Anti-Müllerian hormone (AMH) defines, independent of age, low versus good live-birth chances in women with severely diminished ovarian reserve

Maximal receiver operating characteristic curve inflections, which differentiate between better and poorer delivery chances in women with diminished ovarian reserve (DOR) independent of age, were at anti-Müllerian hormone (AMH) 1.05 ng/mL (improved odds for live birth 4.6 [2.3–9.1), 95% confidence interval; Wald 18.8, df = 1], although live births occurred even with undetectable AMH. Pregnancy wastage was very low at AMH ≤0.04 ng/mL but significantly increased at AMH 0.41–1.05 ng/mL, resulting in similarly low live-birth rates at all AMH levels ≤1.05 ng/mL and significantly improved live-birth rates at AMH ≥1.06 ng/mL. (Fertil Steril® 2010;94:2824–7. ©2010 by American Society for Reproductive Medicine.)

Key Words: Anti-Müllerian hormone (AMH), infertility, ovarian reserve, pregnancy, delivery, dehydroepiandrosterone (DHEA)

Diminished ovarian reserve (DOR) predicts pregnancy chances (1). Younger women usually do better (2, 3). DOR is associated with pregnancy loss, resulting in disappointing live-birth rates (4). Which DOR patients may benefit from treatment is, therefore, potentially important (4). Current ovarian reserve assessments do not allow distinction (1, 5). A suitable test would, therefore, be welcome. Anti-Műllerian hormone (AMH) better predicts DOR than FSH (6, 7).

Whether an AMH value discriminates poorer from better live-birth chances, is, however, unknown. FSH has been unable to do so (8). AMH's specificity decreases as women age and/or develop DOR (7).

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Pregnancies at undetectable (9) and undetectable to low (≤0.4 ng/mL) AMH (10) confirm this. Ultimately important is, however, whether AMH can predict live births. As of July 2009, 295 DOR patients with AMH evaluations reached IVF (507 cycles). DOR was initially defined by FSH above 10.0 mIU/mL and/or ovarian resistance to stimulation (four or fewer oocytes). In 2007, age-specific FSH was introduced (11); in 2009, age-specific AMH levels were established (12), which defined DOR by abnormally high age-specific FSH and/or abnormally low age-specific AMH, a definition used in this study.

One purpose of this study was to determine an AMH cutoff value that discriminates between better and poorer live-birth chances. This was done using receiver operating characteristic (ROC) curves for the whole population and, separately, for different age categories. A maximal inflection point between lower and higher live birth chances was uniformly (independent of age) an AMH level of 1.05 ng/mL (Fig. 1).

An AMH level of 1.05 ng/mL is below the suggested DOR levels (13) or those used by our group (10) but above universal cutoffs, as suggested by others (14). AMH <1.05 ng/mL thus represents more severe DOR. The study encompassed 174 severe (310 IVF cycles) and 121 milder (183 IVF cycles) DOR patients, with characteristics shown in Table 1. Chances of clinical pregnancies, miscarriages, terminations of pregnancy, and viable deliveries were then determined among severe DOR patients, depending on AMH levels (below detection, <0.1 ng/mL, 0.1–0.4 ng/mL, 0.41–0.8 ng/mL, 0.81–1.05ng/mL) and with milder DOR (≥1.06 ng/mL). Our routine protocol for DOR supplements with dehydroepiandrosterone (DHEA) (15) and stimulates with microdose agonist cycles (16).

AMH levels were obtained, using the DSL-10-14400 active Müllerian inhibiting substance/AMH (MIS/AMH) enzyme-linked immunoabsorbent assay (Diagnostic Systems Laboratories, Webster, TX) (17). The theoretical sensitivity or minimum

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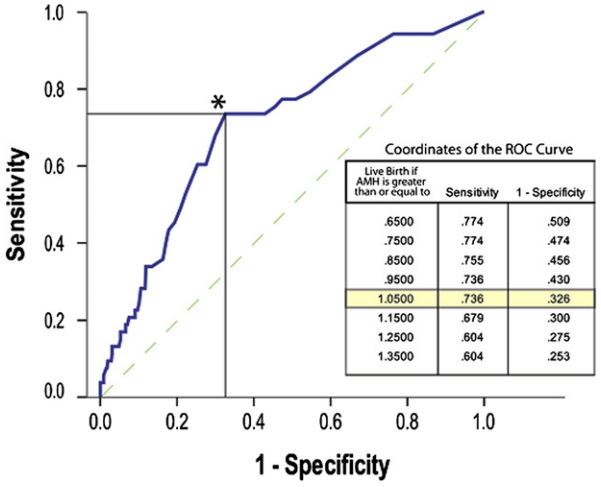
FIGURE 1

ROC curve of AMH at time of presentation and live births involving 507 IVF cycles in 295 women with DOR. *Star* indicates point of maximal inflection, representing, as the set in table demonstrates, an AMH value of 1.05 ng/mL. Not shown here are ROC curves at ages 30–35, 36–40, and >40 years, all demonstrating the same point of maximal inflection between lower and higher live births. The value of 1.05 ng/mL thus represents a uniform cutoff between lower and higher live-birth chance, independent of age.



Gleicher. Live births with very low AMH. Fertil Steril 2010.

TABLE 1

Patient characteristics.

	AMH ≤ 1.05 ng/mL (n = 174)	AMH > 1.05 ng/mL (n = 121)
Age	39.2 ± 4.6	35.2 ± 5.4[a]
AMH, ng/mL	0.44 ± 0.3	2.6 ± 1.8[a]
BMI	25.7 ± 6.4	23.6 ± 6.2[b]
E_2, pg/mL	45.8 ± 20.3	48.1 ± 23.2
FSH, mIU/mL	20.2 ± 18.7	10.8 ± 9.8[a]
Months in treatment	3.9 ± 3.7	4.2 ± 4.1
Race, n (%):		
Caucasian	125 (71.8)	79 (65.3)
African American	17 (9.8)	16 (13.2)
Asian	32 (18.4)	26 (21.5)
Primary infertility diagnoses, n (%):		
DOR	102 (58.6)	36 (29.8)[a]
Endometriosis	8 (4.6)	2 (1.7)
Male factor	39 (22.4)	35 (28.9)
PCOS	1 (0.6)	6 (5.0)[c]
Tubal infertility	7 (4.0)	19 (15.7)[b]
Uterine pathology	0 (0.0)	1 (0.8)
Other	17 (9.8)	22 (18.2)[c]

Note: Data are mean ± SD or n (%). The table demonstrates that women with AMH ≤1.05 ng/mL (severe DOR) are older, have lower AMH, higher FSH, and higher body mass index (BMI) but do not differ in E_2 levels and length of treatments. They also represent a significantly higher prevalence of DOR as primary infertility diagnosis and fewer cases of PCOS, tubal factor infertility, and other diagnoses.

[a] $P<.001$.
[b] $P<.01$.
[c] $P<.05$.

Gleicher. Live births with very low AMH. Fertil Steril 2010.

detection limit is 0.006 ng/mL. The inter- and intra-assay coefficient of variation reported by manufacturer is <10% (17) and was <15% in our laboratory.

Data are shown as means ± standard deviation (SD) or raw numbers and percentages. Normally distributed data were compared by one-way analysis of variance, categorical data by χ^2. Live births were assessed using logistic regression. Logistic regression was performed with live birth as the dependent variable and AMH ≤ or >1.05 ng/mL, adjusted for age, months in treatment, diagnosis, and race.

Data analysis was performed using SPSS for windows, version 17.0 (SPSS Inc., Chicago). Differences were considered to be statistically significant if $P<.05$. Patients sign at initial consultation an informed consent, which allows for review of medical records for research, as long as confidentiality of record and privacy of patient are maintained. Such reviews, therefore, only require expedited review by the Institutional Review Board.

Table 1 demonstrates that patients with AMH ≤1.05 ng/mL were older (39.2 ± 4.6 vs. 35.2 ± 5.4 years; $P<.001$), demonstrated lower AMH ($P<.001$) and higher FSH ($P<.001$), had higher body mass index ($P<.01$), more DOR as admission diagnosis (58.6% vs. 29.8%; $P<.001$), less polycystic ovarian syndrome (PCOS; $P<.05$), and less tubal disease ($P<.01$).

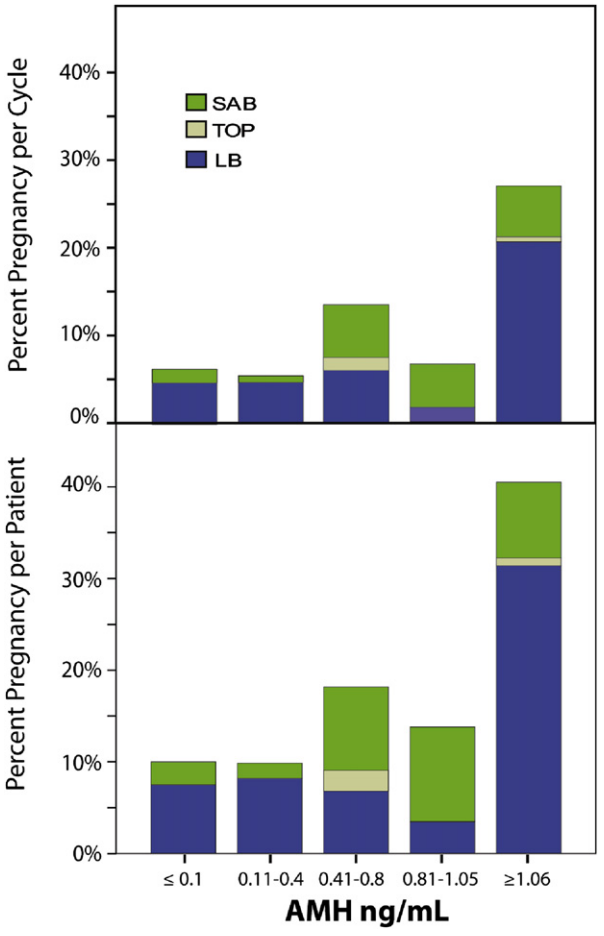
Figure 2 demonstrates pregnancy rates per IVF cycle in the upper panel and cumulative pregnancy rates (independent of length of treatment) in the lower panel. Table 1 demonstrates, however, that length of treatment did not differ below and above AMH 1.05 ng/mL. The figure demonstrates that clinical pregnancies can be established at all AMH levels—even in the absence of detectable AMH. Pregnancy rates remain, however, low (~5.0 percent per IVF cycle and 10.0% cumulatively) up to AMH 0.4 ng/mL.

Rates then increase at AMH 0.41–1.05 ng/mL to approximately 10.0% per cycle/15.0% cumulatively and significantly improve further above AMH 1.06 ng/mL (approximately 25.0%/cycle, 40.0% cumulatively; $P<.001$). Among 507 IVF cycles, 320 were in women with severe DOR and 24 (7.5%) led to clinical pregnancy, while among 136 milder DOR patients, 51 clinical pregnancies were established (37.5%), which is a significantly higher pregnancy rate (χ^2, 62.5, df = 1, $P<.0001$).

Live-birth rates differ significantly from clinical pregnancy rates (Fig. 2) because of higher wastage at AMH 0.41–1.05 ng/mL ($P<.05$), leading to loss of the previously observed statistical advantage in clinical pregnancies at AMH 0.41–1.05 ng/mL in comparison with lower AMH. Consequently, all AMH categories under 1.05 ng/mL demonstrate statistically similar low live-birth rates. In logistic regression for the whole study population, with live births as the dependent variable and AMH ≤1.05/>1.05 ng/mL, adjusted for age, length of infertility treatment, diagnosis, and race, models for all two-way interactions were not significant and neither was a Hosmer-Lemeshow test of goodness of fit.

FIGURE 2

The figure demonstrates at various AMH levels percentages of live births (LB), terminations of pregnancy for aneuploidy (TOP), and spontaneous miscarriages (SAB) per IVF cycle (*upper panel*) and cumulatively over length of infertility treatment with IVF (*lower panel*). For further details, see text.



Gleicher. Live births with very low AMH. Fertil Steril 2010.

Only AMH ($P = .001$) and age ($P<.0001$) were significantly associated with the occurrence of live births. The final model included AMH with age and length of infertility treatment (in months) as covariates: The odds ratio for live births in the presence of an initial AMH >1.05 ng/mL, adjusted for age and length of treatment, was 4.6 (95% confidence interval [2.3–9.2], Wald 18.8, df = 1, $P<.001$).

Correct assessment of ovarian reserve (OR) is crucial. FSH has historically been the tool, but recent studies suggest that AMH may offer improved specificity in predicting ovarian response (18, 19) and pregnancy chances (6, 7). Consequently, AMH has been asserting increasing primacy (6, 7, 20). Recent reviews suggest that AMH has, so far, been used only to predict pregnancy (5, 14, 20–23). Whether AMH can predict live births has never before been addressed.

Pregnancies and live births do not necessarily run in parallel. Levi and associates reported significantly higher miscarriage rates in DOR women than in normal OR patients (4). Patients with more severe DOR, therefore, should experience higher miscarriage and lower live-birth rates.

AMH levels decline (6, 24) and DOR increases with advancing female age (1, 2), which is also associated with increasing aneuploidy (25) and miscarriage rates (26). Increasing miscarriage rates will result in lower live-birth rates and, in turn, be associated with declining AMH levels. Female age and DOR, independently, should therefore be associated with decreasing live-birth rates, as here confirmed, since, among all patient characteristics, only age and OR (per AMH) were statistically associated with live births. Birth rates should, therefore, decline in parallel with declining AMH. Concentrating on pregnancy rates may, therefore, be misleading in directing patient advice. For example, patients with severe DOR may still demonstrate reasonable pregnancy, although they may demonstrate unacceptably low live-birth rates due to high pregnancy wastage.

This study, however, does not support such a parallel decline in live-birth rates and AMH. Surprisingly, pregnancy wastage appears unusually low at the lowest AMH levels, including a complete absence of detectable AMH, peaks at midrange (AMH 0.41–1.05 ng/m/L), and falls again at AMH >1.05 ng/mL (Fig. 1).

Any advantage in clinical pregnancies between AMH 0.41–1.05 ng/mL and lower levels, seen here and in a prior study (10), disappears by delivery, and live-birth rates between undetectable and AMH levels of 1.05 ng/mL are statistically indistinguishably low. Since live births increase significantly above AMH 1.05 ng/mL, it should not be a surprise that an AMH level of 1.05 ng/mL, at all ages, represents maximal inflection on ROC curves, differentiating between lower and higher live-birth chances. As the only AMH cutoff established with live births, it therefore likely represents the most reliable definition of severe DOR.

It also almost perfectly correlates to FSH 10 mIU/mL, while an AMH of 0.8 ng/mL would approximately correlate to an FSH of 11.0 mIU/mL (12, 24). Clinically, these distinctions are important because, especially in younger women, FSH levels at or above 10 mIU/mL have been reported to result in excellent pregnancy chances (8). Since women with premature ovarian senescence do not demonstrate increased embryo aneuploidy (27), such patients should experience only minor pregnancy wastage and satisfactory live births. This study, however, suggests that this will be the case only at AMH >1.05 ng/mL.

Better AMH than FSH specificity has been previously demonstrated (6, 7, 18, 19) and is also supported by this study. AMH <1.05 ng/mL, however, does not define DOR. It only defines DOR with significantly decreased live-birth chances. It also does not warrant withholding of treatment because even DOR patients with very low to undetectable AMH still achieve rather surprising live-birth rates. This is particularly relevant in view of ethics opinions about low pregnancy chances (28).

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