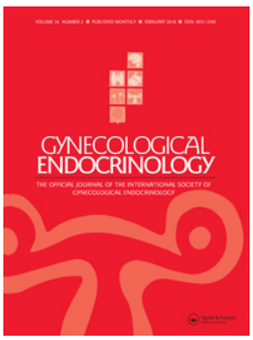

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Anti-Müllerian hormone in type 2 and gestational diabetes during the second half of pregnancy: relationship with sexual steroid levels and metabolic parameters

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ABSTRACT

Hyperandrogenemia and hyperinsulinemia are observed in women with diabetes during pregnancy. The effect of diabetes on anti-Müllerian hormone (AMH) levels during pregnancy is unclear. The aim of this study was to determine the AMH levels in women with type 2 diabetes (T2D) and gestational diabetes (GD) compared to healthy (C) pregnant women during the second half of gestation. A prospective study of 69 pregnant women with T2D (*N*: 21), GD (*N*: 24) and C (*N*: 24) were followed up during the second half of pregnancy. 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. AMH, sexual steroids, insulin, homeostatic model assessment of insulin resistance, HbA1c levels were measured. AMH levels were similar between T2D, GD and C ($p = .07$). A decline of AMH levels during the second half of gestation was observed in the three groups ($p < .0001$). AMH levels were negatively associated with age ($p < .001$). A positive association between AMH and testosterone ($p < .05$) was found in all groups. A progressive decline of AMH levels is observed in diabetic and healthy women during the second half of pregnancy. Testosterone levels are an independent factor that influences AMH levels during pregnancy. However, AMH levels are not affected by the presence of diabetes during gestation.

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KEYWORDS
Anti-Müllerian hormone; androgens; estrogens; diabetes; pregnancy

Introduction

An increase in the prevalence type 2 diabetes mellitus (T2D) and gestational diabetes (GD) in pregnant women in the last decades has been observed [1,2]. Diabetes and the reproductive axis are tightly linked [3,4]. Higher androgen and anti-Müllerian hormone (AMH) levels have been previously described in non-pregnant women with diabetes [5–7].

An inhibition of follicular growth during pregnancy has been previously described [8,9]. This process is critical to prevent ovulation during pregnancy and to avoid the development of multiple gestations and its complications. Recently, higher testosterone and insulin levels in pregnant women with diabetes have been described [10]. However, the effect of diabetes on follicular growth during pregnancy is unclear.

Transvaginal ultrasound is a standard tool to assess follicular count and growth in non-pregnant women. However, the increase in the size of the uterus during gestation makes difficult to use this tool during pregnancy. However, AMH secreted by ovarian follicles can be used as a surrogate marker to study the follicular growth and provide information about its regulation during pregnancy.

AMH is a glycoprotein secreted by the granulosa cells of preantral and small antral follicles [11,12]. AMH is not synthesized by the placenta [13]. This hormone has a significant role in the regulation of gonadotropin-independent follicular growth inhibiting the growth of primordial-to-primary follicle [14]. It also has a role regulating and selecting the number small antral follicles stimulated by the follicle stimulating hormone (FSH) in each menstrual cycle [15,16]. From a clinical point of view, it is a useful marker of ovarian reserve and predictor of the number of oocytes retrieved in IVF [17,18]. Importantly, AMH levels have a good correlation with the small antral follicles number and ovarian volume by ultrasound [19–21]. AMH levels do not change during the menstrual cycle [22]. However, a progressive decline in AMH levels with age which reflects age-related oocyte depletion [23].

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

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. Control pregnant women were recruited from our outpatient pregnancy clinic. T2D pregnant women were diagnosed before pregnancy according to the WHO definition [1]. GD was defined according to the following

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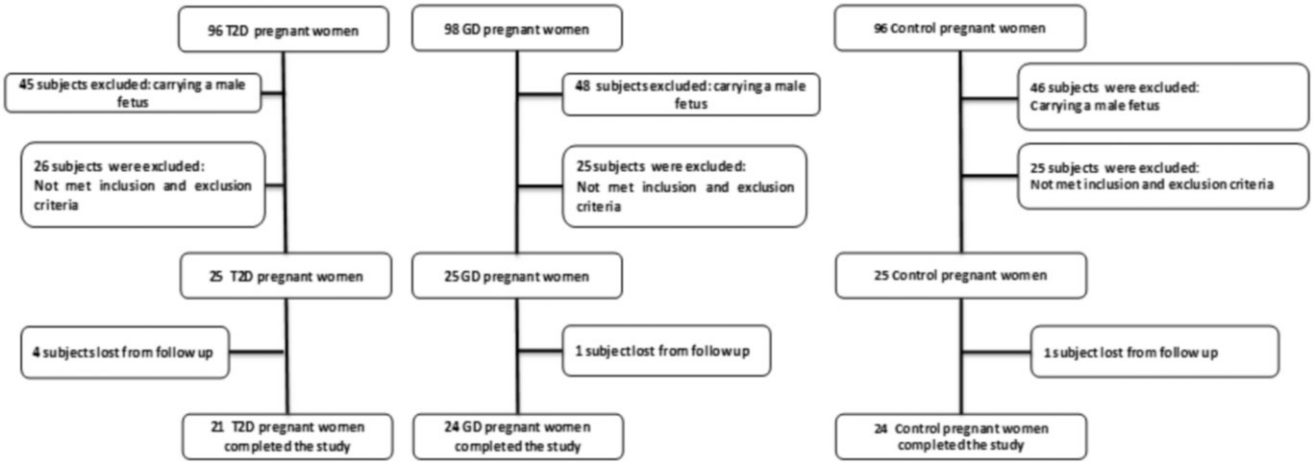

Figure 1. Flowchart: selection of pregnant women participating in the present study. Exclusion criteria before the present pregnancy: a history of oligomenorrhea, hirsutism polycystic ovary syndrome according to Rotterdam Criteria, other causes of hyperandrogenism, the use of corticoids or steroids, ovulation induction drugs, presence of severe chronic diseases. Exclusion criteria in the current pregnancy: multiple gestations, fetuses with severe malformations and preterm delivery before 34 weeks of gestation. Only spontaneous pregnancy was included in the current study.

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 [24]. The C group had a normal first-trimester fasting glucose and 75-g-OGTT at 24–28 weeks of gestation [24], which differs from the 2016 America Diabetes Association definition [25].

A thorough retrospective analysis of the participant's charts to examine the clinical history before pregnancy was performed. Only pregnancies carrying a female fetus were included to avoid differences in steroid levels due to fetal sex [13].

Exclusion criteria included the following: before the present pregnancy: a history of oligomenorrhea, hirsutism, polycystic ovary syndrome (PCOS) according to Rotterdam Criteria [26], other causes of hyperandrogenism, the use of steroids, ovulation induction drugs. During the present pregnancy: multiple gestations, fetuses with severe malformations and preterm delivery before 34 weeks of gestation. Only spontaneous conceptions were included in the current 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 Figure 1. Ninety-six T2D, 98 GD and 96 C pregnant women have been screened in the present study. Forty-five T2D, 48 GD and 46 C subjects carrying a male fetus were excluded from the present study. Twenty-six T2D, 25 GD and 25 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 arm. Six pregnant women came to the first visit and subsequently 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 performed at the beginning of the second half of gestation (median 26.7, range: 25–27.8 weeks of gestation). The second visit was done (Visit 2) at the mid-third trimester (median 34, range, 32–34.9 weeks of gestation). The third visit took place (Visit 3) at late pregnancy (median 37.5, range 37–40 weeks). Gestational age was similar between the three groups at each visit ($p = .9$; $p = .95$ and $p = .49$, respectively).

The clinical and hormonal profile assessments were performed at each visit. Body mass index (BMI), Ferriman–Galwey score and waist-to-hip ratio were determined. Overweight and obesity were defined according to the Chilean national tables for pregnant women [1]. All diabetic patients were under a hypocaloric-hypoglycemic diet and regular physical activity. Insulin and metformin therapy were indicated according to maternal metabolic control when needed.

A fasting blood sample was obtained during each visit for the measurement of testosterone (T), DHEA-S, estradiol (E2), sex hormone-binding globulin (SHBG), glucose, HbA1c, insulin, insulin growth factor 1 (IGF-1) and insulin growth factor binding protein 1 (IGFBP-1). The homeostatic model assessment of insulin resistance (HOMA-IR), FAI = free androgen index, was calculated.

Laboratory assays

Total testosterone (T) and DHEA-S were measured by radioimmunoassay (RIA) from Siemens Healthcare Diagnostics (USA) as previously described [10,27]. E2 (S = S = 0.064 ng/ml) was measured by RIA from Siemens Healthcare Diagnostics. Intra-assay and inter-assay coefficients of variation (CV) were 6.1% and 12.2%, respectively.

Serum AMH was assayed using the AMH/MIS ELISA kit (Immunotech-Beckman, Marseilles, France) as previously described [10].

HbA1c levels were measured using a commercially available automatic system (Siemens DCA Systems) [3]. IGF-1 (sensitivity = 3.4 ng/ml) and IGFBP-1 (sensitivity = 0.1 ng/ml) were measured by RIA and ELISA, respectively (DIAsource ImmunoAssays S.A). 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.

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

Table 1. Clinical characteristics of pregnant women at Visit 1. Data are shown as median (minimum to maximum).

	Type 2 diabetes mellitus	Gestational diabetes	Control
n	21	24	24
Maternal age (years)	33 (25.9–41.8)	32.6 (20–43)	28.1 (17.3–42.1)[a,b]
BMI (kg/m^2)	34.4 (24.3–46)	33.5 (23.1–48.5)	29.3 (23.4–37.9)[a,b]
Obesity (*n*, %)	13 (61.9)	11 (45.8)	0 (0)[a,b]
Mean arterial pressure (mm Hg)	96.0 (80–113)	89 (75–100)	85 (75–101.5)
Waist-to-hip ratio	0.96 (0.82–1.1)	0.96 (0.77–1.2)	0.92 (0.74–1.2)
Ferriman–Gallwey score	3 (0–6)	3 (0–7)	3 (0–7)
Uterine height (cm)	23.5 (16–27)	26 (18–28)	23.5 (19–28)
Treatment of diabetes	–	–	–
Insulin (*n*, %)	6 (28.6)	0 (0.0)	0 (0.0)
Metformin (*n*, %)	6 (28.6)	0 (0.0)	0 (0.0)

[a]$p < .05$ in T2D group versus C group.
[b]$p < .05$ in GD group versus C Group.

by BMI and age). To correct for the 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 AMH levels with clinical and metabolic parameters, including age, BMI, HbA1c and HOMA-IR.

All statistical calculations were conducted with Stata version 14.0 (College Station, TX), and $p < .05$ was considered significant. Data are shown as the median with a minimum and maximum range.

Results

Clinical characteristics of pregnant women with T2D, GD and Control, are shown in Table 1. T2D and GD were older than control pregnant women at Visit 1 (33 [25.9–41.8] years; 32.6 [20–43] years; 28.1 [17.3–42.1] years, $p < .05$; respectively). They also had a higher BMI (34.4 [24.3–46] kg/m^2; 33.5 [23.1–48.5] kg/m^2; 29.3 [23.4–37.9] kg/m^2; $p < .05$, respectively) compared to C expectant mothers during the time of observation. FG score was similar between the three groups (3 [0–6]; 3 [0–7]; 3 [0–7], $p = .12$, respectively).

The hormonal and metabolic characteristics of the participants are shown in Table 2. Results were adjusted for BMI and age. A progressive decline of AMH levels within each group during the time of follow-up was observed ($p < .0001$). AMH levels were similar between T2D, GD and C during the second and third trimester of gestation (p=.07).

The T levels remained higher in the T2D group than in the C group during the second half of gestation ($p < .0001$, Table 2). On the other hand, estradiol levels were lower in T2D and GD compared to C during the second and third trimester of pregnancy ($p < .0001$).

Fasting glucose insulin levels and HOMA-IR were higher in the T2D group than in the GD and C during the second half of pregnancy ($p < .0001$; Table 2). 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 ($p < .0001$), and the levels were similar among the three groups ($p = .3$, Table 2).

Association of AMH levels with clinical and metabolic and hormonal parameters is shown in Table 3. AMH levels were positively associated with total testosterone levels in the T2D, GD and C groups ($p < .05$). AMH was negatively associated with age in the T2D, GD and C groups ($p < .05$, $p < .05$ and $p < .001$,

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

	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
Anti-Müllerian hormone (ng/ml)#	0.6 (0.1–4.4)	0.5 (0.01–2.3)	0.2 (0.01–3.5)	1.8 (0.1–9.3)	1.2 (0.1–6.6)	1.1 (0.01–5.2)	1.2 (0.1–3.1)	0.9 (0.02–11.4)	0.5 (0.1–3.88)
Testosterone (ng/ml)#	0.5 (0.1–1.2)	0.9 (0.2–1.7)	1 (0.3–1.8)	0.5 (0.1–1.3)	0.6 (0.3–1.7)	0.8 (0.2–1.4)	0.4 (0.1–1.3)	0.6 (0.1–1.5)[b]	0.7 (0.3–1.2)[b]
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 (ng/ml)	72.2 (21.9–147.1)	128.7 (48.3–356.3)	193.5 (98.1–348.2)	93.4 (46.2–203.3)	165.6 (75.3–279.7)	213.7 (51.2–424.8)	108.6 (43–314.5)[b,c]	150.9 (66.8–514.6)[b,c]	222.3 (79–456)[b,c]
Glucose (mg/dl)	100.6 (72.8–221)	90.5 (65–144)	83.2 (65.4–144)	80.9 (65.1–153)[a]	81.5 (69.8–166)[a]	80.3 (63.7–113)[a]	72 (64.7–88.6)[b,c]	78 (68.3–98.7)[b,c]	75.9 (62.1–95)[b,c]
HbA1c (%)	5.9 (5–13.7)	–	6.3 (5.3–10.7)	5.3 (4.7–6.3)[d]	–	5.4 (4.8–6.3)[d]	5.2 (4.8–6)[b]	–	5.1 (4.3–5.7)[b]
Insulin (uUI/ml)	16.9 (4–196)	18.7 (5.2–144.4)	19.2 (4.8–42)	10 (2.2–86.9)[a]	9.1 (2–70.9)[a]	8.9 (1.8–38.9)[a]	17.8 (10.3–90.8)[e]	11 (4.9–19.8)[e]	8.5 (3.0–24.9)[e]
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)[a]	2.3 (0.4–12.8)[a]	2 (0.4–9.1)[a]	3.3 (0.2–17.5)[e]	2.2 (0.7–3.3)[e]	1.5 (0.6–5.5)[e]
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)

[a]$p < .05$ in T2D group versus GD group.
[b]$p < .0001$ in T2D group versus C group.
[c]$p < .05$ in GD group versus C group.
[d]$p < .0001$ in T2D group versus GD group.
[e]$p < .05$ in T2D group versus C group.
#$p < .0001$ for an increase in the trend for advancing gestational age during pregnancy.
†<.05 for a decrease in the trend for advancing gestational age during pregnancy.

Table 3. Association of AMH with clinical and hormonal parameters in the T2D, GD and C group during the second half of pregnancy. The results are shown as the β coefficient and 95% coefficient interval (CI) according to generalized estimated equation (GEE) model.

	Anti-Müllerian hormone					
	Type 2 Diabetes		Gestational Diabetes		Control	
	β	95% CI	β	95% CI	β	95% CI
Age	−0.089[a]	−0.164 to −0.013	−0.097[b]	−0.197–0.003	−0.014[b]	−0.096–0.14
BMI	−0.047	−0.094–0.00002	0.054	−0.02–0.13	−0.040	−0.12–0.34
DHEAS	−0.002	−0.009–0.005	−0.004	−0.01–0.023	−0.03	−0.001–0.003
Testosterone	0.033[a]	−0.011–0.172	0.017[a]	−0.043–0.076	1.5[b]	−0.07–3.1
FAI	−0.013	−0.573–0.547	−0.818	−1.94–0.31	−0.6	−2.36–1.16
Estradiol	0.00001	0.00002–0.00003	0.0001	−0.00004–0.00003	0.001	−0.00002–0.00001
Insulin	0.003	−0.002–0.007	−0.007	−0.019–0.004	−0.004	−0.018–0.009
HbA1c (%)	−0.067	−0.25 to −0.12	−0.12	−0.036–0.11	−0.99	−0.72–0.42
IGF-1	0.0005	−0.0002–0.001	0.001	−0.003–0.001	0.0003	−0.001–0.002
IGFBP-1	−0.001	−0.006–0.004	−0.001	−0.002–0.0009	−0.0001	−0.002 to 0.002

[a]$p < .05$.
[b]$p < .001$.

respectively). DHEAS, FAI, estradiol, were not significantly associated with AMH levels in T2D ($p = .56$, $p = .07$ and $p = .35$; respectively), GD ($p = .67$, $p = .12$ and $p = .45$; respectively) and C ($p = .7$, $p = .2$ and $p = .5$; respectively). HbA1c, HOMA-IR and insulin levels were not associated with AMH levels in the T2D ($p = .9$, $p = .8$ and $p = .08$, respectively), GD ($p = .6$, $p = .9$ and $p = .3$) or C groups ($p = .7$, $p = .9$ and $p = .2$). Finally, AMH levels were not significantly associated with IGF or IGFBP-1 levels in the three groups.

Discussion

This study reports a longitudinal cohort of 21 T2D, 21 GD and 24 healthy pregnant women during the second half of pregnancy. We analyzed the effect of T2D and GD over AMH plasmatic levels during gestation. A decrease of AMH levels in diabetic and control pregnant women from the second trimester to the end of gestation was observed. In addition, AMH concentrations were similar in all groups during the second half of gestation. Testosterone, insulin and HOMA-IR levels were higher in T2D compared to GD and control pregnant women. These data suggest that presence of T2D or GD is associated with abnormal secretion of sexual steroids levels, but it does not affect AMH levels during the second half of pregnancy.

We noted a progressive decline of AMH levels in diabetic and control pregnant women from the second trimester to the end of gestation. By the end of the third trimester, AMH levels were similar to the ones reported in non-pregnant women with a low ovarian reserve [28]. Similar results have been previously reported in GD and healthy pregnant women [8,29,30]. This finding is opposite to what is observed in non-pregnant women, where AMH levels are stable during the menstrual cycle and only decrease with increasing age [22,31,32]. Even though AMH is a marker of ovarian reserve, it is produced by different stages of growing preantral to early antral follicles and, it is unclear which follicle class contributes most to the circulating concentrations [19,33]. Similarly, *in vitro* studies have shown that AMH may promote preantral follicle growth [34]. Kelsey et al. have suggested that AMH may mirror the preantral recruitment rate [31,35]. Thus, the progressive decline of AMH levels observed during pregnancy may represent a decrease in AMH secretion by small growing follicles, rather than a loss in the follicular pool.

We analyzed which factors could influence on AMH levels in diabetic and control women during pregnancy. As expected, a negative association with maternal age was observed in all groups. However, we found a positive association of AMH with testosterone, in healthy and pregnant women with T2D and GD during gestation. Similar findings have been found in healthy non-pregnant women, women with low ovarian reserve and in PCOS [19,36,37]. Additionally, *in vitro* studies have shown that testosterone promotes the growth of preantral and small antral follicles [38]. These findings suggest that testosterone is an independent factor that influences in AMH levels in diabetic and healthy pregnant women.

Conversely, no significant association of AMH with BMI, estradiol, insulin, HOMA-IR or IGF-1 levels were observed. This result corresponds with previous findings reported by Nelson et al. in healthy pregnant women [8], suggesting that other factors regulate AMH levels during pregnancy.

As previously reported, T2D and GD pregnant women exhibit two different endocrine and metabolic phenotypes. T2D pregnant women are characterized by higher insulin resistance, testosterone levels and lower estradiol levels compared to control women. On the other hand, GD expectant mothers only showed lower estradiol levels, but not higher insulin resistance, and testosterone levels [10]. Even though we found higher testosterone levels and insulin resistance in T2D pregnant group, the presence of T2D group was not associated with higher AMH levels during pregnancy. This finding can be explained by the fact that higher levels of SHBG levels observed during pregnancy can be associated with a lower bioavailability of androgens and thus inhibiting follicular growth. Additionally, the short time of exposition to hyperandrogenemia during gestation could not be sufficient to affect follicular growth. Finally, low AMH levels observed during the second half of pregnancy could require of more sensitive tests or a bigger size sample to find a significant difference between groups under study.

In summary, the present study indicates that T2D is associated with higher androgen levels and insulin resistance during the second and third trimester of pregnancy. The presence of diabetes does not affect AMH levels. Low levels of AMH were observed, may represent a decrease in AMH secretion during the second half of gestation. On the other hand, testosterone levels had a positive association with AMH in diabetic and control pregnant women, suggesting that T is an independent factor that influences AMH levels.

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Disclosure statement

The authors report no conflicts of interest.

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References

1. WHO. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus. Organization WHO: Geneva; 1999.
2. American Diabetes Association. Standards of medical care in diabetes – 2014. Diabetes Care 2014;37:S14–S80.
3. Codner E, Mook-Kanamori D, Bazaes RA, et al. Ovarian function during puberty in girls with type 1 diabetes mellitus: response to leuprolide. J Clin Endocrinol Metab 2005;90:3939–45.
4. Merhi Z. Advanced glycation end products and their relevance in female reproduction. Hum Reprod 2014;29:135–45.
5. Codner E, Iñiguez G, Hernández IM, et al. Elevated anti-Müllerian hormone (AMH) and inhibin B levels in prepubertal girls with type 1 diabetes mellitus. Clin Endocrinol (Oxf) 2011;74:73–8.
6. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 2006;295:1288–99.
7. Fenske B, Kische H, Gross S, et al. Endogenous androgens and sex hormone-binding globulin in women and risk of metabolic syndrome and type 2 diabetes. J Clin Endocrinol Metab 2015;100:4595–603.
8. Nelson SM, Stewart F, Fleming R, Freeman DJ. Longitudinal assessment of anti-Müllerian hormone during pregnancy – relationship with maternal adiposity, insulin, and adiponectin. Fertil Steril 2010;93:1356–8.
9. La Marca A, Giulini S, Orvieto R, et al. Anti-Müllerian hormone concentrations in maternal serum during pregnancy. Hum Reprod 2005;20:1569–72.
10. Villarroel C, Salinas A, López P, et al. Pregestational type 2 diabetes and gestational diabetes exhibit different sexual steroid profiles during pregnancy. Gynecol Endocrinol 2017;33:212–17.
11. Andersen CY, Schmidt KT, Kristensen SG, et al. Concentrations of AMH and inhibin-B in relation to follicular diameter in normal human small antral follicles. Hum Reprod 2010;25:1282–7.
12. Visser JA. AMH signaling: from receptor to target gene. Mol Cell Endocrinol 2003;211:65–73.
13. Kuijper EAM, Ket JC, Caanen MR, Lambalk CB. Reproductive hormone concentrations in pregnancy and neonates: a systematic review. Reprod Biomed Online 2013;27:33–63.
14. McGee EA, Hsueh AJW. Initial and cyclic recruitment of ovarian follicles. Endocr Rev 2000;21:200–14.
15. Durlinger AL, Gruijters MJ, Kramer P, et al. Anti-Müllerian hormone attenuates the effects of FSH on follicle development in the mouse ovary. Endocrinology 2001;142:4891–9.
16. Durlinger AL, Visser JA, Themmen AP. Regulation of ovarian function: the role of anti-Müllerian hormone. Reproduction 2002;124:601–9.
17. La Marca A, Sighinolfi G, Radi D, et al. Anti-Müllerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update 2010;16:113–30.
18. Broer SL, Dólleman M, Opmeer BC, et al. AMH and AFC as predictors of excessive response in controlled ovarian hyperstimulation: a meta-analysis. Hum Reprod Update 2011;17:46–54.
19. Pigny P, Jonard S, Robert Y, Dewailly D. Serum anti-Müllerian hormone as a surrogate for antral follicle count for definition of the polycystic ovary syndrome. J Clin Endocrinol Metab 2006;91:941–5.
20. Villarroel C, Merino PM, López P, et al. Polycystic ovarian morphology in adolescents with regular menstrual cycles is associated with elevated anti-Müllerian hormone. Hum Reprod 2011;26:2861–68.
21. Lebkowska A, Adamska A, Karczewska-Kupczewska M, et al. Serum anti-Müllerian hormone concentration in women with polycystic ovary syndrome and type 1 diabetes mellitus. Metab Clin Exp 2016;65:804–11.
22. Depmann M, van Disseldorp J, Broer SL, et al. Fluctuations in anti-Müllerian hormone levels throughout the menstrual cycle parallel fluctuations in the antral follicle count: a cohort study. Acta Obstet Gynecol Scand 2016;95:820–8.
23. Kelsey TW, Wallace WHB. Ovarian volume correlates strongly with the number of nongrowing follicles in the human ovary. Obstet Gynecol Int 2012;2012:5.
24. ADA. American diabetes association clinical practice recommendations 2001. Diabetes Care 2001;24:S1–S133.
25. (ADA) PPCPotADA. 2. Classification and diagnosis of diabetes. Diabetes Care 2015;39:S13.
26. The Rotterdam ESHRE/ASRM. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–7.
27. Villarroel C, López P, Merino PM, et al. Hirsutism and oligomenorrhea are appropriate screening criteria for polycystic ovary syndrome in adolescents. Gynecol Endocrinol 2015;31:625–9.
28. Ferraretti AP, La Marca A, Fauser BC, et al. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for *in vitro* fertilization: the Bologna criteria. Hum Reprod 2011;26:1616–24.
29. Koninger A, Schmidt B, Mach P, et al. Anti-Müllerian-hormone during pregnancy and peripartum using the new Beckman Coulter AMH Gen II Assay. Reprod Biol Endocrinol 2015;13:86.
30. Gerli S, Favilli A, Brozzetti A, et al. Anti-Müllerian hormone concentration during the third trimester of pregnancy and puerperium: a longitudinal case-control study in normal and diabetic pregnancy. Endocrine 2015;50:250–5.
31. Kelsey TW, Wright P, Nelson SM, et al. A validated model of serum anti-Müllerian hormone from conception to menopause. PLoS One 2011;6:e22024.
32. Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. Endocr Rev 2009;30:465–93.
33. La Marca A, Sighinolfi G, Radi D, et al. Anti-Müllerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update 2010;16:113–30.
34. Xu J, Bishop CV, Lawson MS, et al. Anti-Müllerian hormone promotes pre-antral follicle growth, but inhibits antral follicle maturation and dominant follicle selection in primates. Hum Reprod 2016;31:1522–30.
35. Wallace WH, Kelsey TW. Human ovarian reserve from conception to the menopause. PLoS One 2010;5:e8772.
36. Cui L, Qin Y, Gao X, et al. Anti-Müllerian hormone: correlation with age and androgenic and metabolic factors in women from birth to postmenopause. Fertil Steril 2016;105:481–5.e1.
37. Fábregues F, Peñarrubia J, Creus M, et al. Transdermal testosterone may improve ovarian response to gonadotrophins in low-responder IVF patients: a randomized, clinical trial. Hum Reprod 2009;24:349–59.
38. Walters KA. Role of androgens in normal and pathological ovarian function. Reproduction 2015;149:R193–218.