Can high antimüllerian hormone mitigate some of the age-related decline in live birth rates? The association between antimüllerian hormone and live birth among women over 40 undergoing in vitro fertilization

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Objective: To examine the association between serum antimüllerian hormone (AMH) and live birth among women aged ≥41 years undergoing in vitro fertilization (IVF).
Design: Retrospective cohort study using the 2012–2014 Society for Assisted Reproductive Technology Clinic Outcome Reporting System database.
Setting: Fertility clinics reporting to the Society for Assisted Reproductive Technology.
Patient(s): The analysis included 7,819 patients aged ≥41 years who underwent a first fresh, autologous IVF cycle during the study period. Cycles with preimplantation genetic testing were excluded.
Intervention(s): None.
Main outcome measure(s): Live birth rate.
Result(s): The empirical distribution of AMH was examined, and extreme values were observed. Therefore, the natural logarithm transformation of AMH (log-AMH) was used in all analyses. Before adjustment for covariates, a one-unit increase in log-AMH was associated with doubling of the odds of live birth up to a log-AMH of −0.34 (equivalently, AMH, 0.71 ng/mL; odds ratio [OR], 2.02; 95% confidence interval [CI], 1.66–2.46). Above an AMH level of 0.71 ng/mL, the odds of live birth increased by only 40% with each unit increase in log-AMH (OR, 1.40; 95% CI, 1.22–1.61). After adjusting for covariates, the odds of live birth increased by 91% with each unit increase in log-AMH up to −0.34 (AMH, 0.71 ng/mL; OR, 1.91; 95% CI, 1.56–2.34). Above an AMH level of 0.71 ng/mL, the odds of live birth increased by only 32% with each unit increase in log-AMH (OR, 1.32; 95% CI, 1.15–1.53).
Conclusion(s): Among women aged ≥41 years undergoing fresh, autologous IVF, the odds of live birth significantly increase with increasing serum AMH level. As the AMH level increases above 0.71 ng/mL, the association maintains statistical significance, but the effect size is diminished. (Fertil Steril Rep® 2021;2:440–7. ©2021 by American Society for Reproductive Medicine.)
Key Words: In vitro fertilization, IVF, antimüllerian hormone, AMH

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Antimüllerian hormone (AMH) is a dimeric glycoprotein produced by the granulosa cells of secondary, preantral, and early antral follicles (≤6 mm) (1). Serum AMH levels have been demonstrated to be age-dependent and decline with increasing age (2, 3). Despite the known age-related decline in ovarian reserve, studies have demonstrated high interindividual variability in AMH levels among similarly aged women (4).

Among patients considering treatment with in vitro fertilization (IVF), patient age is the most significant predictor of live birth (5–8). According to the Centers for Disease Control and Prevention (CDC), the live birth rates for women aged <35 years, 35–37 years, 38–40 years, 41–42 years, 43–44 years, and >44 years are approximately 42%, 32%, 22%, 12%, 5%, and 1% per cycle, respectively (9). In addition to age-based counseling, the serum AMH levels are routinely used to predict an individual patient's response to controlled ovarian stimulation (10). A large retrospective database study using data from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) to analyze outcomes from 5,000 autologous cycles demonstrated that patients with serum AMH levels of <0.16 ng/mL were at greatest risk for cycle cancellation (11). Conversely, elevated AMH levels are associated with high oocyte yields in younger patients (12). It is controversial, however, whether AMH predicts live birth, particularly among older patients (13). Existing studies have been limited by low cutoffs for "high" AMH (14). A single-center retrospective cohort study of 200 IVF cycles demonstrated a modest correlation between AMH and live birth rate, independent of age; however, the study was limited by a small number of patients aged >40 years (15). Larger studies are needed to definitively determine whether older women with elevated AMH levels may expect improved IVF outcomes (9, 16). Therefore, our objective was to use a large national database to examine the association between AMH and live birth among women aged ≥41 years undergoing IVF.

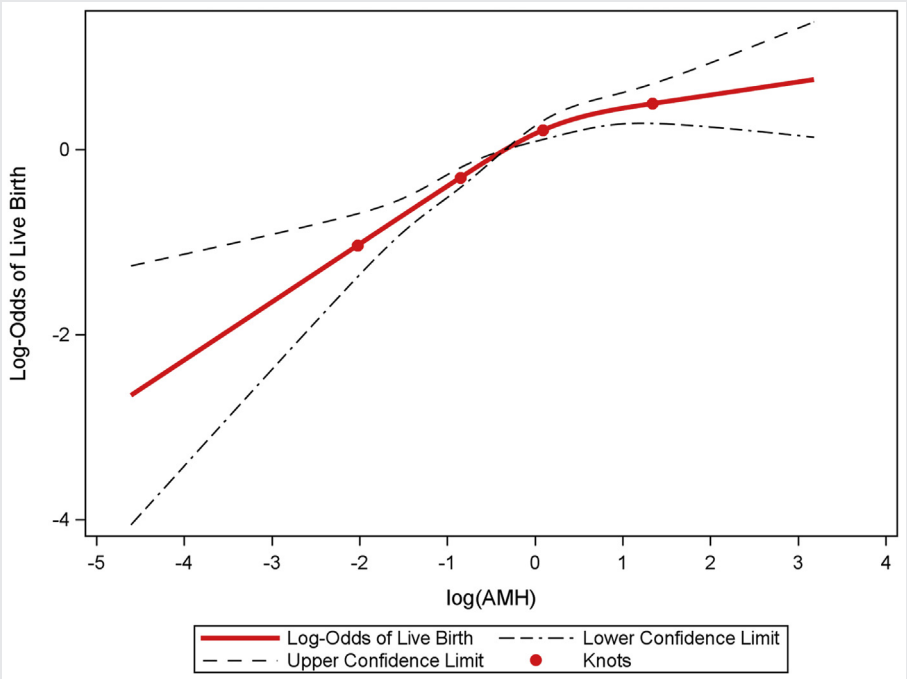
MATERIALS AND METHODS

The study was declared exempt by the Duke Institutional Review Board. The SART CORS database was used to identify all first fresh, autologous IVF cycles performed between 2012 and 2014 in women aged ≥41 years. Cycles with preimplantation genetic testing (PGT) were excluded. The SART CORS database contains comprehensive data from >90% of all clinics performing ART cycles in the United States. The data were collected through voluntary submission, verified by SART, and then reported to the CDC in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). The SART maintains Health Insurance Portability and Accountability Act-compliant business associate agreements with reporting clinics. In 2004, after a contract change with CDC, 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 based on an algorithm for clinic selection (17). During each visit, data reported by the clinic were verified with information recorded in patients' charts (17). 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 review of 1,318 cycles for which a 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 ≤5%. The exception was the diagnosis field, which, depending on the diagnosis, had a discrepancy rate between 2.1% and 9.2% (17).

The primary outcome was live birth rate, defined as the proportion of cycles resulting in live birth. The secondary outcomes included implantation rate, defined by SART as the greater of the number of fetal hearts on ultrasound or the number of live births plus still births divided by the total number of embryos transferred; clinical pregnancy rate, defined as the proportion of cycles with a gestational sac on first-trimester ultrasound; 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 with no transfer because of the risk of ovarian hyperstimulation syndrome was calculated. Similarly, the proportion with no transfer because of the lack of available embryos was also calculated.

Patient and cycle characteristics were described. Continuous variables were summarized as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables were summarized as n (%). The empirical distribution of AMH was examined, and extreme values were observed. Therefore, the natural logarithm transformation of AMH (log-AMH) was used in all analyses presented. The use of the log transformation allows inclusion of extreme values, thereby improving the generalizability of the results. An assumption of generalized linear regression models is that there is a linear relationship between continuous predictors and the outcome (or a transformation of it). That means that the odds ratio (OR) between patients with an AMH level of 2 vs. 1 is the same as 1.5 vs. 2.5. Graphically, there is a single constant slope between AMH and the outcome. To check that assumption, restricted cubic splines (RCSs) with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles were used to assess the functional form of log-AMH for each outcome (18–20). This demonstrated significant nonlinear relationships between log-AMH and the following outcomes: number of oocytes retrieved; cycle cancellation; no transfer because of no available embryos; excess embryos cryopreserved; clinical pregnancy; and live birth. If the linearity assumption did not hold for log-AMH, piecewise linear splines were created and used in the regression model for better interpretability. Cut points for each outcome were then derived by examining plots with the RCS fit (Fig. 1 and Supplemental Figures, available online). Piecewise linear splines were used as opposed to proceeding with RCS for the final models to have better interpretability. This allowed the slope (effect size—mean difference for continuous outcomes and ORs for binary) to be different before and after the chosen cut points. Two key differences between this approach and using log-AMH as a categorical variable are that the actual log-AMH values are still being used and these are nonflat slopes that can be interpreted as per one-unit increase in

FIGURE 1



Association between the natural logarithm transformation of antimüllerian hormone and live birth from restricted cubic splines after controlling for age, body mass index, race/ethnicity, parity, smoking status, and infertility diagnosis.

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log-AMH. The interpretation is the same as a typical regression model with a continuous predictor in that one-unit increase in log-AMH is associated with "x" change in the outcome, but that effect can vary before and after one or more cut points. A multivariable logistic regression model was implemented to investigate the effect of log-AMH on live birth rate with adjustment for the following clinically significant covariates: age; body mass index; parity; smoking status; and infertility diagnosis. Race and ethnicity were combined into one covariate. Missing values in body mass index (15%) were handled with mean imputation. Associations between log-AMH and the secondary outcomes were also assessed but without covariate adjustments. All analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC) at a two-tailed significance level of 0.05.

RESULTS

A total of 7,819 cycles were identified after applying the inclusion and exclusion criteria. The mean age was 42.3 ± 1.4 years (Table 1). The median serum AMH level was 0.70 ng/mL, corresponding to a median log-AMH level of −0.34. The most common infertility diagnosis was diminished ovarian reserve, reported for 70.5% of patients.

The cycle characteristics of the study cohort were as expected for women of advanced reproductive age (Table 1). Despite high doses of follicle-stimulating hormone, the median number of oocytes retrieved was only 5. One out of five cycles was cancelled before oocyte retrieval, and among the cycles that proceeded to retrieval, 20% did not result in a transfer (Table 2). Of the cycles with no embryo transfer, two-thirds had no available embryos. Only 12% of cycles yielded excess embryos for cryopreservation. The clinical pregnancy rate was 14.3%; however, 42.5% of clinical pregnancies resulted in spontaneous abortion, yielding a live birth rate of 8.1% per cycle.

Without covariate adjustment, the RCS analysis demonstrated significant nonlinear relationships between log-AMH and the following outcomes: number of oocytes retrieved; cycle cancellation before retrieval; no embryo transfer among cycles with a retrieval performed; no available embryos for transfer as stated reason for no transfer; excess embryos cryopreserved; clinical pregnancy; and live birth (Table 2). As a result, piecewise linear splines were created, and the effect of log-AMH before and after the observed change in effect for each outcome was estimated. Overall, increasing log-AMH was associated with a higher expected number of oocytes retrieved (Supplemental Fig. 1), but the magnitude of increase was different for log-AMH ≤ -0.84 (equivalently, AMH level of $\leq$0.43 ng/mL) and log-AMH > -0.84. Specifically, among women with log-AMH ≤ -0.84 (equivalently, AMH level of $\leq$0.43 ng/mL), each one-unit increase in log-AMH was associated with an average increase of 0.77 oocytes retrieved ($\beta = 0.77$; 95% confidence interval [CI], 0.55–0.98; $P < .001$). In contrast, among women with log-AMH > -0.84 (equivalently, AMH level of >0.43 ng/mL),

TABLE 1

Patient and cycle characteristics.

Characteristic	N	n (%)
Age (y)[a]	7,819	42.3 ± 1.4
AMH (ng/mL)[b]	7,819	0.70 (0.28, 1.50)
log-AMH[b]	7,819	−0.34 (-1.24, 0.41)
Race/ethnicity	7,819	
Non-Hispanic White		3,286 (42.0%)
Other (Asian/American Indian/Native Hawaiian/multiracial)		913 (11.7%)
Non-Hispanic Black		722 (9.2%)
Hispanic/Latino		540 (6.9%)
Unknown		2,358 (30.2%)
BMI (kg/m^2)[a]	7,819	26.0 ± 5.2
Gravidity ≥ 1	7,819	4,523 (57.8%)
Parity ≥ 1	7,819	2,263 (28.9%)
Smoker	7,819	260 (3.3%)
Infertility diagnosis	7,819	
Diminished ovarian reserve		5,510 (70.5%)
Male factor		1,873 (24.0%)
Tubal factor		946 (12.1%)
Uterine factor		468 (6.0%)
Endometriosis		286 (3.7%)
Polycystic ovary syndrome		244 (3.1%)
Unexplained		539 (6.9%)
Other		1,305 (16.7%)
Reporting year	7,819	
2012		2,191 (28.0%)
2013		2,562 (32.8%)
2014		3,066 (39.2%)
Total FSH dose (IU)[b]	7,819	4,333.5 (3,150, 5,325)
Number of oocytes retrieved[b]	7,819	5 (1, 9)
ICSI	7,819	4,490 (57.4%)
Assisted hatching	7,819	3,393 (43.4%)
Number of embryos transferred[b,c]	4,980	3 (2, 3)
Blastocyst stage at transfer[c]	4,980	1,392 (28.0%)

Note: AMH = antimüllerian hormone; BMI = body mass index; FSH = follicle-stimulating hormone; ICSI = intracytoplasmic sperm injection; IQR = interquartile range; log-AMH = natural logarithm transformation of antimüllerian hormone; SD = standard deviation.

[a] Reported as mean ± SD.

[b] Reported as median (IQR).

[c] Reported among cycles with transfer attempted.

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each one-unit increase in log-AMH was associated with an average increase of 4.71 oocytes retrieved (β = 4.71; 95% CI, 4.54–4.87; $P<.001$). Increasing log-AMH was also associated with decreased odds of cycle cancellation before oocyte retrieval (Supplemental Fig. 2). Among women with log-AMH ≤ −1.00 (equivalently, AMH level of ≤0.37 ng/mL), the odds of the cycle being cancelled vs. not decreased by 26% for each one-unit increase in log-AMH (OR, 0.74; 95% CI, 0.67–0.82; $P<.001$). Among women with −1.00 < log-AMH ≤ 0.50 (equivalently, 0.37 ng/mL < AMH level ≤ 1.65 ng/mL), the odds of the cycle being cancelled vs. not decreased by 72% for each one-unit increase in log-AMH (OR, 0.28; 95% CI, 0.25–0.33; $P<.001$). Finally, among women with log-AMH > 0.50 (equivalently, AMH level of >1.65 ng/mL), the odds of the cycle being cancelled vs. not decreased by 24% for each one-unit increase in log-AMH (OR, 0.76; 95% CI, 0.53–1.09; $P=.119$).

Among women who underwent oocyte retrieval, the association between log-AMH and the odds of not having an embryo transfer differed for log-AMH ≤ 0.29 (equivalently, AMH level of ≤1.33 ng/mL) and log-AMH > 0.29 (equivalently, AMH level of >1.33 ng/mL; Supplemental Fig. 3). Specifically, among women with log-AMH ≤ 0.29 (equivalently, AMH level of ≤1.33 ng/mL), the odds of not having an embryo transfer increased by 64% for each one-unit increase in log-AMH (OR, 1.64; 95% CI, 1.52–1.77; $P<.001$). Among women with log-AMH > 0.29 (equivalently, AMH level of >1.33 ng/mL), the odds of not having an embryo transfer decreased by 27% for each one-unit increase in log-AMH (OR, 0.73; 95% CI, 0.61–0.87; $P<.001$). Associations between log-AMH and the stated reasons for the lack of embryo transfer were then examined. Each one-unit increase in log-AMH was associated with a 4.39 times higher odds that ovarian hyperstimulation syndrome was the stated reason for no transfer (OR, 4.39; 95% CI, 2.76–6.97; $P<.001$; Supplemental Fig. 4). On the other hand, increasing log-AMH was associated with decreased odds of having no embryos for transfer, but the magnitude of the decrease was different for log-AMH ≤ −0.84 (equivalently, AMH level of ≤0.43 ng/mL) and log-AMH > −0.84; Supplemental Fig. 5). Specifically, among women with log-AMH ≤ −0.84 (equivalently, AMH level of ≤0.43 ng/mL), the odds of having no available embryos for transfer decreased by 23% for each one-unit increase in log-AMH (OR, 0.77; 95% CI, 0.61–0.98; $P<.031$).

TABLE 2

Unadjusted associations between log-AMH and cycle outcomes.

Outcome	N	Summary statistics	AMH range	Odds ratio (95% CI)	*P* value
Number of oocytes retrieved[a]	7,819	5 (1, 9)[b]	AMH ≤ 0.43 (log-AMH ≤ −0.84)	0.77 (0.55, 0.98)[c]	< .001
			AMH > 0.43 (log-AMH > −0.84)	4.71 (4.54, 4.87)[c]	< .001
Cycle cancellation before retrieval[a]	7,819	1,623 (20.8%)[d]	AMH ≤ 0.37 (log-AMH ≤ −1.0)	0.74 (0.67, 0.82)	< .001
			0.37 < AMH ≤ 1.65 (−1.0 < log-AMH ≤ 0.5)	0.28 (0.25, 0.33)	< .001
			AMH > 1.65 (log-AMH > 0.5)	0.76 (0.53, 1.09)	.119
No embryo transfer[e]	6,196	1,216 (19.6%)[d]	AMH ≤ 1.33 (log-AMH ≤ 0.29)	1.64 (1.52, 1.77)	< .001
			AMH > 1.33 (log-AMH > 0.29)	0.73 (0.61, 0.87)	< .001
No transfer due to risk of OHSS[f]	1,216	24 (2.0%)[d]		4.39 (2.76, 6.97)[g]	< .001
No transfer because of no available embryos[f]	1,216	782 (64.3%)[d]	AMH ≤ 0.43 (log-AMH ≤ −0.84)	0.77 (0.61, 0.98)	.031
			AMH > 0.43 (log-AMH > −0.84)	0.49 (0.41, 0.59)	< .001
Excess embryos cryopreserved[a]	7,819	937 (12.0%)[d]	AMH ≤ 0.43 (log-AMH ≤ −0.84)	1.90 (1.39, 2.59)	< .001
			AMH > 0.43 (log-AMH > −0.84)	2.91 (2.64, 3.22)	< .001
Implantation	12,943	1,093 (8.4%)[h]			–
Clinical pregnancy[a]	7,819	1,121 (14.3%)[d]	AMH ≤ 0.71 (log-AMH ≤ −0.34)	1.89 (1.63, 2.18)	< .001
			AMH > 0.71 (log-AMH > −0.34)	1.44 (1.29, 1.60)	< .001
Live birth[a]	7,819	636 (8.1%)[d]	AMH ≤ 0.71 (log-AMH ≤ −0.34)	2.02 (1.66, 2.46)	< .001
			AMH > 0.71 (log-AMH > −0.34)	1.40 (1.22, 1.61)	< .001
Miscarriage[i]	1,121	476 (42.5%)[d]		0.94 (0.83, 1.05)[g]	.274
Multiple birth[j]	636	79 (12.4%)[d]		1.24 (0.96, 1.59)[g]	.102
Gestational age[j] (wk)	629	38.3 ± 2.5[k]		0.05 (-0.16, 0.25)[c]	.654
Birth weight[j] (g)	625	3,095.3 ± 679.0[k]		25.5 (−29.4, 80.4)[c]	.363

Note: AMH = antimüllerian hormone; CI = confidence interval; log-AMH = natural logarithm transformation of antimüllerian hormone; OHSS = ovarian hyperstimulation syndrome.
[a] Reported among all cycles.
[b] Reported as median (interquartile range).
[c] Average change in gestational age, birth weight, or number of oocytes retrieved for one-unit increase in log-AMH.
[d] Frequency (percent).
[e] Reported among cycles that were not cancelled before retrieval.
[f] Reported among cycles with no transfer.
[g] Linearity assumption was not violated.
[h] Reported as the proportion of the total number of transferred embryos that implanted.
[i] Reported among cycles with clinical pregnancy.
[j] Reported among cycles with live birth.
[k] Reported as mean (standard deviation).

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Among women with log-AMH > −0.84 (equivalently, AMH level of >0.43 ng/mL), the odds of having no available embryos for transfer decreased by 51% for each one-unit increase in log-AMH (OR, 0.49; 95% CI, 0.41–0.59; *P*< .001).

Before adjusting for potential confounders, log-AMH was nonlinearly associated with live birth. Overall, we observed an increase in the odds of live birth with increasing log-AMH (Supplemental Fig. 6). The magnitude of the odds of live birth was different before and after a log-AMH of −0.34 (equivalently, AMH level of 0.71 ng/mL). Among women with log-AMH ≤ −0.34 (equivalently, AMH level of ≤0.71 ng/mL), the odds of a live birth doubled per one-unit increase in log-AMH (OR, 2.02; 95% CI, 1.66–2.46; *P*< .001). Above a log-AMH of −0.34 (equivalently, AMH level of >0.71 ng/mL), the odds of a live birth increased by 40% per one-unit increase in log-AMH (OR, 1.40; 95% CI, 1.22–1.61; *P*< .001). After controlling for potential confounders, log-AMH was still nonlinearly associated with live birth (Fig. 1). Among women with log-AMH ≤ −0.34 (equivalently, AMH level of ≤0.71 ng/mL), the odds of a live birth increased by 91% per one-unit increase in log-AMH (OR, 1.91; 95% CI, 1.56–2.34; *P*< .001; Table 3). Above a log-AMH of −0.34 (equivalently, AMH level of >0.71 ng/mL), the odds of a live birth increased by 32% per one-unit increase in log-AMH (OR, 1.32; 95% CI, 1.15–1.53; *P*< .001).

DISCUSSION

This large, national study demonstrated a statistically significant association between log-AMH and live birth after

TABLE 3

Multivariable logistic regression model examining association between covariates and live birth among women aged >41 years undergoing in vitro fertilization.

Variable	Odds ratio (95% CI)	*P* value
log-AMH		
≤ −0.34	1.91 (1.56, 2.34)	<.001
> −0.34	1.32 (1.15, 1.53)	<.001
Age	0.64 (0.59, 0.70)	<.001
BMI	1.01 (0.99, 1.02)	.293
Race/ethnicity		.074
Non-Hispanic White	Reference	
Non-Hispanic Black	0.87 (0.63, 1.21)	
Hispanic/Latina	0.87 (0.60, 1.26)	
Other (Asian/American Indian/Native Hawaiian/multiracial)	0.75 (0.56, 1.01)	
Unknown	1.12 (0.93, 1.36)	
Multiparous	1.05 (0.88, 1.27)	.576
Smoker	1.16 (0.74, 1.79)	.522
Infertility diagnosis		
Diminished ovarian reserve	0.96 (0.77, 1.21)	.744
Male infertility	1.04 (0.85, 1.28)	.685
Tubal (ligation, hydrosalpinx, other)	0.78 (0.59, 1.04)	.095
Uterine	1.04 (0.73, 1.48)	.841
Endometriosis	0.75 (0.46, 1.21)	.240
Polycystic ovaries	0.97 (0.63, 1.50)	.899
Unexplained	1.23 (0.87, 1.75)	.242
Other	0.81 (0.63, 1.05)	.119

Note: BMI = body mass index; log-AMH = natural logarithm transformation of antimüllerian hormone.

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adjusting for covariates. Among women with an AMH level of <0.71 ng/mL, the odds of live birth doubled with every unit increase in log-AMH. Beyond 0.71 ng/mL, however, the benefit of higher AMH levels was marginal, despite improved oocyte yield.

The outcomes of IVF among women of advanced reproductive age have been previously published. A large retrospective cohort study from the CDC examined perinatal outcomes and trends in live birth among a cohort of 371,536 fresh and frozen cycles among women aged ≥40 years (21). For fresh cycles from 2007 to 2013 (n = 157,890), the cancellation rate was 17%. Among cycles resulting in transfer (n = 112,414), the live birth rate was 16.1%. The live birth rates per fresh cycle start changed throughout the study period, peaking at 12% in 2010 and then decreasing slightly to 10.6% in 2013. The difference in live birth rates between the CDC study and the present study is likely secondary to different inclusion criteria (40 years of age and above compared with 41 years and above) because the live birth rate declines rapidly with increasing age above 40 years.

There are few existing studies evaluating the association between AMH and live birth among women aged >40 years. Available studies are limited by a small sample size, analysis of AMH as a categorical variable with arbitrarily determined cut points, or inclusion of younger women with better prognoses. A small retrospective study dividing a group of 116 Asian patients with infertility aged >40 years undergoing IVF into low (AMH level of ≤0.48 ng/mL), middle (0.49–1.11 ng/mL), and high (≥1.23 ng/mL) tertiles demonstrated a zero clinical pregnancy rate in the low tertile but a similar pregnancy rate between the middle and high tertiles (23.7% vs. 29.8%, respectively). The results suggest that a very low-AMH level is predictive of poor outcomes, whereas a high-AMH level does not necessarily predict better outcomes than a normal AMH level (22).

A larger single-center retrospective cohort study of over 2,700 patients showed that for every age group except patients aged >40 years, there was a significant trend toward higher pregnancy rates with increasing AMH levels. For patients aged >40 years, there was no significant correlation between AMH and clinical pregnancy rates. Younger patients with a high-AMH level experienced favorable outcomes, whereas their older counterparts with the same AMH level did not. The study was not specifically designed to examine patients aged >40 years, and the number of patients within this group was much smaller than in the younger groups, limiting the interpretation of the results for this age group (23).

In a single-center retrospective cohort analysis of 2,249 first or second fresh, autologous cycles, the AMH levels were divided into low, middle, and high tertiles (≤0.29, 0.30–1.20, and ≥1.21 ng/mL) (14). Among the subgroup of women aged ≥42 years (n = 258), the AMH levels of <0.29 ng/mL were associated with a 3% ± 1% chance of pregnancy, whereas women with AMH levels of >1.21 ng/mL had the same pregnancy rate as women with AMH levels of 0.30–1.20 ng/mL (18% ± 5% vs. 14% ± 2%, respectively). These findings suggest a positive relationship between ovarian reserve and pregnancy rates at the extremes of female reproductive age. However, higher AMH levels of >1.21 ng/mL did not appear to compensate for the decreased oocyte quality associated with advancing age. This study was limited by a small sample size and the treatment of AMH as a categorical variable with arbitrary grouping. Furthermore, the study did not control for multiple cycles in the same woman, which could have affected the interpretation of results.

Subsequently, a single-center retrospective cohort analysis of 200 fresh, autologous cycles evaluated live birth rate across five AMH (0–5 pmol/L, >5 to 10 pmol/L, >10 to 20 pmol/L, >20 to 30 pmol/L, and >30 pmol/L) and four age categories (23–29 years, 23–29 years, 35–39 years, and 40–45 years) (15). In the 40–45-year-old age group, patients with a live birth had a higher median AMH level (19.5 pmol/L) than those without a live birth (4.7 pmol/L). However, there was no statistical significance because of the small sample size, and the study was not adequately powered to evaluate the association between live birth and AMH in women aged >40 years. As with the previous study, this study was also limited by the analysis of AMH as a categorical variable with cut points of unknown clinical significance.

Another retrospective cohort analysis of 5,087 fresh autologous and 243 thawed cycles with ultralow AMH levels (<0.16 ng/mL) from 2012 to 2013 using a large national database (SART CORS) demonstrated that compared with age-matched normal AMH (1–1.2 ng/mL) cycles, cycles with ultralow AMH levels demonstrated more than fivefold

greater preretrieval cancellation rate, twofold less live birth rate per cycle, and a 4.5-fold less embryo cryopreservation rate (11). This study provides valuable prognostic information for women with advanced reproductive age and ultralow AMH levels (<0.16 ng/mL) but does not evaluate the role of higher oocyte quantity among women with known poor oocyte quality. In addition, the study findings are not stratified by age, do not quantify the number of women aged >40 years, or clearly demonstrate the clinical utility of AMH levels specifically in women aged >40 years.

Other studies have examined the AMH levels but have not focused on outcomes among older women. A prospective cohort study of 892 women aged <42 years undergoing IVF-intracytoplasmic sperm injection found that the pregnancy rate per started treatment cycle was positively and linearly associated with log-AMH up to an AMH level of 5 ng/mL, after which the pregnancy rates leveled off (24). Three groups of patients were created based on quartiles of log-AMH, with the middle two quartiles grouped together given similar results. Group 1 (AMH level of <0.84 ng/mL) had a 15.5% live birth rate per ET, whereas groups 2 (AMH level of 0.84–2.94 ng/mL) and 3 (AMH level of >2.94 ng/mL) had a 23.4% and 33.3% live birth rate per ET, respectively ($P<.0001$) Their findings likely differed from those of the present study because of a younger median cohort age (36 compared with 42.3 years) and higher median AMH level (1.6 compared with 0.7 ng/mL).

A retrospective cohort study examined pregnancy outcomes among a cohort of 9,431 women aged 20–51 years (25). Women were divided into younger (<35 years old) and older (>35 years old) groups; AMH was treated as a categorical variable as follows: low (<25th percentile, 0.01–0.62 ng/mL), average (25th to 75th percentile, 0.63–2.41 ng/mL), and high (>75th percentile, 2.41–22.05 ng/mL). Among the older cohort, the live birth rate was significantly higher in the high-AMH group than in the low-AMH group (37.45% vs. 20.34%, $P<.01$), but there was no difference between the high- and average-AMH groups (37.45% vs. 32.46%, $P=.11$). The investigators concluded that the live birth rates did not improve with higher AMH levels in women aged >35 years. Again, differences in the findings of that study compared with the present study are likely attributable to differences in age of the study populations.

In the present study, the benefit of increasing AMH diminished above a level of 0.71 ng/mL. The underlying mechanism is unclear and warrants additional investigation. This finding suggests that in this age bracket, a minimum underlying ovarian reserve is needed for a successful IVF cycle. Beyond a given ovarian reserve level, however, the detrimental impact of age-related aneuploidy likely overrides the clinical relevance of underlying oocyte quantity. A second hypothesis is that women with an AMH level of >0.71 ng/mL may represent a cohort with underlying polycystic ovary syndrome, demonstrated to negatively impact IVF outcomes. During the study period, the SART CORS data field "ovulation disorder polycystic ovaries" was defined as one or more disorders causing reduced fecundity associated with structural, anatomic, or functional impairment of both ovaries. Additionally, the SART CORS database is inherently limited by possible input errors and elective reporting. Given these limitations, it is possible that the polycystic ovary syndrome diagnosis was not adequately controlled for despite adjusting for it in our analyses.

Our study was strengthened by the use of a large national database using recent data from SART CORS (2012–2014), which enhances 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. Furthermore, our analysis determined a clinically relevant cut point where the association between log-AMH and live birth rate changes significantly, which can improve counseling regarding management options. Lastly, we included only first fresh cycles, eliminating the need to adjust for multiple cycles per woman.

The limitations of our study include the retrospective design, lag in data reporting, and possibility of data entry error. In addition, our study results are reported on a log-AMH scale (as opposed to a normal AMH scale), which may limit clinical application and ease of use in patient counseling. Because the log function is not a linear transformation, the increase in the serum AMH level corresponding to a unit increase in log-AMH differs depending on the starting log-AMH value. In addition, we were unable to ascertain from the SART CORS database which specific AMH assay was used or which laboratory performed each assay, which could affect the generalizability of our results. Lastly, we were unable to measure the association between AMH and cumulative live birth rate because linkages between retrieval and subsequent thaw cycles were not available for the first 2 years of our study period. As such, patients undergoing freeze-all with PGT for aneuploidy were excluded from the analysis. This is a significant limitation because these excluded patients would be expected to have favorable prognoses. Now that such linkages are available, we plan to perform a follow-up analysis using a linked data set to assess cumulative outcomes including subsequent thaw cycles with or without PGT for aneuploidy.

CONCLUSION

Our large retrospective, national study demonstrated that among women aged >40 years undergoing a first fresh, autologous IVF cycle, increasing log-AMH is associated with increased odds of live birth after controlling for confounders. Beyond an AMH level of 0.71 ng/mL, however, the beneficial effect of AMH is diminished but remains statistically significant.

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