# Impact of increasing antimüllerian hormone level on in vitro fertilization fresh transfer and live birth rate

Kelly S. Acharya, M.D.,[a] Benjamin S. Harris, M.D., M.P.H.,[a] Jeremy M. Weber, M.S.,[b] Tracy Truong, M.S.,[b] Carl Pieper, Dr.P.H.,[b] and Jennifer L. Eaton, M.D., M.S.C.I.[a,c]

[a] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, North Carolina; [b] Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, North Carolina; and [c] Women & Infants Fertility Center, Providence, Rhode Island

**Objective:** The objective of our study was to assess the association between AMH and live birth among women with elevated AMH undergoing first fresh IVF. Serum antimüllerian hormone (AMH) correlates with oocyte yield during in vitro fertilization (IVF). However, there are limited data regarding IVF outcomes in women with elevated AMH levels.
**Design:** Retrospective cohort study using the Society for Assisted Reproductive Technology Clinical Outcomes Reporting System database from 2012–2014.
**Setting:** Fertility clinics reporting to Society for Assisted Reproductive Technology.
**Patient(s):** First, fresh, autologous IVF cycles with elevated AMH levels (≥5.0 ng/mL). Subanalyses were performed to examine patients with or without polycystic ovary syndrome (PCOS).
**Intervention(s):** None.
**Main Outcome Measure(s):** Odds of live birth.
**Result(s):** Our cohort included 10,615 patients with elevated an AMH level, including 2,707 patients with PCOS only. The adjusted odds of live birth per initiated cycle were significantly lower per each unit increase in the AMH level (odds ratio, 0.97; 95% confidence interval, 0.96–0.98). Increasing AMH level was associated with increased cancellation of fresh transfer (odds ratio, 1.12; 95% confidence interval, 1.10–1.15) up to an AMH level of 12 ng/mL. The decrease in the live birth rate appears to be caused by the increasing incidence of cancellation of fresh transfer because the live birth rate per completed transfer was maintained. Similar trends were observed in the PCOS and non-PCOS subanalyses.
**Conclusion(s):** Among patients with AMH levels of ≥5 ng/mL undergoing fresh, autologous IVF, each unit increase in AMH level is associated with a 3% decrease in odds of live birth because of the increased incidence of fresh embryo transfer cancellation. (Fertil Steril Rep® 2022;3:223–30. ©2022 by American Society for Reproductive Medicine.)
**Key Words:** AMH, PCOS, IVF outcomes, live birth

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Antimüllerian hormone (AMH) is a polypeptide hormone in the transforming growth factor $\beta$ superfamily. It is secreted by the granulosa cells of preantral and small antral follicles (1–3), inhibiting recruitment of primordial follicles by counteracting the effects of follicle-stimulating hormone (FSH) and reducing the follicle's FSH sensitivity (4). In clinical practice, AMH is used to estimate ovarian reserve and predict an individual's response to ovarian stimulation with gonadotropins. Antimüllerian hormone has been found to approximate the antral follicle count more closely than FSH (5); further, it can be drawn at any point of the menstrual cycle (6).

Although the utility of AMH for gonadotropin dosing and estimation of the expected egg yield in in vitro fertilization (IVF) is well established, the association with natural fecundability or age at menopause is not that clear-cut. The initial analysis from the Time To Conceive study revealed that, after adjusting for age, women with low AMH levels had reduced fecundability compared with women with higher AMH levels (7, 8). However, follow-up analysis showed no association between low AMH level and fecundability (9). Similarly, AMH has

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Reprint requests: Kelly S. Acharya, M.D., Duke Fertility Center, 5601 Arringdon Park Drive, Suite 210, Morrisville, North Carolina 27560 (E-mail: kelly.acharya@duke.edu).

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been lauded as a potential marker for time to menopause (10, 11); however, discrepant findings may be because of the limited ability of older AMH assays for detection of the ultra-low levels reached in the perimenopausal state (12). Conversely, most existing literature surrounding elevated AMH levels has focused on the association between AMH and polycystic ovary syndrome (PCOS) (6, 13–19). Studies have shown that women with PCOS, as defined by the Rotterdam criteria (20, 21), have 1.5–3 times higher AMH levels than non-PCOS controls. Among women with PCOS, an elevated AMH level is associated with anovulation, hirsutism, and hyperandrogenism.

Multiple studies have examined whether AMH predicts pregnancy or live birth after assisted reproductive technology (ART); however, results have been inconsistent. These studies have largely focused on the lower end of the ovarian reserve spectrum (22). However, existing data on the upper end of the AMH spectrum are sparse (23, 24). One study showed the predictive ability of AMH for clinical pregnancy in a population with diminished ovarian reserve but not in women with PCOS (24).

Thus, the primary objective of our study was to assess the association between AMH and live birth rates among women with elevated AMH levels undergoing fresh autologous IVF. Given the clear association between elevated AMH levels and high oocyte yield in ART as well as previous studies showing that high oocyte yield and high hormone levels during ART are associated with increased risk of ovarian hyperstimulation syndrome (OHSS) and decreased endometrial receptivity, we hypothesized that live birth rates with fresh embryo transfer would decline as AMH level increased. Our secondary objective was to determine whether an AMH level cutoff could be established above which pregnancy and live birth rates decline.

## MATERIALS AND METHODS

Because this was a retrospective analysis of deidentified data, the study was deemed exempt for approval by the Duke institutional review board. The Society for Assisted Reproductive Technology (SART) Clinical Outcomes Reporting System (CORS) was used to identify the first fresh autologous IVF cycles among women aged $<44$ years with an AMH level of $\geq 5$ ng/mL. This cutoff was selected on the basis of a previously published study on elevated AMH level (25) and was consistent with previous nomograms on AMH throughout the reproductive lifespan, with an AMH level of $>5$ ng/mL falling above the 90th percentile in normoovulatory reproductive-aged women (26) or well over the 50th percentile in all women of reproductive age throughout the reproductive lifespan from 25–45 years (27).

The SART CORS database contains comprehensive data from >90% of all clinics performing ART cycles in the United States (28). The data were collected through voluntary submission, verified by SART, and then reported to the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). The SART maintains business associates agreements that are compliant with the Health Insurance Portability and Accountability Act of 1996 with reporting clinics. In 2004, after a contract change with the Centers for Disease Control and Prevention, the SART gained access to the SART CORS data system for the purposes of conducting research. The data in the SART CORS are validated annually, with select clinics having on-site visits for chart review on the basis of an algorithm for clinic selection (28). During each visit, data reported by the clinic were verified with the information recorded in patients' charts (28). In 2012, records for 2,045 cycles at 35 clinics were randomly selected for full validation, along with 238 egg or embryo banking cycles. The full validation included a review of 1,318 cycles for which pregnancy was reported. Among the nondonor cycles, 331 were multiple-fetus pregnancies. Ten out of 11 data fields selected for validation were found to have discrepancy rates of $\leq 5\%$. The exception was the diagnosis field, which, depending on the diagnosis, had a discrepancy rate between 2.1% and 9.2% (28).

The exclusion criteria were preimplantation genetic testing, planned oocyte/embryo banking, and missing AMH level value. Cycles with AMH levels of $>100$ ng/mL were also excluded because this level was considered to be outside the physiologic range. The primary outcome was the live birth rate, defined as the proportion of initiated cycles resulting in a live birth. The secondary outcomes included clinical pregnancy rate, defined as the proportion of cycles with a gestational sac on first trimester ultrasound; miscarriage rate, defined as the proportion of clinical pregnancies ending in miscarriage; and cycle cancellation rate, defined as the proportion of initiated cycles without subsequent oocyte retrieval. Among cycles that proceeded to oocyte retrieval but not embryo transfer, the proportion of cycles with no transfer because of the risk of OHSS was calculated. Similarly, the proportion of cycles with no transfer because of a lack of available embryos was also calculated. A subsequent analysis was performed, in which the cycles were separated empirically into quartiles of AMH levels (5–100 ng/mL). The primary and secondary outcomes were then reported for each quartile, including live birth per initiated cycle (the primary outcome), per oocyte retrieval, and per embryo transfer. The number of canceled cycles was described per quartile, and the percentage of these cancellations because of the OHSS risk was also compared. All proportions were compared using $\chi^2$ tests.

All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC) at a 2-tailed significance level of .05. Summary statistics were calculated for patient and cycle characteristics in the entire cohort and in the PCOS and non-PCOS subgroups. Continuous variables are reported as either mean $\pm$ SD or median (interquartile range [IQR]), and categorical variables are summarized as frequency and column percentage. Logistic regression models were used to assess associations among AMH and binary outcomes of interest. Similarly, linear regression was used for continuous outcomes. Models for live birth and clinical pregnancy were fit before and after adjusting for age, body mass index, race/ethnicity, nulliparity, smoking status, and infertility diagnoses. Missing values for body mass index (13.6%) and total FSH dose (3.5%) underwent mean imputation. Models for secondary outcomes, including miscarriage, fresh transfer canceled, no transfer

because of the risk of OHSS, multiple births, gestational age at delivery, birthweight, and excess embryos being frozen, were unadjusted. The functional form of AMH was checked using restricted cubic splines, with 3 knots placed at the 10th, 50th, and 90th percentile. If there was a significant nonlinear association between the outcome of interest and AMH, then AMH was modeled with piecewise linear splines.

A subgroup analysis was performed in women with PCOS as their only infertility diagnosis. The same aforementioned covariates were included in the models for live birth and clinical pregnancy, except for the infertility diagnoses variables. A similar subgroup analysis was performed in women without a diagnosis of PCOS.

## RESULTS

After applying the exclusion criteria, 10,615 patients remained in our cohort of women with AMH levels of ≥5 ng/mL undergoing their first fresh IVF cycle. The PCOS-only subgroup included 2,707 women, whereas the non-PCOS subgroup included 5,980 women.

Serum AMH values ranged from 5–71 ng/mL, with a median of 7.1 ng/mL (IQR, 5.8–9.5) (Table 1). The cohort was comprised mostly of non-Hispanic White women (51.3%) with a mean age of 31.7 years (range, 19–44 years). The 2 most common infertility diagnoses were PCOS and male infertility. The median number of oocytes retrieved was 18 (IQR, 13–25), and nearly three quarters of women who underwent transfer had excess embryos available for cryopreservation.

Among all cycles, 39.8% resulted in a live birth at a mean gestational age of 37.7 ± 3.1 weeks (Table 2). The clinical pregnancy rate was 46.5%. Thirteen percent of clinical pregnancies ended in miscarriage. Fresh embryo transfer was performed in 77.9% of initiated cycles (8,273 fresh transfers among 10,615 cycles) (Table 2) or among 81.5% of cycles that progressed to oocyte retrieval (8,273 fresh transfers among 10,155 retrievals) (Table 2); fresh embryo transfer was canceled after retrieval in 18.5% of cycles. Among the cycles in which oocyte retrieval was performed but embryo transfer was canceled, 37.8% designated "risk of OHSS" as the reason for no transfer.

Without adjusting for confounders, increasing AMH level was negatively associated with live birth per initiated cycle (odds ratio [OR], 0.97, 95% confidence interval [CI], 0.96–0.98; $P<.001$) (Table 2). After adjusting for covariates, the odds of live birth decreased by 3% per unit increase in AMH level (OR, 0.97; 95% CI, 0.96–0.98; $P<.001$). There was no AMH level cutoff point above which the slope of the decrease in live birth rate changed (Supplemental Fig. 1, available online). Similarly, AMH was negatively associated with clinical pregnancy before and after covariate adjustment (OR, 0.97, 95% CI, 0.97–0.98; $P<.001$ and OR, 0.97; 95% CI, 0.96–0.98; $P<.001$, respectively). There was no obvious cutoff point for an AMH level that was too high for clinical pregnancy (Supplemental Fig. 2).

Increasing AMH concentration was associated with an increased risk of canceled fresh embryo transfer up to an AMH level of 12 ng/mL (OR, 1.12; 95% CI, 1.10–1.15) (Table 2). The restricted cubic splines method showed that the relationship between AMH levels and the outcomes was nonlinear. Graphical inspection of the relationship showed that a cutoff point at AMH level of 12 ng/mL would sufficiently describe this nonlinear relationship. Among women who had their fresh embryo transfer canceled, each 1-unit increase in AMH level was associated with an 11% increase in the odds of embryo transfer cancellation because of the OHSS risk (OR, 1.11; 95% CI, 1.07–1.16) (Table 2; Supplemental Fig. 3) when AMH level was <12 ng/mL. Beyond an AMH level of 12 ng/mL, this association was attenuated. Transfer cancellation because of lack of embryo to transfer was low at 5.1%, whereas the reason for fresh transfer cancellation was not listed in 31.5% of cycles. Among the cohort that did undergo fresh embryo transfer, each 1-unit increase in AMH level was associated with a 1% increase in the odds of having excess embryos to freeze (OR, 1.01; 95% CI, 1.00–1.03) (Table 2). Antimüllerian hormone was not significantly associated with multiple birth, gestational age, or birthweight.

A subanalysis was performed in patients with only PCOS listed as their infertility diagnosis (n = 2,707) (Table 3). In this group, the median AMH level was 8.4 ng/mL, with a range of 5–63 ng/mL. Other baseline patient characteristics were similar to those of the entire study cohort. The median number of oocytes retrieved in this group was 19 (IQR, 13–25), and

**TABLE 1**

**Baseline patient and cycle characteristics among the entire cohort of women with an elevated AMH level (>5 ng/mL).**

| Characteristic | N = 10,615 |
|---|---|
| AMH (ng/mL), median (IQR) | 7.1 (5.8–9.5) |
| Age (y), mean ± SD | 31.7 ± 4.0 |
| Race/ethnicity, n (%) | |
| Non-Hispanic White | 5446 (51.3) |
| Non-Hispanic Black | 605 (5.7) |
| Hispanic/Latina | 585 (5.5) |
| Other (Asian, American Indian, and multiracial) | 1061 (10.0) |
| Unknown | 2918 (27.5) |
| BMI (kg/m$^2$), mean ± SD | 25.8 ± 5.4 |
| Nulligravid, n (%) | 6885 (64.9) |
| Nulliparous, n (%) | 8907 (83.9) |
| Fertility diagnosis, n (%) | |
| Polycystic ovaries | 4635 (43.7) |
| Male infertility | 4146 (39.1) |
| Tubal factor | 1412 (13.3) |
| Endometriosis | 802 (7.6) |
| Uterine factor | 423 (4.0) |
| Unexplained | 1249 (11.8) |
| Smoker, n (%) | 430 (4.1) |
| Total FSH dose (IU), mean ± SD | 2061 ± 927 |
| Number of oocytes retrieved,[a] median (IQR) | 18 (13–25) |
| ICSI, n (%) | 7448 (70.2) |
| Blastocyst transfer,[b] n (%) | 5898/8273 (71.3) |
| Number of embryos transferred,[b] median (IQR) | 2 (1–2) |

*Note:* AMH = antimüllerian hormone; BMI = body mass index; FSH = follicle-stimulating hormone; ICSI = intracytoplasmic sperm injection; IQR = interquartile range.
[a] Among 10,155 cycles that were not canceled before oocyte retrieval.
[b] Among 8,273 embryo transfers.

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## TABLE 2

**Unadjusted cycle outcomes among the entire cohort.**

| Outcome | n/N (%) | AMH effect size, OR (95% CI) | *P* value |
|---|---|---|---|
| Live birth | 4226/10615 (39.8) | 0.97 (0.96 to 0.98) | < .001 |
| Clinical pregnancy | 4941/10615 (46.5) | 0.97 (0.97 to 0.98) | < .001 |
| Multiple birth[a] | 1168/4226 (27.6) | 0.99 (0.98 to 1.01) | .538 |
| Miscarriage[b] | 650/4941 (13.2) | 1.02 (1.00 to 1.04) | .113 |
| Fresh transfer canceled[c] | 1882/10155 (18.5) | | < .001 |
| AMH ≤ 12 ng/mL | | 1.12 (1.10 to 1.15) | |
| AMH > 12 ng/mL | | 1.03 (1.01 to 1.05) | |
| No transfer because of OHSS risk[c] | 711/1882 (37.8) | | < .001 |
| AMH ≤ 12 ng/mL | | 1.11 (1.07 to 1.16) | |
| AMH > 12 ng/mL | | 1.01 (0.98 to 1.04) | |
| Excess embryos cryopreserved[d] | 5907/8273 (71.4) | 1.01 (1.00 to 1.03) | .029 |
| Gestational age, wk | 37.7 ± 3.1 | −0.02 (−0.04 to 0.01)[e] | .193 |
| Birthweight, g | 2951 ± 741 | −1.90 (−7.83 to 4.04)[e] | .531 |

*Note:* AMH = antimüllerian hormone; CI = confidence interval; OHSS = ovarian hyperstimulation syndrome; OR = odds ratio.
[a] Among cycles resulting in a live birth.
[b] Among cycles resulting in a clinical pregnancy.
[c] Among cycles with embryo transfer canceled after oocyte retrieval.
[d] Among cycles with at least 1 embryo transferred.
[e] Mean difference.

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71.9% of those who underwent embryo transfer had excess embryos frozen. Cycle outcomes in the PCOS group were similar to those of the larger cohort (Table 4); the live birth rate was 40.7%, and AMH was negatively associated with live birth (OR, 0.93; 95% CI, 0.90–0.96) up to an AMH level of 12 ng/mL. Beyond 12 ng/mL, the association was attenuated (OR, 1.01; 95% CI, 0.99–1.04). After adjustment for covariates, the findings were similar (OR, 0.93; 95% CI, 0.89–0.96 up to an AMH level of 12 ng/mL; OR, 1.01; 95% CI, 0.98–1.03 beyond an AMH level of 12 ng/mL). Similarly, clinical pregnancy rates were negatively associated with an AMH level of up to 12 ng/mL (OR, 0.94; 95% CI, 0.91–0.97) and not significantly associated beyond that (OR, 1.01; 95%, CI 0.99–1.04). Among patients with PCOS, AMH was not associated with higher odds of transfer cancellation because of OHSS, miscarriage, multiple birth, excess embryos, gestational age, or birthweight.

## TABLE 3

**Baseline patient and cycle characteristics among the subgroup of women with polycystic ovary syndrome.**

| Characteristic | N = 2,707 |
|---|---|
| AMH (ng/mL), median (IQR) | 8.4 (6.3–12.0) |
| Age (y), mean ± SD | 31.2 ± 3.7 |
| Race/ethnicity, n (%) | |
| Non-Hispanic White | 1473 (54.4) |
| Non-Hispanic Black | 126 (4.7) |
| Hispanic/Latina | 146 (5.4) |
| Other (Asian and American Indian) | 256 (9.5) |
| Unknown | 706 (26.1) |
| BMI (kg/m$^2$), mean ± SD | 26.8 ± 6.0 |
| Nulligravid, n (%) | 1811 (66.9) |
| Nulliparous, n (%) | 2304 (85.1) |
| Smoker, n (%) | 91 (3.4) |
| Total FSH dose (IU), mean ± SD | 1969 ± 927 |
| Number of oocytes retrieved,[a] median (IQR) | 19 (13–25) |
| ICSI, n (%) | 1536 (56.7) |
| Blastocyst transfer,[b] n/N (%) | 1489/2063 (72.2) |
| Number of embryos transferred,[b] median (IQR) | 2 (1–2) |

*Note:* AMH = antimüllerian hormone; BMI = body mass index; FSH = follicle-stimulating hormone; ICSI = intracytoplasmic sperm injection; IQR = interquartile range.
[a] Among 2,581 cycles that were not canceled before oocyte retrieval.
[b] Among 2,063 embryo transfers.

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A similar subgroup analysis was performed in women with elevated AMH levels but without a diagnosis of PCOS (n = 5,980) (Supplemental Table 1, available online). For this subgroup, the median AMH level was 6.6 ng/mL (IQR, 5.6–8.3), which was lower than that in the PCOS subgroup. The median number of oocytes retrieved was 18 (IQR, 13–25). The live birth rate was 40.3% (Supplemental Table 2), and AMH was negatively associated with live birth (OR, 0.96; 95% CI, 0.95–0.98; $P<.001$) after adjusting for covariates. The clinical pregnancy rate was 46.6% and was similarly affected by the unit rise in AMH level (OR, 0.96; 95% CI, 0.95–0.98; $P<.001$) after adjusting for covariates. Fresh embryo transfer was canceled in 16.8% of cycles, with increasing odds of fresh transfer cancellation with increasing AMH level (OR, 1.08; 95% CI, 1.06–1.10; $P<.001$).

Finally, an additional analysis was performed to determine the cycle outcomes by quartile of elevated AMH level (Supplemental Table 3). The quartile cutoff points were found to be AMH levels of 5.8, 7.1 (median), and 9.5 ng/mL. The number of cycles per quartile was approximately 2,600. The live birth per initiated cycle decreased from 42.6% in the lowest quartile (AMH ≤ 5.8 ng/mL) to 34.9% in the quartile with an AMH level of >9.5 ng/mL. The implantation rate and live birth rate per embryo transfer did not decrease with increasing AMH level ($P = .62$). The risk of fresh transfer cancellation increased with increasing AMH quartile; 17.4% of transfers were canceled in quartile 1 with an AMH level of 5–5.8 ng/mL, 18.9% of transfers were canceled in quartile 2 with an AMH level of 5.8–7.1 ng/mL, 21.1% of transfers

## TABLE 4

**Outcome information among the polycystic ovary syndrome subgroup.**

| Outcome | n/N (%) | AMH effect size, OR (95% CI) | *P* value |
|---|---|---|---|
| Live birth | 1102/2707 (40.7) | | .001 |
| AMH ≤ 12 ng/mL | | 0.93 (0.90 to 0.96) | |
| AMH > 12 ng/mL | | 1.01 (0.99 to 1.04) | |
| Clinical pregnancy | 1291/2707 (47.7) | | .001 |
| AMH ≤ 12 ng/mL | | 0.94 (0.91 to 0.97) | |
| AMH > 12 ng/mL | | 1.01 (0.99 to 1.04) | |
| Multiple births[a] | 304/1102 (27.6) | 1.01 (0.98 to 1.03) | .690 |
| Miscarriage[b] | 167/1291 (12.9) | 1.02 (0.99 to 1.05) | .331 |
| Fresh transfer canceled[c] | 518/2581 (20.1) | | < .001 |
| AMH ≤ 12 ng/mL | | 1.10 (1.06 to 1.15) | |
| AMH > 12 ng/mL | | 1.03 (1.00 to 1.05) | |
| No transfer because of OHSS risk[c] | 205/518 (39.6) | 1.03 (1.00 to 1.06) | .061 |
| Excess embryos cryopreserved[d] | 1483/2063 (71.9) | 1.01 (0.99 to 1.03) | .414 |
| Gestational age, wk | 37.5 ± 3.3 | −0.01 (−0.04 to 0.03)[e] | .795 |
| Birthweight, g | 2926 ± 755 | −1.11 (−9.87 to 7.64)[e] | .803 |

AMH = antimüllerian hormone; CI = confidence interval; OHSS = ovarian hyperstimulation syndrome; OR = odds ratio.
[a] Among cycles resulting in a live birth.
[b] Among cycles resulting in a clinical pregnancy.
[c] Among cycles with embryo transfer canceled after oocyte retrieval.
[d] Among cycles with at least 1 embryo transferred.
[e] Mean difference.

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were canceled in quartile 3 with an AMH level of 7.1–9.5 ng/mL, and 30.9% of transfers were canceled in quartile 4 with an AMH level of >9.5 ng/mL ($P<.0001$). The reason for transfer cancellation was listed as being because of the risk of OHSS in 21.4% of canceled cycles in quartile 1 vs. 36.4% of canceled cycles in quartile 4 ($P<.0001$).

## DISCUSSION

This large national study demonstrated that among women with AMH levels of ≥5 ng/mL undergoing a first fresh IVF cycle, live birth rates per initiated cycle decline with increasing AMH concentrations. This appears to be primarily because of the higher risk of fresh embryo transfer cancellation in patients with high AMH levels because of concerns regarding OHSS. Findings were similar in the subgroup analyses of women with only PCOS and those without PCOS. Our analyses did not demonstrate a clear AMH level cutpoint at which live birth rates were dramatically reduced.

There is a paucity of studies evaluating the association between ultrahigh AMH levels and live birth among women using ART. The available studies are limited by sample size, analysis of AMH as a categorical variable, lack of live birth as an outcome of interest, and/or lack of specific focus on women with high and ultrahigh AMH levels. Furthermore, data remain heterogeneous regarding the relationship between pregnancy outcomes and varying levels of AMH (23, 29–31). In 2014, Tal et al. (25) conducted a small, single-center retrospective cohort analysis (n = 134) evaluating ART outcomes among women with elevated AMH levels of >5 ng/mL. Women were subdivided into cohorts with AMH levels of 5–10 ng/mL, >10–14 ng/mL, and >14 ng/mL (designated ultrahigh). The likelihood of a diagnosis of PCOS increased with the increasing level of AMH, with the ultrahigh AMH level cohort having the greatest prevalence of PCOS. Ultrahigh AMH levels were associated with increased clinical pregnancy rates, the number of oocytes retrieved, the number of good quality embryos available, and higher OHSS rates compared with women with AMH levels of 5–10 ng/mL; these outcomes reflect the expected positive relationship between high AMH concentration and robust response to gonadotropin stimulation (6, 32, 33). Importantly, the study findings were limited by the small sample size, single-center design, and no comparison of live birth rates. More recently, the same group published a retrospective cohort analysis of 184 first, fresh, autologous IVF/intracytoplasmic sperm injection cycles among women with PCOS (34). The AMH levels were divided into 3 categories: <3.32 ng/mL (<25th percentile), 3.32–8.27 ng/mL, and >8.27 ng/mL (>75th percentile). The study investigators demonstrated a significant decline in live birth rates with increasing AMH level. However, this study was also limited by small sample size and a single-center design, limiting its external validity. Similarly, a small prospective cohort analysis (n = 164) demonstrated that women undergoing IVF with AMH levels of >8.82 ng/mL had decreased rates of implantation and clinical pregnancy compared with those in women with moderate (4.85–8.22 ng/mL) and low AMH levels (<4.85 ng/mL) (35). Live birth rates were not examined. Given the paucity and limitations of existing literature, our large national study strengthens the evidence for a negative association between ultrahigh AMH level and ART outcomes.

The reason for poor ART outcomes among women with ultrahigh AMH levels is not yet understood (34, 35). Prior studies have shown that these women may have decreased oocyte quality (36, 37); however, this is in contrast to the aforementioned study, which showed an increased number of high-quality embryos in patients with elevated AMH levels (25). Other studies have postulated that increased AMH levels

may affect endometrial receptivity directly (38) or indirectly via alteration of angiogenic factors (39) or the increased luteinizing hormone levels observed in PCOS (35). Most notably, studies have consistently shown decreased live birth rates with fresh embryo transfer in high responders, a designation inherent to most patients with elevated AMH levels and PCOS (40, 41). These studies have demonstrated improved pregnancy and live birth rates after frozen embryo transfer, indicating that the altered hormonal milieu and negatively impacted endometrium can be overcome with a freeze-all cycle in high responders. Given that our cohort analyzed first fresh transfers among women with high and ultrahigh AMH levels, it is reasonable to postulate that the observed decreased fresh transfer success rates with increasing AMH levels could be overcome with planned frozen embryo transfer.

It is worth highlighting that women with ultrahigh AMH levels are at significantly increased odds of no transfer because of OHSS, and women should be cautioned regarding that risk. Existing literature has shown that preventive measures, such as lower gonadotropin dosing, gonadotropin-releasing hormone antagonist stimulation protocols, and gonadotropin-releasing hormone agonist triggers, may be used to maximize patient safety and the likelihood of cycle success (42). According to our analyses, patients with high AMH levels who are initiating an IVF cycle should be counseled regarding their generally elevated risk of fresh transfer cancellation. The risk of fresh transfer cancellation was significantly higher in patients with the highest AMH levels (30.9%) than in those in the lowest quartile with more mildly elevated AMH levels (17.4%). Similarly, of the canceled fresh transfers, the reason was listed as being because of the risk of OHSS in 1 in 5 patients with mildly elevated AMH levels (5–5.8 ng/mL) vs. > 1 in three for patients with the highest levels of AMH (>9.5 ng/mL). Understanding this risk may help providers counsel patients and manage expectations for a fresh vs. "freeze-all" cycle; for those patients with the highest AMH concentration and at the greatest risk of transfer cancellation, planning on a freeze-all approach may result in decreased changes to the plan of care (and the patient dissatisfaction that can ensue).

Notably, our study sought to assess whether there was a cutoff value for AMH level above which live birth rates were significantly affected; however, in the PCOS-only cohort, we instead observed an incremental decrease in live birth and clinical pregnancy rates between AMH levels of 5 and 12 ng/mL, with a lack of linear correlation over an AMH level of 12 ng/mL. The investigators hypothesize that this differential effect is likely because of 2 factors: the relatively low number of patients with an AMH level of >12 ng/mL compared with the cohort with an AMH level of 5–12 ng/mL and the heterogeneity of the population with ultrahigh AMH levels, rendering the results (in a smaller population of patients) less predictable. In a future study, it may be interesting to assess all values of AMH level (including those that are not elevated) to determine whether the cutoff point for worse fresh transfer live birth rates lies at a level of <5 ng/mL.

It is interesting to note that although studies show an AMH concentration >5 ng/mL to have high specificity for PCOS (43, 44), only 43% of cycles in our study listed PCOS as the cause of infertility (Table 1). This indicates that PCOS may have actually been underrecognized or underreported in the SART database during our study period.

A major strength of our study was the use of a large national database, which enhanced the generalizability of our study findings. In addition, the large sample size allowed for a robust analysis using AMH as a continuous variable. Analyzing AMH as a continuous variable allows the clinician to provide more precise prognostic information on the basis of individual values of AMH.

Limitations of our study include the retrospective design, lag in data reporting, and the possibility of data entry error. Further, the AMH levels for all of the patients in this study were drawn in different laboratories and with different assays, theoretically largely increasing the variability of the AMH results. In addition, we were unable to measure the effect of ultrahigh AMH levels on the cumulative live birth rate because we were unable to link subsequent frozen embryo transfer data with this fresh cycle data. However, because it has recently become possible to obtain a data set with retrievals linked to all subsequent fresh and frozen transfers, this prompts a possible future study to determine whether cumulative live birth rates are affected by AMH levels in those with elevated AMH concentrations and PCOS. Finally, during the study period, information about the planned fresh transfer was not available through the SART. We were unable to distinguish between planned freeze-all cycles and those that were converted to freeze-all during the ovarian stimulation stage.

## CONCLUSION

Our large, retrospective, national study demonstrated that among women with elevated AMH levels, increasing AMH concentrations are associated with decreased live birth and clinical pregnancy rates and higher odds of cancellation of fresh embryo transfer because of concerns for OHSS. These findings can be used to counsel women with elevated AMH levels that more is not always better for patient outcomes.

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