Elevated antimüllerian hormone levels are not associated with preterm delivery after in vitro fertilization or ovulation induction

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Objective: To investigate the association between antimüllerian hormone (AMH) and preterm birth risk in a larger cohort of patients who underwent either in vitro fertilization or ovulation induction with intrauterine insemination at a US academic fertility center.
Design: Retrospective cohort study.
Setting: Single academic fertility center.
Patient(s): Live singleton births from patients who underwent in vitro fertilization or ovulation induction between 2016 and 2020 at a single academic fertility center were included in this study. Patients were excluded if they had a missing prepregnancy AMH level, a pregnancy using donor oocytes or a gestational carrier, multiple gestations, a delivery before 20 weeks gestation, or a cerclage in place.
Intervention(s): AMH level.
Main Outcome Measure(s): The primary outcome was the proportion of preterm delivery. Secondary outcomes included the rate of pregnancy-induced hypertension, gestational diabetes, and small for gestational age.
Result(s): In the entire cohort (n = 875), 8.4% of deliveries were preterm. The mean AMH values were similar between those with term and preterm births (3.9 vs. 4.2 ng/mL). Similar proportions of patients with term and preterm deliveries had AMH levels greater than the 75th percentile (25% vs. 21%). The odds of preterm birth were similar by AMH quartile after adjusting for the history of preterm birth. Similarly, in the polycystic ovary syndrome (PCOS) cohort, there was no difference between mean AMH values of term and preterm births (n = 139, 9.6 vs. 10.0 ng/mL). The proportions of patients with PCOS with AMH levels greater than the 75th percentile were similar between those with term and preterm deliveries (25% vs. 22%). The odds of preterm birth were similar by the AMH quartile after adjusting for the history of preterm birth.
Conclusion(s): Elevated AMH levels were not associated with an increased risk of preterm birth in patients who conceived after in vitro fertilization and ovulation induction, including patients with PCOS. Although studies suggest that AMH levels may help stratify the risk of preterm birth in this population, our findings indicate that further studies are needed before clinical application. (Fertil Steril® 2023;120:1013–22. ©2023 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Antimüllerian hormone, preterm birth, preterm delivery, in vitro fertilization, ovulation induction

Preterm birth, defined as delivery before 37 weeks of gestation, affects approximately 11% of pregnancies worldwide and 10% of pregnancies in the United States with increasing rates every year (1,2). It is a significant global health issue because complications related to preterm deliveries are the leading cause of death in children younger than 5 years of age and are associated also with long-term morbidities, including neurologic and developmental disabilities and cardiovascular diseases (3). Preterm deliveries are either spontaneous secondary to preterm labor or premature rupture of membranes, or medically indicated due to maternal and/or fetal indications. Many known biological and environmental factors can increase the risk of spontaneous preterm birth, including a prior history of preterm delivery, multiple gestations, Black race, tobacco use, and prior uterine or cervical surgeries (4). The use of assisted

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reproductive technology is another known risk factor for preterm birth (5–7).

In recent years, there has been significant research in identifying biomarkers that can predict preterm delivery to improve risk stratification and guide the development of potential interventions. Such biomarkers include fetal fibronectin (FFN), inflammatory cytokines, and various metabolomic markers (8–11). The presence of FFN, a protein present in amniotic fluid and placental tissue (12), when detected in cervicovaginal secretions may indicate a high risk of spontaneous preterm delivery (8,13). However, the presence of FFN has been studied only in the context of symptomatic pregnant patients with leakage of fluid or contractions and thus would not provide risk stratification before conception (14). Similarly, inflammatory markers, such as C-reactive protein or leukocyte subtypes, have been studied only in patients presenting with symptoms of preterm labor (9). Studies using metabolomic markers, such as nitric oxide metabolites from vaginal secretions (15) and ferritin from serum and/or cervical samples (16,17), to determine preterm birth risk have shown mixed results (18). Similar to FFN, screening with these metabolites was studied in symptomatic patients to determine the risk of imminent preterm delivery. Despite these research efforts, there are no effective screening biomarkers to predict preterm births, particularly in asymptomatic patients.

Antimüllerian hormone (AMH), or Müllerian-inhibiting substance, is a homodimeric glycoprotein in the transforming growth factor-β superfamily that may play a role in the pathogenesis of preterm birth. In males, AMH induces the regression of the Müllerian ducts whereas in females, AMH is expressed in the granulosa cells of the preantral and antral follicles of the ovary and plays an important role in folliculogenesis (19,20). Previous studies have found that Müllerian-inhibiting substance type 2 receptors are expressed in the uterine mesenchyme (21,22). It is hypothesized that elevated AMH may stimulate these receptors in the uterus, potentially impacting uterine development or inhibiting myometrial hyperplasia during pregnancy with subsequent restrictions on uterine capacity (23). This interplay between AMH and the pregnant uterine environment may have important implications for those women with polycystic ovary syndrome (PCOS), who often have higher AMH levels than those without PCOS (24).

PCOS, the most common endocrine disorder in reproductive-aged women (8–13% prevalence), typically presents with anovulation, hyperandrogenism, and polycystic ovarian morphology (25). In addition to the multiple metabolic co-morbidities associated with PCOS, women with PCOS are at a higher risk of pregnancy-related complications such as gestational diabetes (GDM), pregnancy-induced hypertension (PIH), and preterm birth (26–28). Recent studies have suggested that elevated AMH levels, greater than the 75th percentile, are associated with an increased risk of preterm birth in patients with PCOS after assisted reproductive technology (29–32), indicating the use of AMH as a potential marker to identify patients at high risk for preterm delivery. On further examination of these studies, we identified limitations such as small sample sizes and lack of adjustment for risk factors of preterm birth or time between AMH measurements and conception. All 4 studies did not account for the history of preterm births, and 3 of the 4 studies did not account for prior uterine or cervical surgeries. To further understand the potential relationship between preconception AMH levels and preterm birth and to overcome prior study limitations, we investigated the association between AMH and the risk of preterm birth in a large cohort of patients who underwent in vitro fertilization (IVF) or ovulation induction with intrauterine insemination (OI/IUI) at a US academic medical center. We hypothesized that increased AMH levels would be associated with higher rates of preterm birth.

MATERIALS AND METHODS

Study participants

Our study included patients older than 18 years who underwent IVF or OI/IUI and had a live singleton birth between January 2016 and December 2020 at the University of Pennsylvania Health System. Given the inclusion of pregnancies resulting from either IVF or OI/IUI, gestational ages were confirmed based on embryo transfer dates or IUI dates, respectively. This confirmation allowed us to use the most accurate gestational dates to distinguish between preterm and term deliveries. Patients with pregnancies resulting from ovulation induction with intercourse were excluded because the gestational dating would be based on the last menstrual period or ultrasound, which was not reliably available in the electronic medical records. Patients were excluded if they had a missing prepregnancy AMH level, a pregnancy using donor oocytes or a gestational carrier, multiple gestations, a delivery before 20 weeks of gestation, or a cerclage in place. For patients who had more than one pregnancy during the study period, only clinical information from the patient's first pregnancy was included. Using the Rotterdam criteria, which requires at least 2 of the 3 following characteristics: irregular menses, clinical or biochemical evidence of hyperandrogenism, or polycystic-appearing ovaries on ultrasound, PCOS was diagnosed in patients (33). This study was approved by the University of Pennsylvania Institutional Review Board.

Data collection

Demographic and clinical information collected from the electronic medical record (Epic, Epic Systems, Verona, WI) included the maternal age, race, pregestational body mass index (BMI), AMH level before pregnancy, date of AMH measurement, antral follicle count, smoking status, history of uterine surgeries (e.g., myomectomy, dilation and curettage, and cesarean section), history of cervical surgeries (e.g., cold knife conization or loop electrosurgical excision procedure), history of preterm delivery, history of hypertension, history of diabetes mellitus, gravidity, and parity. We extracted detailed information relevant to the pregnancy such as infertility diagnoses (anovulation, diminished ovarian reserve, endometriosis, male factor, PCOS, tubal factor, unexplained, uterine, other, or multiple), type of IVF cycle resulting in pregnancy (fresh or frozen embryo transfer), type of OI (natural,

clomiphene citrate, letrozole, or controlled ovarian hyperstimulation), gestational age at delivery, BMI at the time of delivery, indication for preterm birth when applicable, mode of delivery, indication for cesarean delivery when applicable, sex of infant, infant birth weight, and pregnancy complications (GDM, PIH, chorioamnionitis, premature rupture of membranes, placental abruption, placenta previa, or placental accreta spectrum). The date of conception was determined by subtracting the gestational age from the date of delivery. All pregnancies were confirmed by the presence of a single gestational sac in the first-trimester ultrasound documented in the electronic medical records. Deliveries were classified as term if delivery occurred after 37 weeks of gestational age or preterm if earlier than 37 weeks.

AMH levels were measured during the patient's fertility workup. If more than one level was available, we used the value closest to the first positive pregnancy test. AMH levels were analyzed with the Roche Elecsys (electrochemiluminescence) AMH assay (lower detection limit 0.01 ng/mL; intra-assay coefficient of variation 0.7–3.4%; and inter-assay coefficient of variation 4.0–5.0%) (34).

Statistical analysis

Three cohorts were established: all patients (n = 875), patients with PCOS (n = 139), and patients without PCOS (n = 736). Among these cohorts, the demographic, treatment, and pregnancy characteristics were compared between patients who delivered at term vs. preterm. Categorical variables were compared using the χ^2 test for independence or Fisher's exact test. Continuous variables were compared using Student's *t* test or Wilcoxon rank-sum test.

To investigate the association between AMH values and preterm delivery, the mean and median serum AMH values were compared between those who delivered at term vs. those who delivered preterm. AMH quartiles were established for each cohort as well as the corresponding preterm delivery rates. Proportions of term vs. preterm births were then compared in the highest AMH quartiles. Multivariable logistic regression models were performed to assess the association between AMH quartiles and preterm delivery. Covariates for the final models were selected on the basis of a backward stepwise selection with any covariate having $P<.1$. Any variables that confounded the relationship between AMH and preterm birthby at least 15% were included. The final models for the entire cohort, PCOS cohort, and non-PCOS cohort were adjusted for the history of preterm delivery. In addition, multivariable logistic regression models were used to assess the association between AMH quartiles and secondary pregnancy outcomes. Stratified analyses evaluating the association between AMH and preterm birth risk were performed for pregnancies from IVF only and OI/IUI only. Furthermore, there was no restriction on the number of days between AMH measurement and the date of conception. Thus, a sensitivity analysis was performed including only those with an AMH value within 2 years from the date of conception. $P<.05$ was considered statistically significant.

Our power analysis was based on the study by Hsu et al. (32) who found a 22% difference in those with an AMH value in the highest quartile between subjects with a preterm birth vs. term birth. According to this study, with a preterm birth prevalence of 9%, a sample size of 523 would be sufficient to detect a 20% difference in subjects with an AMH level ≥75th percentile (preterm vs. term) with 80% power. In our study, we had a preterm birth prevalence of 8% and would, therefore, need a sample size of 575 to detect a 20% difference in subjects with an AMH level ≥75th percentile with 80% power. According to the same article, a sample of 430 with a preterm birth prevalence of 9% would have 80% power to detect a mean AMH difference of 4.0 ng/mL between those with preterm vs. term birth. Alternatively, a sample size of 478 with a preterm birth prevalence of 8% would have 80% power to detect a mean AMH difference of 4.0 ng/mL. Therefore, we were powered adequately to detect both of these outcomes.

RESULTS

Demographic and clinical characteristics

The demographic, treatment, and pregnancy characteristics of 875 patients meeting our inclusion criteria are summarized in Tables 1 and 2, respectively. Of the 875 patients, PCOS was diagnosed in 139 patients using the Rotterdam criteria.

Compared with the patients who delivered at term, the preterm group had a higher proportion of patients with prior preterm delivery (4% vs. 16%, $P=.001$). This association with prior preterm delivery was seen also in the PCOS cohort, with 33% of the preterm PCOS group having a history of preterm birth compared with 7% of the term PCOS group ($P=.006$). Prepregnancy diabetes differed between the 2 groups in the PCOS cohort only (2% vs. 22%, $P=.03$). In the entire cohort, a larger proportion of patients underwent cesarean delivery in the preterm group than in the term group (39% vs. 53%, $P=.02$).

Among those with a history of uterine or cervical surgeries within the entire cohort, 265 patients had a history of uterine surgeries only, 30 had a history of cervical surgeries only, and 23 had a history of both types of surgeries. Among those with a history of uterine surgeries, 55.6% had a prior dilation and curettage, 29.8% had a prior cesarean section, and 13.2% had a prior hysteroscopic polypectomy. Among those with a history of cervical surgeries, 85.2% had a prior loop electrocautery excision procedure and 16.7% had a prior cold knife conization.

AMH level and preterm delivery in all patients

We first examined the mean AMH values between patients who delivered preterm compared with those who delivered at term and found no statistically significant differences (4.2 vs. 3.9 ng/mL, $P=.6$) (Table 3). Of note, the number of days between AMH measurement and conception was similar between the 2 groups (223 vs. 228 days, $P=.7$) Next, on the basis of previous studies, we examined the association between the highest AMH quartile (≥75th percentile) and preterm vs. term delivery and did not find statistically

TABLE 1

Baseline demographic characteristics of all patients.

	All patients (n = 875)			Patients with PCOS (n = 139)			Patients without PCOS (n = 736)		
Demographic characteristics	**Term (n = 807)**	**Preterm (n = 68)**	***P* value**	**Term (n = 130)**	**Preterm (n = 9)**	***P* value**	**Term (n = 677)**	**Preterm (n = 59)**	***P* value**
Age (y), median [IQR]	35 [32-38]	35 [33-38]	.45	33 [31-36]	33 [32-34]	.82	35 [33-38]	36 [33-39]	.38
Race			.34			.50			.50
White	72%	72%		70%	56%		73%	75%	
Black	9%	15%		8%	22%		9%	14%	
Asian	10%	6%		15%	11%		9%	5%	
Other	8%	7%		6%	11%		9%	7%	
Pregestational BMI, median [IQR]	24.0 [21.5-28.3]	24.3 [21.4-30.6]	.37	25.0 [22.0-29.9]	27.1 [21.3-33.8]	.79	23.9 [21.4-28.0]	24.2 [21.6-29.8]	.34
Smoking status	15%	15%	.99	12%	0%	.60	15%	17%	.72
History of surgery			.45			.13			.54
None	64%	57%		68%	44%		64%	59%	
Prior uterine	30%	34%		28%	44%		30%	32%	
Prior cervical	3%	4%		2%	11%		4%	3%	
Both	3%	4%		3%	0%		2%	5%	
History of preterm delivery	4%	16%	**.001**	7%	33%	**.006**	4%	14%	**.004**
History of hypertension	9%	16%	.07	11%	22%	.30	9%	15%	.13
History of diabetes	2%	6%	.053	2%	22%	**.03**	2%	3%	.31
Gravidity			.13			.27			.30
1	43%	41%		51%	44%		42%	41%	
2	30%	22%		27%	11%		31%	24%	
3+	26%	37%		22%	44%		27%	36%	
Parity			.09			.78			.058
0	72%	65%		70%	67%		72%	64%	
1	24%	25%		27%	33%		23%	23%	
2+	4%	10%		3%	0%		5%	12%	

Note: Bolded *P*-values signify those that are < .05. BMI = body mass index; IQR = interquartile range; PCOS = polycystic ovary syndrome.

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TABLE 2

Treatment and pregnancy characteristics of patients who underwent IVF or ovulation induction and had a singleton live birth.

	All patients (n = 875)			Patients with PCOS (n = 139)			Patients without PCOS (n = 736)		
Demographic characteristics	**Term (n = 807)**	**Preterm (n = 68)**	***P* value**	**Term (n = 807)**	**Preterm (n = 68)**	***P* value**	**Term (n = 807)**	**Preterm (n = 68)**	***P* value**
Gestational age (y), median [IQR]	39.4 [38.9-40.3]	35.6 [34.1-36.6]	**< .001**	39.4 [38.7-40.1]	35.7 [35.1-36.7]	**< .001**	39.4 [38.9-40.3]	35.6 [33.9-36.3]	**< .001**
Antral follicle count, median [IQR]	18 [12-26]	17 [10-23]	.25	32 [23-40]	40 [30-42]	.23	17 [11-23]	16 [10-20]	.17
IVF			.85			.31			.79
Fresh	31%	39%		30%	100%		31%	33%	
Frozen	69%	70%		70%	0%		69%	67%	
Ovulation Induction			.16			.60			.16
Natural	14%	13%		3%	0%		17%	18%	
Clomiphene citrate	51%	38%		20%	0%		60%	47%	
Letrozole	29%	29%		67%	75%		18%	18%	
COH	6%	19%		11%	25%		5%	18%	
Infertility diagnosis			.08			.91			**.03**
Unexplained	33%	26%		-	-		39%	31%	
DOR	7%	7%		-	-		8%	8%	
Anovulation	2%	3%		-	-		2%	3%	
Endometriosis	2%	1%		-	-		2%	2%	
Tubal	5%	3%		-	-		6%	3%	
PCOS	11%	9%		69%	67%		-	-	
Uterine	0%	3%		-	-		1%	3%	
Male	19%	12%		-	-		23%	14%	
Other	10%	19%		-	-		13%	22%	
Multiple	11%	16%		32%	33%		7%	14%	
BMI at time of delivery, median [IQR]	29.5 [26.7-33.5]	29.2 [25.8-35.0]	.93	30.3 [27.4-36.1]	33.0 [26.5-42.1]	.66	29.3 [26.5-33.3]	29.1 [25.7-33.9]	.98
Mode of delivery			**.02**			.62			**.02**
Vaginal	61%	47%		64%	56%		61%	46%	
Cesarean	39%	53%		36%	44%		39%	54%	
Sex of infant			.41			.48			.53
Female	49%	44%		45%	33%		50%	46%	
Male	51%	56%		55%	67%		50%	54%	
Birthweight (g), median [IQR]	3,360 [3,070-3,670]	2,415 [2,065-2,857]	**< .001**	3,390 [3,104-3,690]	2,730 [2,430-3,110]	**.002**	3,353 [3,062-3,665]	2,365 [2,010-2,850]	**< .001**

Note: Bolded *P*-values signify those that are < .05. COH = controlled ovarian hyperstimulation; DOR = diminished ovarian reserve; IQR = interquartile range; IVF = in vitro fertilization; PCOS = polycystic ovary syndrome.

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TABLE 3

Mean and median AMH levels, number of days between AMH measurement and the date of conception, and proportions of delivery among patients with AMH ≥75th percentile were compared between the term and preterm groups.

Demographic characteristics	Term	Preterm	*P* value
AMH (ng/mL)			
All patients			
Mean (SD)	4.2 (4.8)	3.9 (3.7)	.59
Median (range)	2.7 (1.4-5.2)	2.9 (1.5-4.6)	.98
Patients with PCOS			
Mean (SD)	10.0 (8,1)	9.6 (5.8)	.88
Median (range)	7.6 (4.5-12.3)	8.4 (6.5-11.7)	.77
Patients without PCOS			
Mean (SD)	3.1 (2.7)	3.0 (2.2)	.84
Median (range)	2.3 (1.3-4.2)	2.6 (1.4-4.1)	.83
Days between AMH and conception			
All patients			
Median [IQR]	223 [114-385]	228 [117-431]	.66
Patients with PCOS			
Median [IQR]	231 [114-511]	245 [146-364]	.85
Patients without PCOS			
Median [IQR]	221 [113-376]	217 [110-432]	.58
AMH distribution/value			
All patients			
≥75th percentile / >4.89 ng/mL	203/807 (25%)	14/68 (21%)	.40
Patients with PCOS			
≥75th percentile / >12.30 ng/mL	32/130 (25%)	2/9 (22%)	.87
Patients without PCOS			
≥75th percentile / >4.00 ng/mL	170/677 (25%)	14/59 (24%)	.81

AMH = antimüllerian hormone; PCOS = polycystic ovary syndrome; SD = standard deviation.

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significant differences. We then stratified the data by AMH quartile (Table 4). Preterm birth rates ranged between 6.5% and 9.5% in the entire cohort. When adjusting for the history of preterm delivery, the prevalence of preterm delivery did not differ with each quartile when compared with the lowest quartile. The adjusted odds ratios (aORs) of preterm delivery for the 2nd, 3rd, and 4th quartiles were 0.92 (95% CI 0.45–1.89), 1.30 (0.66–2.57), and 0.78 (0.37–1.63), respectively.

TABLE 4

AMH quartiles were determined for each group. Associations between the proportion of preterm births and the AMH quartile were determined using adjusted multivariable logistic regression models.

AMH Quartiles (ng/mL)	Preterm	OR	95% CI	*P* value
All patients*				
Q1 (n = 219): ≤1.43	7.8%	-	-	-
Q2 (n = 219): 1.44-2.75	7.3%	0.92	0.45-1.89	.83
Q3 (n = 220): 2.76-5.15	9.5%	1.30	0.66-2.57	.44
Q4 (n = 217): >5.15	6.5%	0.77	0.37-1.63	.51
Patients with PCOS*				
Q1 (n = 35): ≤4.52	5.7%	-	-	-
Q2 (n = 35): 4.53-7.65	5.7%	1.38	0.17-11.58	.77
Q3 (n = 35): 7.66-12.30	8.6%	2.50	0.33-18.69	.37
Q4 (n = 34): >12.30	5.9%	1.84	0.21-16.55	.58
Patients without PCOS*				
Q1 (n = 184): ≤1.25	7.6%	-	-	-
Q2 (n = 184): 1.26-2.31	6.5%	0.89	0.40-1.99	.77
Q3 (n = 184): 2.32-4.20	10.3%	1.48	0.71-3.07	.30
Q4 (n = 184): >4.20	7.6%	1.03	0.47-2.23	.95

AMH = antimüllerian hormone; CI = confidence interval; OR = odds ratio; PCOS = polycystic ovary syndrome.
* Models were adjusted for history of preterm birth.

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When stratifying patients who became pregnant after IVF (n = 574), the AMH quartile was not associated with an increased risk of preterm birth when adjusting for a history of preterm birth. Similarly, there was no difference in the rates of preterm birth between AMH quartiles in patients who became pregnant after OI/IUI (n = 294) when adjusting for a history of preterm birth. When restricting to patients who had an AMH level drawn within 2 years from the date of conception (n = 777), there was still no association between the AMH level and preterm birth rate (2nd: aOR 1.05, 95% CI 0.48–2.29; 3rd 1.59, 0.78–3.27; and 4th: 1.08, 0.50–2.36). When we examined the rate of spontaneous preterm delivery (n = 23), we did not detect statistically significant differences between the AMH quartiles.

AMH level and preterm delivery in patients with PCOS

As expected, patients with PCOS had a higher mean AMH value than that of the entire cohort (Table 3). However, the mean AMH values were similar between the term and preterm groups (10.0 vs. 9.6 ng/mL, *P*=.9). Both groups had a similar

number of days between the date of AMH measurement and the date of conception (231 vs. 245 days, $P=.8$). Similar proportions of patients with term and preterm deliveries had AMH levels greater than the 75th percentile (>12.30 ng/mL). In patients with PCOS, preterm birth rates ranged between 5.7% and 8.6% when stratifying by quartile (Table 4). The rates of preterm delivery were similar with each quartile compared with the lowest quartile when adjusting for history of preterm birth, with aORs of 1.38 (0.17–11.58), 2.50 (0.33–18.69), and 1.85 (0.21–16.55) for the 2nd, 3rd, and 4th quartiles, respectively.

Furthermore, when adjusting for a history of preterm delivery, the AMH quartile was not associated with elevated preterm birth risk in patients with PCOS with pregnancies after IVF (n = 74) or after OI/IUI (n = 65). When restricting to patients with AMH measured within 2 years (n = 114), the preterm birth rate did not differ between the AMH quartiles (2nd: aOR 3.75, 0.24–58.0; 3rd: 6.31, 0.43–93.3; and 4th: 6.41, 0.35–118.19). When we examined only patients with spontaneous preterm delivery (n = 5), there was no statistically significant difference between the AMH quartiles.

Relationship between the AMH level and other pregnancy outcomes

Given the previously described relationships between PCOS and the prevalence of GDM, PIH, and small for gestational age, these associations were explored by the AMH quartile. There were no observed associations between the AMH quartile and other pregnancy outcomes in patients with PCOS (Supplemental Table 1, available online).

DISCUSSION

Our large retrospective study demonstrated that elevated AMH levels, specifically in the highest quartile, were not associated with an increased risk of preterm birth in patients undergoing IVF or OI/IUI. Furthermore, there was no association between prepregnancy AMH levels and the prevalence of preterm birth in patients with PCOS. Our findings did not replicate the associations previously described in patients with PCOS who conceived with either IVF or OI/IUI after adjusting for history of preterm birth, a known confounder that increases the preterm birth risk. In addition, the history of cervical and uterine surgeries was ascertained, but it was not found to be different between the term and preterm groups.

Four clinical studies to date have analyzed the relationship between serum AMH levels and preterm birth rates in patients who have undergone IVF or OI. Hsu et al. (32) first described this relationship in a retrospective US cohort study of 432 non-smoking patients after treatment with IVF. In a smaller subgroup of 47 patients with PCOS, patients who delivered preterm had significantly higher median AMH levels than those who delivered at term (18 vs. 6.4 ng/mL, $P=.003$). Furthermore, 67% (8/12) of preterm deliveries had AMH levels greater than the 75th percentile (≥13 ng/mL) as opposed to 11% (4/35) of term deliveries. Interestingly, the association between AMH and preterm birth rates was not seen in patients without PCOS. Prepregnancy AMH levels were compared, which is useful in the setting of establishing preconceptual risk. However, it is difficult to comment on the timing of when AMH should be drawn relative to the date of conception or delivery because this information was not reported. Another retrospective cohort study by Kaing et al. (29) examined the association between AMH and preterm birth in patients with PCOS who conceived after OI. In this secondary analysis of the PPCOS II cohort (n = 118), participants that delivered preterm had a higher median AMH level than those who delivered at term (11.1 vs. 6.5 ng/dL, $P=.02$). Notably, the AMH levels were drawn in the first trimester, likely limiting the use of these data for prepregnancy screening (35). The investigators reported that 63% (5/8) of preterm deliveries had AMH levels greater than the 75th percentile (≥9.3 ng/mL) as opposed to 24% (26/110) of term deliveries. An important limitation of both of these US studies was the lack of ascertainment of prior history of preterm birth in the different groups, which is an important risk factor for preterm deliveries. Furthermore, the PPCOS II study did not account for the history of cervical or uterine surgeries.

Two larger retrospective cohort studies were conducted in China. Hu et al. (30) analyzed a total of 3,743 IVF patients, 468 of whom had PCOS. Among patients with PCOS, 48.9% (22/45) of preterm deliveries had AMH levels greater than the 75th percentile (>9.75 ng/mL) with an aOR of 4.0 (95% CI 1.94–8.08). Again, this relationship between AMH and preterm birth rates was not seen in patients without PCOS. Du et al. (31) assessed the risk of preterm birth related to AMH in patients with PCOS undergoing IVF (n = 2,368), stratified by BMI. They found that patients with an elevated AMH level (>6.45 ng/mL, >75th percentile) and a BMI greater than 24 kg/m^2 had a higher rate of preterm birth (OR 2.47, 95% CI 1.34–4.55), whereas those with a BMI less than 24 kg/m^2 did not have a higher rate of preterm birth. Of note, our study had a mean pregestational BMI of approximately 25 kg/m^2. Furthermore, both of these studies did not account for prior preterm births and a history of cervical or uterine surgeries. Both studies used prepregnancy AMH levels, but the timing of when AMH was measured was not specified. The timing between AMH measurement and the date of conception or delivery may vary considerably and likely limit our understanding of using the AMH level to determine the preconceptual risk of preterm birth.

Our study includes the largest infertility and PCOS cohorts in the US to date, including both patients who conceived using IVF or ovulation induction. We were able to overcome many limitations that were observed in previous studies. All patient information, including pregnancy and delivery outcomes, was confirmed using the electronic medical records, thereby overcoming the limitations of self-report in the PPCOS II cohort and the 2 Chinese cohorts. Of note, we performed an in-depth chart review to confirm the date of delivery and definition of preterm delivery. Importantly, we ascertained and accounted for 2 important risk factors of preterm birth including history of preterm birth and prior cervical or uterine surgeries, which had not been done previously. We excluded patients who had a cerclage in place, given their utilization to reduce the risk of preterm birth in certain high-risk patients (4). However, we did not account for the use of vaginal progesterone, which may limit the interpretation of

our findings. Vaginal progesterone is currently recommended to prevent preterm delivery in patients without a history of preterm birth with a singleton pregnancy and a short cervix (36). Other preventative interventions, such as intramuscular progesterone and pessaries, were not included in our study as well; however, these interventions are not recommended at this time for the prevention of preterm birth (4). Of note, we did not find differences in the proportions of patients with a history of uterine surgeries, history of cervical surgeries, or both between the term and preterm groups, although this is likely due to a lack of power to describe such differences. We compared also the date of AMH level with respect to the date of conception across all groups, further adding rigor to our study design. Our results may differ because of some differences in the study populations, such as our PCOS cohort having a relatively low BMI (mean 25) and a higher age (35 years). Although the use of different AMH assays between studies should not impact the association with preterm birth, it is interesting to note the wide range in the lower level of the group in the highest quartile (6.5–13 ng/mL).

CONCLUSION

In conclusion, our findings did not show an association between elevated AMH levels and the risk of preterm delivery in patients either with or without PCOS undergoing IVF or OI/IUI. PCOS is associated with an increased risk of preterm delivery and the unique underlying mechanisms remain unclear. Although studies suggest that AMH levels may help stratify the risk of preterm birth in this population, our findings indicate that further studies are needed before clinical application.

Declaration of interests: A.E.K. has nothing to disclose. M.K.S. has nothing to disclose. A.N. has nothing to disclose. N.K. has nothing to disclose. A.D. has nothing to disclose.

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Los niveles elevados de hormona antimülleriana no están asociados con parto pretérmino luego de fecundación in vitro o inducción de la ovulación

Objetivo: Investigar la asociación entre hormona antimülleriana (AMH) y riesgo de parto pretérmino en una cohorte de pacientes que se sometieron tanto a fecundación in vitro o inducción de la ovulación con inseminación intrauterina en un centro académico de fertilidad en US.

Diseño: Estudio retrospectivo de cohorte.

Ámbito: Un centro académico de fertilidad.

Paciente(s): Se incluyeron en este estudio nacimientos únicos vivos de pacientes que se sometieron a fecundación in vitro o inducción de la ovulación entre 2016 y 2020 en un centro académico de fertilidad. Las pacientes fueron excluidas si no tenían nivel de AMH antes del embarazo, embarazo con donante de ovocitos o gestación subrogada, embarazos múltiples, fin de las gestación antes de la semana 20, o cerclaje.

Intervención(es): Nivel de AMH.

Medida(s) de resultado principal: El resultado primario fue la proporción de partos pretérmino. Los resultados secundarios incluyeron la tasa de hipertensión inducida por el embarazo, diabetes gestacional, y pequeño para la edad gestacional.

Resultados: En toda la cohorte (n=875), 8.4% de los partos fueron pretérmino. La media de valores de AMH fue similar entre aquellas con parto de término y pretérmino (3.9 vs. 4.2 ng/ml). Proporciones similares de pacientes con partos a término y pretérmino tuvieron niveles de AMH mayores que el percentilo 75 (25% vs. 21%). La probabilidad de parto pretérmino fue similar por cuartil de AMH luego de ajustar por historia de parto pretérmino. Del mismo modo, en la cohorte de síndrome de ovario poliquístico (PCOS), no hubo diferencia entre la media de valores de AMH de partos de término y pretérmino (n=139, 9.6 vs. 10.0 ng/ml). Las proporciones de pacientes con PCOS con niveles de AMH mayores que el percentilo 75 fueron similares entre aquellas con partos de término y pretérmino (25% vs. 22%). La probabilidad de parto pretérmino fue similar por cuartil de AMH luego de ajustar por historia de parto pretérmino.

Conclusiones: Niveles elevados de AMH no se asociaron con aumento de riesgo de parto pretérmino en pacientes que concibieron luego de fecundación in vitro o inducción de la ovulación, incluyendo pacientes con PCOS. Aunque algunos estudios sugieren que los niveles de AMH podrían ayudar a estratificar el riesgo de parto pretérmino en esta población, nuestros hallazgos indican que se necesitan estudios adicionales antes de aplicación clínica.