

**Statistical Analysis**

All analyses were performed using IBM SPSS Statistics version 24. Data distributions were assessed for normality visually using histograms. Serum cortisol levels were normally distributed among the study population. Levels of all excreted urinary glucocorticoid metabolites were positively skewed, and log base 10–transformed before statistical analysis.

Demographic data are presented as mean ± SD. Change of urinary metabolite excretion between the second and third trimester was tested using paired t tests, and the degree of change is represented through the ratio of the geometric means (RGM), with 95% CIs. To assess whether peripheral metabolism has a maintained trait component across pregnancy, the rank stability—the similarity of where participants’ estimated enzymatic function fell within the study population’s distribution, at the second compared to the third trimester—was tested by a linear regression model adjusting for the gestation of urine sampling. The relationship between maternal total urinary glucocorticoid excretion and serum cortisol levels was tested using the Pearson coefficient within both the whole study population and in a subgroup of patients with blood sampled before 10 am. Finally, the association of maternal total
urinary glucocorticoid excretion and offspring birth weight z score was tested by linear regression adjusting for confounding factors. These included the gestation at urine sampling and maternal ethnicity, smoking status, age, preeclampsia, gestational hypertension, diabetes mellitus (pregestational and gestational), BMI, and gravidity. Associations with birth weight z score were tested both for second and third trimester glucocorticoid excretion, and for mean glucocorticoid excretion across pregnancy. A P value less than .05 was considered statistically significant.

Results

Demographics

Table 1 shows the characteristics of study participants. Mothers were age 30.5 ± 5.0 years, with BMI 27.6 ± 7.1 kg/m², and were predominantly white nonsmokers. Mean gestational age at birth was 39.4 ± 1.4 weeks, and mean birth weight was 3487 ± 489 g.

Changing glucocorticoid levels across pregnancy

Fig. 2 and Table 2 depict urinary glucocorticoid metabolite excretion for collections during the second and third trimester. Across pregnancy total urinary glucocorticoid excretion increased (RGM 1.37, P < .001). Excretion of all individual metabolites increased except for α-THF, which decreased between the second and third trimester (RGM 0.55, P < .001). Assessing individual metabolic pathways, the ratio of F/E (RGM 0.90, P < .001) decreased, likely representing increased estimated 11β-HSD2 (inactivation of cortisol to cortisone) activity across pregnancy. Total body 11β-HSD activity represented by (THF + α-THF)/THE (RGM 1.27, P < .001) shifted in favor of excretion of cortisol metabolites relative to cortisone metabolites. The activity of A-ring reductases shifted toward 5β-reductase metabolism compared to 5α-reductase metabolism, with increased THF/α-THF ratio (RGM 3.41, P < .001). Between the second and third trimester serum cortisol also increased (ratio of means 1.63, 95% CI 1.40-1.85, P < .001).

Individual stability in peripheral glucocorticoid metabolism

Table 3 and Fig. 3 represent rank-order stability of total urinary glucocorticoid excretion and estimates of peripheral metabolism of glucocorticoids for participants across the second and third trimester. Despite the whole-group changes in peripheral glucocorticoid metabolism across pregnancy, the relative enzymatic activity of individual participants compared to the whole group was well maintained across both time points, with women with higher estimated activity for peripheral glucocorticoid metabolism during the second trimester tending to have higher estimated enzyme activity measured in the third trimester.

Associations between total urinary glucocorticoid excretion and serum cortisol levels

During the second trimester serum cortisol was not associated with total urinary glucocorticoid excretion (r = 0.076, P = .358). During the third trimester, total urinary glucocorticoid excretion was negatively
associated with serum cortisol within the whole group ($r = -0.179, P = .029$). This association between third trimester serum cortisol and total urinary glucocorticoid excretion was largely driven by the subgroup of participants with third trimester blood samples taken before 10 AM ($n = 66, r = -0.354, P = .004$). In contrast, participants’ results with third trimester blood taken after 10 AM were $n = 83, r = -0.096, P = .390$.

Associations between total urinary glucocorticoid excretion and infant birth weight z score

In the adjusted models, there were positive associations between total urinary glucocorticoid excretion during the second trimester and offspring birth weight z score ($\beta = 0.198, r$-square change $0.028, P = .033$), total urinary glucocorticoid excretion during the third trimester and offspring birth weight z score ($\beta = 0.202, r$-square change $0.032, P = .023$), and mean total glucocorticoid excretion across both trimesters with offspring birth weight z score ($\beta = 0.314, r$-square change $0.066, P = .001$). In contrast, there was no association between mean serum cortisol levels and offspring birth weight z score. A visual representation of maternal glucocorticoid excretion across trimesters according to infant birth weight z score quintile is shown in Fig. 4.

Associations between glucocorticoid metabolite ratios, with serum cortisol and infant birth weight z score

Having demonstrated that total urinary glucocorticoid excretion was negatively associated with serum cortisol during the third trimester and positively associated with birth weight z score, further exploratory analysis was undertaken to investigate whether these effects were being driven by the action of individual metabolic pathways. In this exploratory analysis, higher

Table 2. Changes in urinary metabolites excretion and ratios across pregnancy

<table>
<thead>
<tr>
<th>Metabolites</th>
<th>Second Trimester: Median (Lower Quartile-Upper Quartile)</th>
<th>Third Trimester: Median (Lower Quartile-Upper Quartile)</th>
<th>Change Across Gestations: RGM (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>1043 (691-1397)</td>
<td>1768 (1066-3269)</td>
<td>1.88 (1.65-2.15)$^b$</td>
</tr>
<tr>
<td>$\alpha$-THF</td>
<td>494 (331-781)</td>
<td>291 (177-436)</td>
<td>0.55 (0.50-0.61)$^b$</td>
</tr>
<tr>
<td>THE</td>
<td>2500 (1588-3579)</td>
<td>2799 (1805-4222)</td>
<td>1.13 (1.04-1.23)$^a$</td>
</tr>
<tr>
<td>$\alpha$-cortol</td>
<td>586 (368-917)</td>
<td>641 (455-1140)</td>
<td>1.19 (1.05-1.34)$^a$</td>
</tr>
<tr>
<td>$\beta$-cortol</td>
<td>545 (259-947)</td>
<td>849 (540-1410)</td>
<td>1.65 (1.45-1.88)$^b$</td>
</tr>
<tr>
<td>$\alpha$-cortolone</td>
<td>2420 (1589-4473)</td>
<td>3685 (2371-6241)</td>
<td>1.46 (1.25-1.71)$^b$</td>
</tr>
<tr>
<td>$\beta$-cortolone</td>
<td>632 (424-979)</td>
<td>796 (574-1189)</td>
<td>1.29 (1.13-1.47)$^b$</td>
</tr>
<tr>
<td>F</td>
<td>231 (160-315)</td>
<td>272 (215-361)</td>
<td>1.23 (1.13-1.35)$^b$</td>
</tr>
<tr>
<td>E</td>
<td>228 (171-292)</td>
<td>316 (227-410)</td>
<td>1.36 (1.26-1.48)$^b$</td>
</tr>
<tr>
<td>Total urinary glucocorticoids</td>
<td>9691 (6157-12 805)</td>
<td>13 523 (8955-18 269)</td>
<td>1.37 (1.22-1.52)$^b$</td>
</tr>
</tbody>
</table>

Ratios of metabolites

$11\beta$-HSD2 activity = $F/E$

0.99 (0.78-1.28) 0.88 (0.73-1.16) 0.90 (0.86-0.95)$^b$

$11\beta$-HSD total activity = (THF + $\alpha$-THF)/THE

0.61 (0.52-0.85) 0.76 (0.48-1.23) 1.27 (1.14-1.42)$^b$

Relative $5\beta$-reductase and $5\alpha$-reductase activity = THF/$\alpha$-THF

1.78 (1.33-2.83) 7.19 (3.64-11.74) 3.41 (3.04-3.83)$^b$

$5\alpha$-reductase activity = $F/\alpha$-THF

0.45 (0.27-0.60) 0.98 (0.61-1.51) 2.24 (2.00-2.50)$^b$

$5\beta$-reductase metabolism of $F$ = $F/(THF + \alpha$-cortol + $\beta$-cortol)

0.10 (0.07-0.14) 0.07 (0.05-0.11) 0.72 (0.65-0.81)$^b$

$5\beta$-reductase metabolism of $E$ = $E/(THE + +\alpha$-cortolone+ $\beta$-cortolone)

0.04 (0.02-0.06) 0.04 (0.03-0.06) 1.05 (0.96-1.15)$^b$

Paired t test (2-tailed) of log-transformed urine values.

Abbreviations: $E$, cortisone; $F$, cortisol; HSD, hydroxysteroid dehydrogenase; HSD2, hydroxysteroid dehydrogenase type 2; RGM, ratio of geometric means; THE, tetrahydrocortisone; THF, $5\beta$-tetrahydrocortisol.

$^a$P less than .01. $^b$P less than .001.
third trimester serum cortisol was associated with estimates of reduced 5α-reductase activity (F/α-THF; whole group \( r = 0.168, P = .041 \); venipuncture < 10 AM subgroup \( r = 0.318, P = .009 \)), and reduced 5β-reductase activity (F/(THF + α-cortol + β-cortol)); whole group \( r = 0.206, P = .012 \); venipuncture < 10 AM subgroup \( r = 0.281, P = .022 \)) and (E/(THE + α-cortolone + β-cortolone)); whole group \( r = 0.252, P = .002 \); venipuncture < 10 AM subgroup \( r = 0.251, P = .042 \)). No associations were seen between third trimester serum cortisol and estimated 11β-HSD1 or 11β-HSD2 activity. Additionally,
undervirilization of male offspring (29). 5α-reductase metabolism of progesterone has also been investigated in the context of parturition, with 5α-reductase type 1–deficient mice failing to undergo cervical ripening at term (30). However, to our knowledge the physiological importance of 5α-reductase metabolism of cortisol in pregnancy has not previously been considered.

Changes in glucocorticoid metabolism may offer specific advantages to the mother and fetus. In addition to controlling systemic cortisol inactivation and clearance, peripherally located enzymes play an important role in regulating glucocorticoid exposure to specific tissues. This is most commonly discussed in relation to the kidney, where local 11β-HSD2 acts to prevent excessive activation of mineralocorticoid receptors by cortisol (13). 5α-reductase influences cortisol clearance and action within the liver, and its activity has been shown to be modifiable either by early life stress (31) or by variation in nutritional demands (32, 33). Within pregnancy, marked reduction in 5α-reductase activity during the third trimester may act to enhance cortisol activity in the liver, allowing mobilization of fuels at a time of increased metabolic requirements.

Alternatively, changing glucocorticoid metabolism across pregnancy may be a bystander influenced by other physiological changes in the mother across pregnancy. Maternal glucocorticoid metabolism could be influenced by a changing inflammatory milieu. For example, it has been both been demonstrated that tumor necrosis factor alpha (TNF-α) increases across pregnancy (27), and that inhibiting TNF-α in patients with inflammatory arthritis increases 5α-reductase activity (34). Changing biliary physiology may also influence maternal glucocorticoid metabolism, with bile acids holding the potential to inhibit A-ring reductases and 11β-HSDs (35). Increases in insulin resistance across pregnancy may also influence glucocorticoid metabolism. However, insulin-sensitizing therapies and weight loss have both previously been associated with decreases in 5α-reductase activity (36, 37), making it unlikely that changes in insulin sensitivity are driving the reductions in 5α-reductase activity seen during the third trimester. There is also likely to be a placental contribution to maternal whole-body glucocorticoid metabolism estimated through urinary glucocorticoids. In an ex vivo placental perfusion model, the majority of cortisol converted from cortisol at term gestation was transferred back into the maternal circulation rather than fetal circulation (38).

During the second trimester there was no association between maternal urinary glucocorticoid excretion and serum cortisol, whereas during the third trimester higher serum cortisol correlated with lower total urinary glucocorticoid excretion. Additionally, in exploratory analysis, higher serum cortisol in the third trimester was associated with lower estimated activity of 5β-reductase and 5α-reductase. Individual differences in peripheral glucocorticoid metabolism and clearance may influence serum cortisol levels in the later stages of pregnancy. In healthy, nonpregnant populations differences in peripheral glucocorticoid metabolism are generally not associated with serum cortisol levels, likely because of compensatory glucocorticoid release by the HPA axis in response to changing negative feedback (39, 40). However, in critically ill patients reduced peripheral metabolism and clearance of cortisol contributes to increased serum cortisol levels (16). Throughout pregnancy regulation of the maternal HPA axis changes, becoming progressively less sensitive to negative feedback by glucocorticoids (12). It therefore seems physiologically plausible that by the third trimester individual differences in glucocorticoid metabolism and clearance influence serum cortisol levels.

An unexpected finding was the modest positive association between total urinary glucocorticoid excretion and offspring birth weight z score, with maternal total urinary glucocorticoid excretion measured in the second and third trimesters of pregnancy explaining 6.6% of variance in offspring birth weight z score. Previous studies have typically reported a negative association between synthetic glucocorticoid exposure (2), or maternal cortisol levels measured in saliva (7) or blood (41), with infant birth weight. A negative association has also previously been reported between urinary free cortisol measured in the morning between 18 and 20 weeks’ gestation and fetal growth (42). The relationship between total urinary glucocorticoid excretion and infant birth weight z score has not previously been tested. Increased maternal peripheral metabolism and clearance of glucocorticoids may serve as a mechanism reducing cortisol exposure to the fetus. This theory is strengthened by the negative association found between serum cortisol and total urinary glucocorticoids observed in the third trimester. In the exploratory analyses no associations were found between birth weight z score and any of the urinary metabolite ratios used to estimate peripheral enzymatic function, so it cannot be concluded that this relationship is driven through the effects of a single enzyme’s function. Alternatively, the relationship between maternal total urinary glucocorticoid excretion and infant birth weight z score could be mediated by other maternal factors. For example, increased urinary glucocorticoid excretion has previously been associated with insulin resistance (36), and increased maternal insulin resistance during pregnancy may also act to increase offspring birth weight (43).
Despite whole-group changes in peripheral metabolism across pregnancy, individuals’ rank within the cohort remained relatively stable with those who had higher calculated enzymatic activity during the second trimester also tending to have higher activity during the third trimester. This implies that individual’s peripheral metabolism shows a consistent trait across pregnancy, increasing the likelihood that peripheral glucocorticoid metabolism could influence fetal exposure to cortisol and play a role in fetal development.

Strengths of this study include the use of a modern technique for accurate quantification of urinary glucocorticoid metabolites (26), the large sample size, and longitudinal study design allowing comparison of urinary metabolites across pregnancy. Limitations include the fact that there was variation in the time of day blood samples were collected, that participants did not fast before venipuncture, and the lack of measurement of other serum glucocorticoid metabolites in addition to cortisol.

Conclusions

Between the second and third trimester the ratios of urinary glucocorticoids, acting as markers of peripheral metabolism, changed suggesting a relative decrease in 5β-reductase metabolism and a relative increase in 5α-reductase metabolism of cortisol. However, interindividual differences among study participants were relatively well preserved between the 2 testing periods. The negative association between total urinary glucocorticoids and third trimester serum cortisol, along with the positive association between total urinary glucocorticoids and birth weight z score, provides preliminary data that peripheral glucocorticoid metabolism may influence fetal glucocorticoid exposure and fetal growth.

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data that peripheral glucocorticoid metabolism may influence fetal glucocorticoid exposure and cortisol.

Additional Information

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Disclosure Summary: The authors have nothing to disclose.

Data Availability: The data set generated during the present study is not publicly available but is available from the corresponding author on reasonable request.

References


