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SEX STEROID PROFILE DURING PREGNANCY IN GDM AND PRE-GESTATIONAL T2D

Pregestational type 2 diabetes and gestational diabetes exhibit different sexual steroid profiles during pregnancy

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Abstract

Higher androgen levels are observed in non-pregnant women with diabetes. Whether this hormonal profile is found during pregnancy is unknown. The aim of this study was to determine the sexual steroids levels in pregnant women with pregestational type 2 (T2D) and gestational diabetes (GD) compared to healthy control (C) pregnant women during the second half of pregnancy. A prospective study of 69 pregnant women with T2D ($n = 21$), GD ($n = 24$) and control (C, $n = 24$) was followed up during the second half of gestation. Clinical assessments and blood samples were collected at 26.7 (25–27.8); 34 (32–34.9) and 37.5 (37–40) weeks of gestation. Androgens, sex hormone-binding globulin (SHBG), estrogens, estradiol/testosterone (E/T) ratio, insulin, glucose, HOMA-IR, were measured. Testosterone, insulin and homeostatic model assessment of insulin resistance (HOMA-IR) levels were higher in T2D compared with C at each sampling point during pregnancy, even after adjusting for BMI and age. Estrogens levels and estradiol/testosterone ratio were lower in T2D and GD compared with C. Hyperandrogenemia, and higher insulin resistance is observed in T2D, but not in GD during pregnancy. Decreased estrogen and E/T ratio found in T2D and GD suggests a diminished aromatase activity during gestation. T2D and GD are associated with specific changes in sexual steroids and insulin resistance levels during pregnancy.

Keywords

Androgens insulin resistance, diabetes, estrogens, gestational diabetes, hyperandrogenism, polycystic ovary syndrome, pregnancy

History

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Introduction

During the last decades, the prevalence of type 2 diabetes mellitus (T2D) and gestational diabetes (GD) in pregnant women has increased. One every thousand and 3–5% pregnancies are affected by pregestational diabetes and gestational diabetes, respectively [1,2]. Diabetes and the reproductive axis are closely linked [3], but the effects of diabetes during pregnancy on the maternal sexual steroidal milieu are unknown.

Higher testosterone and lower sex hormone-binding globulin (SHBG) levels have been observed in non-pregnant women with diabetes [4,5,6,7]. Elevated insulin levels due to non-physiologic insulin replacement or due to insulin resistance has been proposed as a mechanism in the pathogenesis of high-androgen levels in non-pregnant women with type 1 or type 2 diabetes [3,8].

The placenta is the primary organ responsible for sexual steroids production during pregnancy by conversion of DHEA-S to androgens [9]. On the other hand, estrogens are produced from the metabolism of androstenedione (A2) and testosterone (T) to estrone (E1) and estradiol (E2) by placental P450 aromatase activity [10,11]. Previous studies have shown that insulin and IGF-1inhibits P450 aromatase and P450 cholesterol side-chain cleavage enzymatic activity in cultures of human placental cytotrophoblasts [12,13]. However, the sexual steroid levels have not been studied *in vivo* in pregnant women with different types of diabetes nor has been compared the effects of pregestational T2D diabetes with gestational diabetes over the sexual steroid milieu during pregnancy.

The aim of the study was to determine the sexual steroids levels in pregnant women affected by T2D and GD compared to healthy pregnant women during the second half of pregnancy. For this purpose, we performed a longitudinal study and compared hormonal and metabolic profile between T2D, GD and healthy pregnant women during the second half of pregnancy.

Subjects and methods

Subjects: A prospective study of pregnant women with T2D, GD and control (C) group were performed. Pregnant women with diabetes were recruited from the Fetal–Maternal Unit of the Hospital Clínico San Borja Arriaran, a tertiary hospital. Control pregnant women were recruited from nearby local clinics. The study took place from September 2012 to October 2015. T2D pregnant women were diagnosed before pregnancy according to the WHO definition [1]. GD was defined according to the following criteria: a normal fasting glucose level during the first trimester of gestation (<100 mg/dl) and a fasting glucose level ≥ 100 mg/dl and/or a 2 h-glucose level on a 75-gr-oral glucose tolerance test (OGTT) ≥ 140 mg/dl at 24–28 weeks [14]. The C group had a normal first-trimester fasting glucose and

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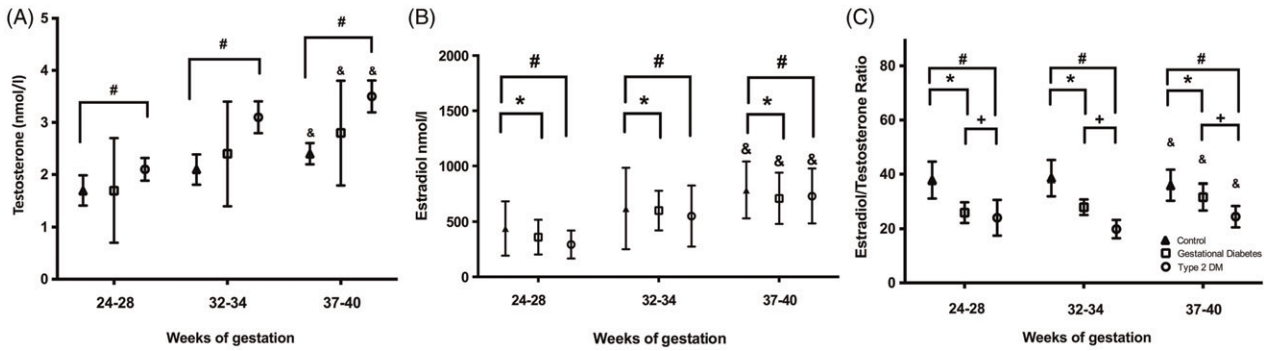

Figure 1. Testosterone, estradiol levels and estradiol/testosterone ratio in T2D (open circle), GD (open square) and control (open triangle) pregnant women during the second half of pregnancy, (A) testosterone (nmol/l), (B) estradiol (nmol/l) levels and (C) estradiol/testosterone ratio. Results are shown data are presented as medians (25th–75th percentile). #$p < 0.001$ in T2D group versus C group, +$p < 0.001$ in GD group versus C group, *$p < 0.05$ in T2D group versus GD group and &$p < 0.0001$ for an increase in the trend for advancing gestational age during pregnancy.

75-g-OGTT at 24–28 weeks of gestation [14], corresponding to higher cutoff levels compared to the 2015 ADA definition [15].

A thorough retrospective review of the charts of the participants to examine the clinical history before pregnancy, at the first visit, was performed. Only pregnancies carrying a female fetus were included to avoid differences in steroid levels due to fetal sex [16].

Exclusion criteria included the following: Before the present pregnancy: a history of oligomenorrhea, hirsutism, polycystic ovary syndrome (PCOS) according to Rotterdam criteria, other causes of hyperandrogenism, the use of corticoids or steroids, ovulation induction drugs, presence of severe chronic diseases. During the present pregnancy, multiple gestations, pregnancies carrying male fetuses, or fetuses with severe malformations and preterm delivery before 34 weeks of gestation, were excluded. Only spontaneous pregnancy was included in this study.

The Institutional Review Board of the San Borja Arriarán Hospital approved the protocol, and all subjects signed an informed consent form.

Two hundred and ninety expectant mothers were invited to participate in the study as depicted in Supplementary Figure 1. Ninety-six T2D, ninety-eight GD and ninety-six C pregnant women were screened. Forty-five T2D, forty-eight GD and forty-six C subjects carrying a male fetus were excluded. Twenty-six T2D, twenty-five GD and twenty-five C pregnant women were excluded since they did not fulfill the inclusions/exclusions criteria. Finally, 75 pregnant women were enrolled with 25 subjects in each branch. Six pregnant women came to the first visit and were lost to follow-up. Sixty-nine pregnant women completed the three visits as follows: T2D ($n = 21$), GD ($n = 24$) and control (C, $n = 24$).

Study protocol: Pregnant women were studied prospectively during the second half of pregnancy. The first visit (visit 1) was at the beginning of the second half of pregnancy (median 26.7, range: 25–27.8 weeks of gestation), the second one (visit 2) at the mid-third trimester (median 34, range, 32–34.9 weeks of gestation) and the third visit (visit 3) at late pregnancy (median 37.5, range 37–40 weeks). Gestational age was similar at the three visits the three groups in the three visits ($p = 0.9$; $p = 0.95$ and $p = 0.49$, respectively).

The clinical and hormonal profile assessments were performed at each visit. Body mass index (BMI), Ferriman-Galway (FG) score and waist-to-hip ratio (WHR) were determined. Overweight and obese were defined according to the Chilean national tables for pregnant women [17]. All diabetic patients were treated with hypocaloric-hypoglycemic diet and regular physical activity.

A fasting blood sample was obtained during each visit for the measurement of T, A2, DHEA-S, E2, E1, estriol (E3), SHBG, glucose, HbA1c, insulin, IGF-1 and IGFBP-1. The homeostatic model assessment of insulin resistance (HOMA-IR), free androgen index (FAI), estradiol/testosterone (E/T) ratio and free IGF-1 were calculated. Free IGF-1 was calculated according to the following equation: (IGF-1 $\times$ 1.3)/(IGFBP1 $\times$ 0.36).

Laboratory assays: Total T, A2, and DHEA-S were measured by RIA from Siemens Healthcare Diagnostics (Los Angeles, CA) as previously described [18]. E1 (sensitivity [S] = 0.12 pmol/l)), E2 ($S = 0.23$ pmol/l) and E3 ($S = 0.075$ ng/ml) were measured by RIA from Siemens Healthcare Diagnostics. Intra-assay coefficients of variation (CV) were 6.3, 6.1 and 3.6% for E1, E2 and E3, respectively. Inter-assay CVs were 8.6, 12.2 and 7.5% for E1, E2 and E3, respectively.

HbA1c levels were measured using a commercially available automatic system (Siemens DCA Systems, Tarrytown, NY) [19]. IGF-1 ($S = 3.4$ ng/ml) and IGFBP-1 ($S = 0.1$ ng/ml) were measured by RIA and ELISA, respectively (DIAsource ImmunoAssays S.A, Louvain-La-Neuve, Belgium). Intra-assay CVs were 4.2% for IGF-1 and 6.8% for IGFBP-1. Inter-assay CVs were 6.55% for IGF-1 and 7.4% for IGFBP-1.

Statistical analysis

The sample size was calculated according to the levels of total T at 34 weeks of gestation in pregnant women with and without PCOS [20]. The sample size calculation was performed estimating a difference of the means of 0.2 with an alpha error of 0.05 and a power of 80%. This analysis determined the required number of subjects in each group in 25 pregnant women.

Clinical and hormonal characteristics are shown as the median with a minimum and maximum range. Obesity and the use of insulin and metformin are reported as frequencies and proportions. The clinical characteristics at visit 1 and weight gain during pregnancy were analyzed with a one-way ANOVA and Bonferroni post hoc test. Variations in the prevalence of obesity and the use of insulin and metformin at different times of gestation were assessed with Fisher's exact test.

A normal distribution of the variables was assessed using the Kolmogorov–Smirnov test. The hormonal parameters did not pass the normality test. The assessment of hormonal variations throughout the study was analyzed by using generalized equation estimation (GEE) methodology and by comparing trends between the same subject within the group and between groups (adjusted by BMI and age). To correct for lack of a normal distribution and the dispersion of data, the GEE models were analyzed with a link function of the identity using a gamma family distribution.

The GEE methodology was also used to evaluate the association of androgen levels with clinical and metabolic parameters, including age, BMI, HbA1c and HOMA-IR.

All statistical calculations were conducted with Stata 14.0 (College Station, TX), and $p<0.05$ was considered significant. Data are shown as the median with a minimum and maximum range.

Results

Clinical characteristics (Supplementary Table 1): T2D and GD pregnant women were older and had a higher BMI and prevalence of obesity than C pregnant women at visit 1 ($p<0.05$). FG scores were similar in the three groups. All subjects presented with FG scores under 8 at visit 1. The uterine heights were similar among the three groups. Only the T2D group was receiving medical treatment as follows: six (28.6%) were receiving insulin-only therapy, six (28.6%) were receiving metformin-only therapy and 9 (42.8%) did not require medication treatment.

Three (14.3%) of the T2D, two (8.3%) of the GD and none of C group pregnant women developed hypertensive syndrome or pre-eclampsia during pregnancy.

The clinical characteristics during the second and third trimester of pregnancy are also shown in Supplementary Table 2. We observed an increase in BMI in all groups from 24–28 to 37–40 weeks of gestation. The mean weight gain during the second half of pregnancy was higher in the C group than in the T2D and GD groups (6.1 ± 0.9, 3.7 ± 0.7 and 2.2 ± 0.2 kg, respectively; $p<0.05$). However, the BMI remained significantly higher in the T2D and GD groups than in the C group during the second half of pregnancy ($p<0.0001$). The FG score increased throughout the second half of pregnancy among the three groups ($p<0.0001$) and was significantly higher in the GD group than in the C group ($p<0.05$). The T2D group had a higher uterine height than the C group during the second half of pregnancy ($p<0.05$). The prevalence of subjects receiving insulin or metformin treatment was higher in the T2D group than in the GD group ($p<0.05$). The mean dose of insulin or metformin did not change significantly in the diabetic groups from 24–28 to 37–40 weeks of pregnancy.

Metabolic control of diabetes, insulin and growth factors (Table 1): Gestational age was similar in the three visits among the three groups ($p=0.9$; $p=0.95$ and $p=0.49$, respectively). Fasting glucose, HbA1c, insulin levels and HOMA-IR were higher in the T2D group than in the GD and C groups at 24–28 weeks and remained higher during the second half of pregnancy ($p<0.0001$; Table 1). The fasting glucose level was also higher in the GD group than in the C group during the second half of pregnancy ($p<0.05$, Table 1). The HOMA–IR index decreased from the second to third trimester of gestation ($p<0.05$, Table 1). However, the glucose, HbA1c and insulin levels did not change during the second half of pregnancy.

Regarding growth factors, IGF-1 (but not IGFBP-1 or free IGF-1) serum levels increased in the three groups during the second half of pregnancy ($p<0.0001$), and the levels were similar among the three groups (Table 1).

Serum sexual steroid findings (Table 2, Figure 1): An increase in T and A2 levels and free androgen index were observed in the three groups during the second and third trimesters of gestation compared with the baseline visit (all $p<0.0001$ for each hormone, Table 2, Figure 1A). The T levels remained higher in the T2D group than in the C group during the second half of gestation ($p<0.05$, Table 2, Figure 1A). In contrast, FAI, A2 and DHEA-S levels were similar between the three groups during the observation period (Table 2).

Table 1. Metabolic control of diabetes, insulin and growth factors during the second half of pregnancy. Data are presented as medians (minimum to maximum).

	Type 2 diabetes $n=21$			Gestational diabetes $n=24$			Control $n=24$		
	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
Glucose (mmol/l)	5.6 (4.0–12.3)	5.0 (3.6–8.0)	4.6 (3.6–8.0)	4.5 (3.6–8.5)*	4.5 (3.9–9.2)*	4.5 (3.5–6.3)*	4.0 (3.6–4.9)†‡	4.3 (3.8–5.5) †‡	4.2 (3.4–5.3) †‡
HbA1c (%)	5.9 (5–13.7)	–	6.3 (5.3–10.7)	5.3 (4.7–6.3)¶	–	5.4 (4.8–6.3)¶‖	5.2 (4.8–6) †	–	5.1 (4.3–5.7) †
Insulin (uUI/ml)	16.9 (4–196)	18.7 (5.2–144.4)	19.2 (4.8–42)	10 (2.2–86.9)*	9.1 (2–70.9)*	8.9 (1.8–38.9)*	17.8 (10.3–90.8)§	11 (4.9–19.8)§	8.5 (3.0–24.9)§
‖HOMA-IR	4.2 (0.9–62.9)	4.5 (0.9–32)	4.5 (1.2–8.6)	2.1 (0.4–20.4)*	2.3 (0.4–12.8)*	2 (0.4–9.1)*	3.3 (0.2–17.5)§	2.2 (0.7–3.3)§	1.5 (0.6–5.5)§
IGF 1 (ng/ml)#	389.5 (136–1084)	598 (167–1168)	521 (246–989)	353 (125–1204)	488 (140–1386)	510 (144–840)	390.5 (130–652)	500 (31.2–953)	396 (170–913)
IGFBP 1 (ng/ml)	29.5 (11.1–96.5)	37.8 (7.5–154.3)	56.1 (12.4–147.6)	30.1 (5.9–175.6)	36 (7.3–151)	24.7 (8.4–157.2)	38.8 (10.8–127.6)	63.4 (12.4–156.4)	33 (14.9–375)
Free IGF 1 (%)	46.8 (9.5–133.4)	58 (11.2–175.5)	48.9 (9.4–158.2)	32.6 (0.8–296.6)	42 (6.6–321.2)	78.9 (6.2–307.7)	51.3 (4.2–98.7)	25.8 (6.4–86.2)	35.4 (9.8–21.1)

*$p<0.05$ in T2D group versus GD group,
†$p<0.0001$ in T2D group versus C group,
‡$p<0.05$ in GD group versus C group,
¶$p<0.0001$ in T2D group versus GD group and §$P<0.05$ in T2D group versus C group.
#$p<0.0001$ for an increase in the trend for advancing gestational age during pregnancy.
‖$p<0.05$ for a decrease in the trend for advancing gestational age during pregnancy.

Table 2. Hormonal findings during the second half of pregnancy. Data are presented as medians (minimum to maximum).

	Type 2 diabetes $n=21$			Gestational diabetes $n=24$			Control $n=24$		
	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
Testosterone (nmol/l)#	1.7 (0.4–4.2)	3.1 (0.7–5.9)	3.5 (1.0–6.2)	1.7 (0.4–4.5)	2.1 (1.0–5.9)	2.7 (2.4–4.9)	1.4 (3.5–4.5)†	2.1 (0.4–5.2)†	2.4 (1.0–4.2)†
DHEA-S (nmol/l)#	211.7 (91.3–661)	174.2 (57.3– 669.4)	172.5 (83.3–250.2)	228.7 (35.7–941.4)	143.3 (55.2–1668)	147.8 (70.4–769.7)	240.8 (41.3–485.1)	187.4 (43.4–411.2)	171.1 (38.5–361.6)
Androstenedione (nmol/l)#	19.9 (9.1–33.5)	34.9 (14–71.2)	36.7 (19.2–97)	19.5 (5.9–36)	26.9 (16.8– 50.7)	33.2 (19.2–65.3)	22 (7.3–45.4)	27.2 (10.5–58.3)	38.7 (19.5–62.5)
SHBG (nmol/l)	651.1 (289.3–1243.6)	704.8 (181.5–2361.1)	716 (288.2–1793.2)	597.2 (216.5–1470.1)	578.1 (184.3–1487.2)	625.5 (247.5– 1901.7)	758.1 (130.9–1350.7)	750 (137.5–1516.5)	604.9 (122.1–1272.6)
FAI (%)#	0.2 (0.1–0.7)	0.4 (0.2–1.1)	0.4 (0.1–1.7)	0.3 (0.1–1.1)	0.4 (0.1–1.3)	0.4 (0.1–1.1)	0.2 (0.1–1.3)	0.3 (0.1–1.3)	0.4 (0.1–1.6)
Estradiol (nmol/l)#	265 (80.41–540)	472.5 (177.3– 1308)	710.3 (360.1–1278.2)	342.9 (169.6–746.3)	607.9 (276.4–1026.7)	784.5 (188–1559)	398.7 (157.9–1155)†‡	554 (245.2–1889)†‡	816.1 (290–1674)†‡
Estrone (nmol/l)#	071.9 (325.6–3735.2)	1574 (525.6–7229)	1452.3 (898–11 574)	1703.1 (285.6–3361)*	1675.7 (668.2–489)*	1969 (162.8–6174.2)*	1646.5 (41.8–723.6)†	698.3 (211.3– 13 808)†	735.7 (716.7–15 858)
Estriol (nmol/l)#	22.5 (10.7–82.9)	44 (12.5–128.3)	64.1 (28.4–179.9)	24.6 (13.9–44)	52.5 (18.7–92.6)	69.7 (32.6–152.5)	22.5 (14.6–32.9)	38.5 (22.5–70.4)	65.5 (26.7–113.7)

*$p < 0.05$ in T2D group versus GD group,
†$p < 0.05$ in T2D group versus C group.
‡$p < 0.05$ in GD group versus C group,
#$p < 0.0001$ for an increase the trend for advancing gestational age during pregnancy.

An increase in E1, E2 and E3 were observed during the second half of gestation ($p < 0.0001$ for each hormone). The E1 and E2 levels were lower in the T2D and GD groups than in the C group during the second half of pregnancy ($p < 0.05$, Table 2, Figure 1B). We observed an increase in the E2/T ratio in each group during the second half of pregnancy ($p < 0.0001$). Lower E2/T ratios were observed in the T2D and GD groups than in the C group. The E2/T ratio was also significantly lower in the T2D group than in the C group (Figure 1C).

Association of T levels with clinical and metabolic parameters: BMI and T levels were positively associated in the T2D and GD groups (β coefficient $= 0.04 \pm 0.01$ and $\beta = 0.02 \pm 0.01$; respectively, $p < 0.05$) but not in the C group ($p = 0.6$). Testosterone was negatively associated with age in the T2D, GD and C groups ($\beta = -0.04 \pm 0.01$, $\beta = -0.03 \pm 0.01$ and $\beta = -0.02 \pm 0.01$, respectively, $p < 0.05$). HbA1c, HOMA-IR, and insulin levels were not associated with T levels in the T2D ($p = 0.7$, $p = 0.6$ and $p = 0.4$, respectively), GD ($p = 0.5$, $p = 0.3$ and $p = 0.4$) or C groups ($p = 0.3$, $p = 0.4$ and $p = 0.4$).

Discussion

This prospective study evaluated 69 pregnant women carrying a female fetus and analyzed the effect of T2D and GD on serum sexual steroids levels during the second half of pregnancy. The pregnant women with T2D exhibited higher T and lower estrogen levels compared with GD and C pregnant women. Previous studies have shown higher androgen levels in non-pregnant women with T2D compared to control [6,7].The present data suggests that hyperandrogenemia is also observed during pregnancy. Even more, the T serum levels observed in the T2D pregnant group were similar to the T levels that have been previously reported in pregnant women with PCOS [21,22]. On the other hand, GD and C groups did not exhibit elevated T levels and were similar to the serum levels that have been previously reported in healthy pregnant women during the second half of gestation [16,22].

T2D and GD pregnant women exhibited lower E1 and E2 serum levels and a lower E2/T ratio compared to control. Physiologically, healthy pregnant women show a rapid conversion of androgens to estrogens due to placental aromatase activity during pregnancy [10,11,23]. Recently, Maliqueo et al. have a reported higher 3β-HSD-1 activity, responsible for the conversion of DHEA to T and A2, and lower P450 aromatase activity in the placenta of women with PCOS [20]. In our study, T2D and GD pregnant women had lower E1 and E2 serum levels and a lower E2/T ratio suggesting a lower conversion of T to estrogens.

Differences in the hormonal profile of the GD and T2D women, particularly the association with elevated T levels, suggest that the time of onset of diabetes or the duration of exposure time to the diabetic milieu may play a role in the development of higher androgen levels in women with T2D. The possibility that T2D patients were hyperandrogenic before becoming pregnancy and had persistent hyperandrogenism during gestation is a mechanism that would explain why GD subjects did not exhibit hyperandrogenemia.

We did not observe an association of HbA1c, HOMA-IR and insulin levels with T levels in the diabetic groups. This finding differs from data reported in non-pregnant women with diabetes, which showed an association between androgen level and insulin dose [24,25], insulin resistance [26].

T2D was a significant factor affecting the T level, even after adjusting for BMI and age. It is interesting to note the high prevalence of obesity among T2D, GD and control groups. BMI was associated with T levels in the three groups, suggesting that it is an important modifiable factor that could be managed for the prevention of higher T levels during pregnancy. Adipokines and

inflammatory factors released by the adipose tissue play a role in the pathogenesis of hyperandrogenism in non-pregnant obese hyperandrogenic women; the positive association of BMI and T levels that were observed during pregnancy in the three groups suggests that a similar relationship between excessive weight and hyperandrogenism exists during pregnancy.

Elevated androgen levels during pregnancy are associated with adverse pregnancy outcomes. Animal models suggest a possible link between T levels and the development of hypertension during pregnancy [27]. Likewise, pregnant women with PCOS who have higher androgen levels during pregnancy and have a higher prevalence of pregnancy-induced hypertension [28]. Accordingly, in this study T2D group had a higher prevalence of hypertensive syndrome or pre-eclampsia during pregnancy.

According to multiple studies, the offspring of mothers with pregestational and GD during pregnancy are at higher risk of developing chronic diseases during childhood and adolescence, such as obesity, hypertension and metabolic syndrome [29,30]. Whether the higher androgen levels that we report in T2D pregnant women and lower estrogen levels found in the T2D and GD pregnant women will affect fetus/newborn development should be studied in future studies.

The strengths of this article are that a longitudinal study of pregnant women from 24 weeks of gestation to delivery that analyzed sex steroids serum levels was carried-out. Even though a small sample size can be argued, the number of subjects that was studied had the statistical power to support the present conclusions. The main limitation of this study is that the subjects were not matched according to the type of the treatment of diabetes or complications of pregnancy. Future studies should be performed to assess the effect of variables related to metabolic control on sexual steroid levels.

In summary, the presence of T2D during the second and third trimester of pregnancy is associated with higher T levels. These data confirms that hyperandrogenemia, previously described in non-pregnant T2D is also observed during gestation. Decreased estrogen levels and T /E ratio found in the T2D and GD groups suggest diminished aromatase activity in pregnant women with diabetes.

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Declaration of interest

The authors report no conflicts of interest. This work was supported by the Fondo Nacional de Desarrollo Ciéntifico y Tecnológico (FONDECYT Grant No. 11121460, 2012) to Claudio Villarroel.

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Supplementary material available online