RESEARCH

AMH predicts miscarriage in non-PCOS but not in PCOS related infertility ART cycles

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Abstract

Background To study whether AMH levels were associated with miscarriage rates in index ART cycles undergoing fresh autologous transfers in PCOS and non-PCOS related infertility.

Methods In the SART CORS database 66,793 index cycles underwent fresh autologous embryo transfers with AMH values reported within the last 1-year between 2014 and 2016. Cycles that resulted in ectopic or heterotopic pregnancies, or were performed for embryo/oocyte banking were excluded.

Data were analyzed using Graphpad Prism-9. Odds ratios (OR) were calculated with 95% confidence intervals (CI) along with multivariate regression analysis adjusting for age, body mass index (BMI), and number of embryos transferred. Miscarriage rates were calculated as miscarriage per clinical pregnancies.

Results Of the total 66,793 cycles, the mean AMH was 3.2 ng/ml and were not associated with increased miscarriage rates for AMH < 1 ng/ml (OR 1.1, CI 0.9–1.4, $p = 0.3$). Of the 8,490 PCOS patients, the mean AMH was 6.1 ng/ml and were not associated with increased miscarriage rates for AMH < 1 ng/ml (OR 0.8, CI 0.5–1.1, $p = 0.2$). Of the 58,303 non-PCOS patients, the mean AMH was 2.8 ng/ml and there was a significant difference in miscarriage rates for AMH < 1 ng/ml (OR 1.2, CI 1.1–1.3, $p < 0.01$). All findings were independent of age, BMI and number of embryos transferred. This statistical significance did not persist at higher thresholds of AMH. The overall miscarriage rate for all cycles, and cycles with and without PCOS were each 16%.

Discussion The clinical utility of AMH continues to increase as more studies investigate its predictive abilities regarding reproductive outcomes. This study adds clarity to the mixed findings of prior studies that have examined the relationship between AMH and miscarriage in ART cycles.

AMH values of the PCOS population are higher than the non-PCOS. The elevated AMH associated with PCOS decreases its utility in predicting miscarriages in IVF cycles as it may be representing the number of developing follicles rather than oocyte quality in the PCOS patient population. The elevated AMH associated with PCOS may have skewed the data; removing this sub-population may have unmasked significance within the non-PCOS associated infertility.

Conclusions AMH < 1 ng/mL is an independent predictor of increased miscarriage rate in patients with non-PCOS infertility.

Keywords AMH, Miscarriage, PCOS, IVF

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Introduction

Anti-mullerian hormone (AMH) is a member of the transforming growth factor β (TGF-β) expressed by granulosa cells of preantral and small antral follicles within the ovary [1]. Serum AMH levels rise from birth and plateau around 25 years of age, after which it is inversely associated with advancing age [2, 3]. Overall, AMH has become a well-established marker of functional ovarian reserve [4–6]. Ovarian stimulation has a known dose dependent response to AMH levels and elevated levels, as present in polycystic ovarian syndrome (PCOS), are associated with increased risk of ovarian hyperstimulation syndrome (OHSS) [7]. AMH has also been shown to have weak predictive ability for pregnancy and live birth [8, 9]. However, the utility of AMH in predicting miscarriage in assisted reproductive technology (ART) cycles is unresolved with some studies concluding that increased AMH levels were associated with decreased miscarriage rates [10]. This inconsistency may be due to the inclusion of patients with PCOS related infertility in prior studies as the association of PCOS with abnormally elevated AMH may mask an association between low AMH levels and the probability of miscarriage in non-PCOS women with infertility [11–13].

Our objective was to examine the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database to examine whether AMH levels were associated with miscarriage rates in initial index IVF/ICSI cycles undergoing fresh autologous transfers in non-PCOS and PCOS related infertility.

Materials and methods

The data used for this study were obtained from the SART CORS. Data were collected through voluntary submission, verified by SART, and reported to the Centers for Disease Control and Prevention (CDC) in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102–493). SART maintains HIPAA-compliant business associates agreements with reporting clinics. In 2004, following a contract change with the CDC, SART gained access to the SART CORS data system for the purposes of conducting research. In 2019, 81% of clinics were SART members reporting 90% of all IVF cycles in the United States [14].

The data in the SART CORS are validated annually with some clinics receiving on-site visits for chart review based on an algorithm for clinic selection. During each visit, data reported by the clinic were compared with information recorded in patients' charts. In 2021, records for 1,945 cycles at 33 clinics were randomly selected for full validation, along with 262 fertility preservation cycles selected for partial validation. Nine out of ten data fields selected for validation were found to have discrepancy rates of ≤ 5% [14]. The exception was the diagnosis field, which, depending on the diagnosis, had a discrepancy rate between 0.7% and 9.1%.

For this study, the SART CORS database identified 533,463 cycles reported between 2014 and 2016. Only initial index cycles of patients who underwent fresh autologous embryo transfers with AMH values reported within the last 1 year were included. Index cycles were defined as the initial cycle for each patient identified documented in the SART CORS database. Thus, each cycle represented a single patient and there were no patients with multiple cycles included in this study. Cycles that underwent preimplantation genetic testing, resulted in ectopic or heterotopic pregnancies, that were performed for embryo or oocyte banking, or cycles performed for a transfer to a gestational carrier were excluded, see Appendix Figure 2 for summary of excluded cycles. For the included 66,793 cycles, we examined cycles with AMH values of < 1 ng/ml. We chose AMH < 1 ng/ml as a widely accepted threshold as a low age-specific AMH value in women ≤ 40 years old.

Data were analyzed using Graphpad Prism-9. Odds ratios of miscarriage for AMH < 1 ng/ml were calculated with 95% confidence intervals (CI). Multivariate regression analysis was performed adjusting for age, body mass index (BMI), and number of embryos transferred.

Secondary analysis was performed on non-PCOS (58,303 cycles) and PCOS (8,490 cycles) patients separately given the association between PCOS and elevated AMH. The diagnosis of PCOS was identified as a designated category in the SART CORS database. Miscarriage rates were calculated as number of miscarriages per clinical pregnancies. Miscarriage was determined by documented intrauterine pregnancies (IUPs) with cardiac activity that did not result in a live or still birth.

This study was approved by the SART research committee and was exempted from review by the institutional review board of Yale School of Medicine.

Results

The baseline characteristics of the non-PCOS infertility patients were notable for having a lower mean AMH of 2.8 ng/ml compared to 6.1 ng/ml in the patients with PCOS. The baseline characteristics of non-PCOS and PCOS patients are summarized in Table 1. The etiology of infertility was documented according to the type of infertility field in the SART CORS database. The etiologies of infertility included in the analysis were diminished ovarian reserve, male factor, tubal factor, endometriosis, uterine factor, PCOS related infertility, and unexplained infertility. The patient distribution of each etiology is summarized in Table 1.

Cycle specific data was also collected. Specifically, the number of oocytes retrieved per cycle and the number of embryos transferred per cycle were analyzed. The summary of stimulation responses including number of oocytes retrieved and embryos transferred are summarized in Table 2.

In the combined analysis of all patients with infertility which included 66,793 cycles (non-PCOS and PCOS cycles), patient's mean age was 34.3 years with a mean BMI of 26.3 kg/m². The mean AMH was 3.2 ng/ml, and the mean number of embryos transferred was 1.8. AMH levels were not associated with increased miscarriage rates for AMH < 1 ng/ml (OR 1.1, CI 0.9–1.4, $p = 0.3$)

independent of age, BMI and number of embryos transferred when examining all patient cycles regardless of etiology of infertility.

Of the non-PCOS patients alone which included 58,303 cycles, the mean age was 34.6 years with a mean BMI of 26 kg/m². The mean AMH was 2.8 ng/ml, and the mean number of embryos transferred was 1.8. In non-PCOS cycles, there was a significant difference in miscarriage rates for AMH < 1 ng/ml (OR 1.2, CI 1.1–1.3, $p < 0.01$) independent of age, BMI and number of embryos transferred, unadjusted means are summarized in Table 3. This statistical significance did not persist at higher thresholds of AMH ≥ 1 ng/ml, see Appendix Supplementary Table 1.

Table 1 Summary of baseline characteristics

Baseline Characteristics	Non-PCOS (*n*=58,303) Average +/- SD (Range)	PCOS (*n*=8,490) Average +/- SD (Range)	Total Cycles (*n*= 66,793) Average +/- SD (Range)	*P* value
Age	34.6 +/- 4.5 (17-52)	32.4 +/- 4.1 (19-46)	34.3 +/- 4.5 (17-52)	<0.01
AMH (ng/mL)	2.8 +/- 2.6 (0-66)	6.1 +/5.2 (0-68.2)	3.2 +/- 3.3 (0-68.2)	<0.01
BMI (Kg/m2)	26 +/- 6 (10.7-161.2)	28.1 +/- 7.2 (10.65-161.2)	26.3 +/- 6.2 (10.7-161.2)	<0.01
Gravidity	0.9 +/- 1.3 (0-10)	0.7 +/-1.1 (0-10)	0.9 +/- 1.3 (0-10)	<0.01
% Non-Caucasian	31923 (55%)	4148 (49%)	30071 (54%)	<0.01
Infertility Etiology				
	n (%)	*n* (%)	*n* (%)	
Diminished Ovarian Reserve	15165 (26%)	337 (4%)	15502 (23%)	<0.01
Male Factor	23304 (40%)	2702 (31%)	26006 (39%)	<0.01
Tubal	9870 (17%)	620 (7.3%)	10556 (16%)	<0.01
Endometriosis	5769 (9.9%)	493 (5.8%)	6262 (9.4%)	<0.01
Unexplained	10525 (18%)	0 (0%)	10525 (16%)	Not calculated
Uterine	2783 (4.8%)	322 (3.8%)	3105 (4.6%)	<0.01
PCOS	0 (0%)	8490 (100%)	8490 (13%)	Not Calculated

AMH Anti-mullerian hormone, *BMI* Body mass index, *PCOS* Polycystic ovarian syndrome, *SD* Standard deviation

Table 2 Summary of stimulation results

Stimulation Characteristics	Non-PCOS (*n*=58,303) Average +/- SD (Range)	PCOS (*n*=8,490) Average +/- SD (Range)	Total Cycles (*n*= 66,793) Average +/- SD (Range)	*P* value
No. Eggs Retrieved	12.1 +/- 7.3 (1-99)	16 +/- 8.6 (1-92)	12.6 +/- 7.6 (1-99)	<0.01
No. Embryos Transferred	1.8 +/- 0.7 (1-10)	1.7 +/- 0.6 (1-8)	1.8 +/- 0.73 (1-10)	<0.01

PCOS Polycystic ovarian syndrome, *SD* Standard deviation

Table 3 Unadjusted baseline characteristics for non-PCOS patients

	Total Count (cycles)	Age (years)	BMI (kg/m2)	Gravidity	No. Eggs Retrieved	No. Embryos Transferred
AMH <1	13896	36.8, (19-52)	26.3, (10.7-64.6)	1, (0-10)	6, (1-55)	1.9, (1-8)
AMH ≥1	52901	33.6, (17-50)	26.2, (10.7-73.2)	0.8, (0-10)	14.2, (1-93)	1.7, (1-10)

AMH Anti-mullerian hormone, *BMI* Body mass index

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The overall miscarriage rate for all index cycles, and cycles with or without PCOS was 16%.

Of the PCOS patients alone, which included 8,490 cycles, the mean age was 32.4 years with a mean BMI of 28.1 kg/m [2]. The mean AMH was 6.1 ng/ml, and the mean number of embryos transferred was 1.7. AMH levels were not associated with increased miscarriage rates for AMH < 1 ng/ml (OR 0.8, CI 0.5–1.1, $p = 0.2$) independent of age, BMI and number of embryos transferred.

When analyzed as a continuous variable AMH was a statistically significant predictor of miscarriage for non-PCOS patients (OR 0.97, CI 0.96–0.98). Receiver operating characteristic (ROC) curves were performed, the area under the curve (AUC) were calculated with 95% confidence interval (CI). The 95% confidence interval for AUC for non-PCOS patients was 0.56–0.58 and PCOS patients was 0.53–0.58. Thus, the ROC analysis suggested that AMH was a weak independent predictor of miscarriage after ART (Appendix: Figure 1).

Discussion

These data show an association between low serum AMH values in women with non-PCOS related infertility and miscarriage following ART. This study adds clarity to the mixed findings of prior studies that have examined the relationship between AMH and miscarriage in ART cycles. Since this study analyzed initial index cycles that underwent fresh transfers, none of the cycles underwent pre-implantation genetic testing. This study improves our ability to provide patient counseling before the start of their initial cycle.

It has been previously shown that the AMH values of the PCOS population are higher than the non-PCOS population [12] and that the higher the AMH, the greater the severity of PCOS [13]. The abnormally elevated AMH levels associated with PCOS likely decrease its utility in predicting miscarriages in IVF cycles as it correlates with the high AMH-secreting arrested follicles rather than oocyte quality in the PCOS patient population [15]. We speculate that the elevated AMH associated with PCOS appears to skew the data when examining all patients with infertility. Thus, removing this sub-population (ie. PCOS) may have unmasked the association of miscarriage in women with AMH < 1 ng/ml with non-PCOS associated infertility.

Existing literature highlight the inconsistent findings regarding AMH and miscarriage rates. Some studies that have found no association between AMH and miscarriage rates included PCOS related infertility in their study population [16]. Other studies attempted to remove PCOS related infertility patients based on AMH levels > 6 ng/ml, which likely did not adequately exclude all PCOS patients [17]. Prior studies have reviewed AMH's ability to predict live birth and miscarriage and have found it is inversely associated with miscarriage in naturally conceived pregnancies [10, 18]. Similarly, AMH has been strongly associated with cumulative live birth rate in women with diminished ovarian reserve [19]. We believe these inconsistent findings may be related to inclusion of cycles for both PCOS and non-PCOS related infertility. Some studies have noted similar findings, low AMH of 0.08–1.6 ng/ml, being associated with miscarriage independent of age in IVF cycles [20]. AMH is correlated with clinical live birth rate in patients with diminished ovarian reserve regardless of their age [19]. The present study examined a broader patient group including other types of infertility beyond diminished ovarian reserve.

Low AMH has been previously associated with recurrent pregnancy loss (RPL) [21]. This finding persisted even after excluding women with PCOS. One limitation of this study is that RPL was not listed in the SART CORS database as a specific data field and thus we were unable to control for RPL as a confounder. However, given that the estimated prevalence of RPL within the population is 1–2%, we do not anticipate inclusion of RPL would have affected our reported findings [22]. Noting that higher AMH was associated with increased miscarriage rates within the PCOS related infertility patient population suggests that different levels of AMH may be representing different ongoing biomedical processes related to sustainable implantation within PCOS and non-PCOS patients [23]. This is an area for further investigation.

Additional research may also be warranted to better identify the most clinically relevant cutoff for AMH values. Previous studies have used 0.4 ng/ml when looking at naturally conceived pregnancies [10]. Our study supports the clinical utility of a higher cutoff of < 1 ng/ml when counseling the non-PCOS patient undergoing ART on the risk of miscarriage before undergoing their initial ART cycle.

Conclusions

AMH of < 1 ng/mL is an independent predictor of increased miscarriage rate in patients with non-PCOS infertility undergoing ART without pre-implantation genetic testing.

During initial index cycles of all combined patients with a diagnosis of PCOS and non-PCOS infertility undergoing fresh autologous embryo transfers, AMH < 1 ng/ml was not associated with increased miscarriage rates. Given these findings, AMH is of limited clinical value for predicting miscarriage in cycles with PCOS but may offer clinical utility for women with non-PCOS related infertility patients undergoing ART. Both AMH and age-based counseling should be considered when discussing the probability of clinical success for women without PCOS related infertility when undergoing ART.
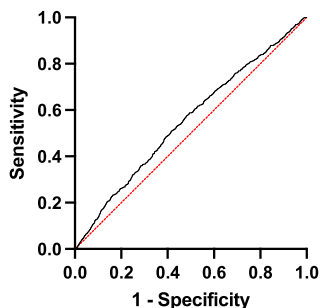
Appendix

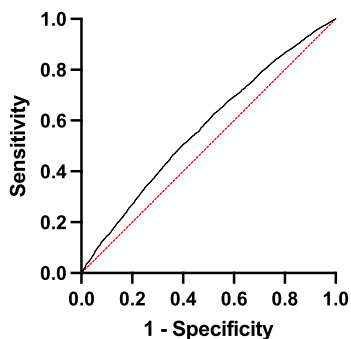**ROC curve: AMH and Miscarriage: PCOS and Non-Infertility.**
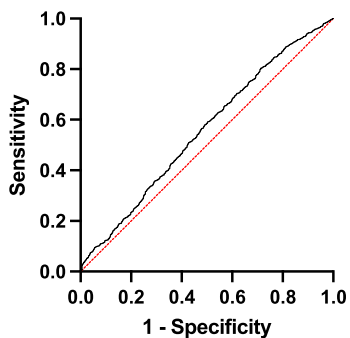
Area	0.5561
Std. Error	0.01263
95% confidence interval	0.5313 to 0.5808

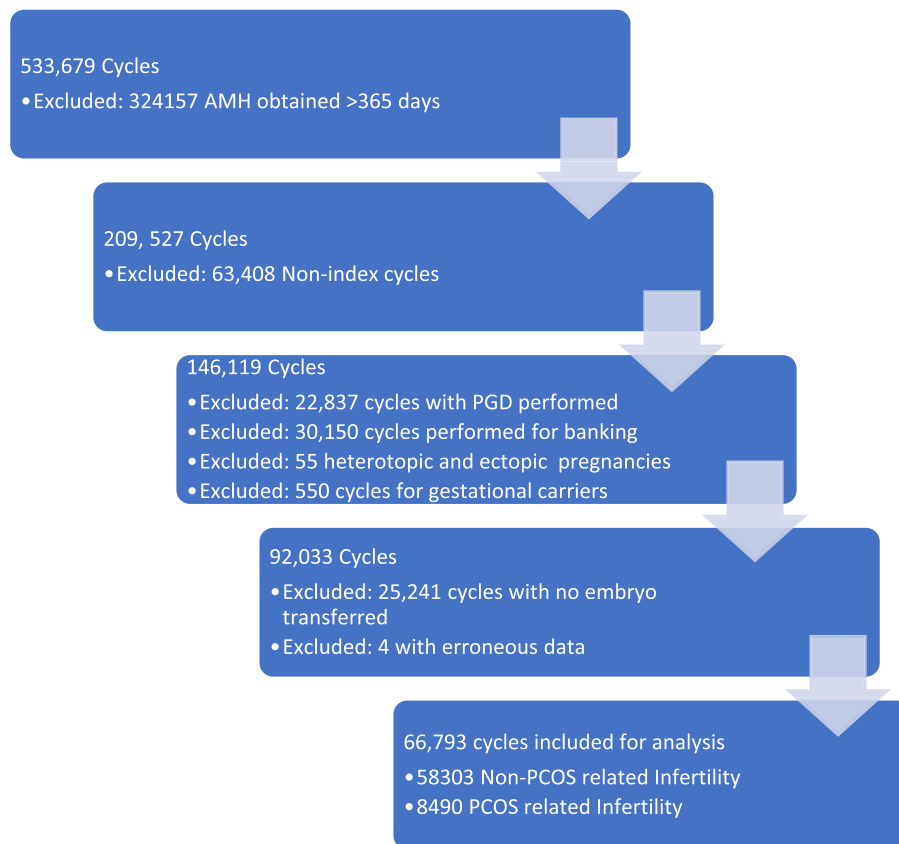**ROC curve: AMH and Miscarriage: PCOS Infertility.**

Area	0.5536
Std. Error	0.01186
95% confidence interval	0.5303 to 0.5768

ROC curve: AMH and Miscarriage: Non-PCOS Infertility.

Area	0.5700
Std. Error	0.004718
95% confidence interval	0.5608 to 0.5793

Fig. 1 ROC curve for all subjects, all patients with PCOS related infertility, and non-PCOS related infertility. Legend: AMH *anti-mullerian hormone*, PCOS *polycystic ovarian syndrome*

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533,679 Cycles
• Excluded: 324157 AMH obtained >365 days

209, 527 Cycles
• Excluded: 63,408 Non-index cycles

146,119 Cycles
• Excluded: 22,837 cycles with PGD performed
• Excluded: 30,150 cycles performed for banking
• Excluded: 55 heterotopic and ectopic pregnancies
• Excluded: 550 cycles for gestational carriers

92,033 Cycles
• Excluded: 25,241 cycles with no embryo transferred
• Excluded: 4 with erroneous data

66,793 cycles included for analysis
• 58303 Non-PCOS related Infertility
• 8490 PCOS related Infertility

Fig. 2 Flow chart summarizing cycles excluded from analysis. Legend: AMH *anti-mullerian hormone*, PGD *preimplantation genetic testing*, PCOS *polycystic ovarian syndrome*

Abbreviations

AMH	Anti mullerian hormone
PCOS	Polycystic ovarian syndrome
IVF	In vitro fertilization
BMI	Body mass index
ICSI	Intracytoplasmic sperm injection
SART CORS	Society for assisted Reproductive Technology Clinic Outcome Reporting System

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-023-01087-5.

Additional file 1: Supplementary Table 1. Summary of AMH Strata of Non-PCOS patients' association with Miscarriage

Disclosure Statement

Dr. David B. Seifer receives royalties from a licensing agreement between Rutgers Medical School/MGH and Beckman Coulter for the use of MIS/AMH in determining ovarian reserve. The other authors have nothing to disclose.

Attestation Statement

- Data regarding any of the subjects in the study has not been previously published unless specified.
- Data will be made available to the editors of the journal for review or query upon request.

Authors' contributions

Regarding authorship, D. Seifer and R. Tal helped with conceiving the idea and study design, E. Han helped with data collection and analysis, C. Arkfeld helped with data collection, analysis, and composed the first draft of the manuscript. All authors contributed equally to subsequent manuscript revisions. The authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from SART CORS but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of SART CORS.

Declarations

Ethics approval and consent to participate

Exempted from review by the institutional review board of Yale School of Medicine.

Competing interests

The authors declare no competing interests.

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