



Anti-Müllerian hormone does not predict cumulative pregnancy rate in non-infertile women following four IUI cycles with donor sperm

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Received: 29 March 2024 / Accepted: 25 June 2024

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Abstract

Purpose To evaluate the predictive value of serum AMH for clinical pregnancy in non-infertile population undergoing intrauterine insemination with donor sperm (ds-IUI).

Methods This multicenter prospective study (ClinicalTrials.gov ID: NCT06263192) recruited all non-infertile women undergoing ds-IUI from June 2020 to December 2022 in three different fertility clinics in Spain and Chile. Indications for ds-IUI included severe oligoasthenoteratozoospermia, female partner, or single status. Clinical pregnancy rates were compared between women with AMH ≥ 1.1 and < 1.1 ng/mL. The main outcome measure was the cumulative clinical pregnancy rate after up to 4 ds-IUI cycles.

Results A total of 458 ds-IUI cycles were performed among 245 patients, of whom 108 (44.08%) achieved clinical pregnancy within 4 cycles, 60.2% of these occurring in the first attempt and 84.2% after two attempts. We found no significant differences in AMH levels or other parameters (such as age, BMI, FSH, AFC) between women who became pregnant and those who did not. Cumulative pregnancy rates and logistic regression analysis revealed that AMH ≥ 1.1 ng/mL was not predictive of ds-IUI success. While a high positive correlation was observed between AFC and AMH ($r = 0.67$, $p < 0.001$), ROC curve analyses indicated that neither of these ovarian reserve markers accurately forecasts cumulative ds-IUI outcomes in non-infertile women.

Conclusions The findings of this multicenter study suggest that AMH is not a reliable predictor of pregnancy in non-infertile women undergoing ds-IUI. Even women with low AMH levels can achieve successful pregnancy outcomes, supporting the notion that diminished ovarian reserve should not restrict access to ds-IUI treatments in eligible non-infertile women.

Keywords Anti-Müllerian hormone · AMH · Intrauterine insemination · IUI · Predictive value · Cumulative pregnancy rate

Introduction

Anti-Müllerian hormone (AMH) is secreted by the granulosa cells of preantral and antral ovarian follicles. Its serum levels peak at 20–25 years of age and gradually decrease after that, along with antral follicle counts (AFC), due to

the decrease in ovarian reserve [1–4]. This age-related follicle loss accelerates from 35 and furthermore from 37 and 40 years of age, while serum levels of AMH become undetectable and follicle-stimulating hormone (FSH) increases until reaching menopausal ranges [5, 6].

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Serum AMH level is a widely used marker of ovarian reserve and predictor of follicular response to controlled ovarian stimulation (COS) [1, 7–9], being < 1.1 ng/mL a well-established cut-off point for poor ovarian response (POR) [10]. AMH levels have been correlated with the ovarian sensitivity index [9], the number of oocytes retrieved [7], and live birth rates following ovarian stimulation and in vitro fertilization (IVF) by the most comprehensive and recent meta-analysis by Peigné et al. [11]. However, the authors highlighted that data for AMH predictive value is lacking after IUI or in women trying to conceive without ART [11]. Indeed, despite occasional references, it is important to avoid misusing AMH as a “fertility test” since the likelihood of becoming pregnant depends on many factors, with age being the most reliable predictor [12–15].

Particularly, pregnancy rates significantly decrease with advancing maternal age from 35 years due to oocyte quality deterioration related to impaired DNA integrity and meiosis competence, oxidative stress, and early apoptosis [16–27]. Based on this rationale, some authors raise doubt about the predictive value of AMH for natural conception and intrauterine insemination (IUI) [28–33]. This skepticism arises from the fact that in these predominantly monofollicular cycles, the critical factor for achieving pregnancy is the quality of the ovulated oocyte rather than the quantity of oocytes remaining in the ovary. In contrast, other authors report better pregnancy rates following IUI in patients with high AMH levels [3, 34–37], while observing poorer outcomes in those with low AMH levels [38]. In fact, all the published studies to date are retrospective and methodologically heterogeneous, and the only available meta-analysis is focused on assessing the association between AMH and spontaneous pregnancy [39]. After IUI with donor sperm (ds-IUI), it has been reported that the cumulative pregnancy rate can reach up to 60% in appropriately selected, non-infertile women without advanced maternal age [40], remaining the impact of low AMH uncertain in this group. However, despite the lack of conclusive evidence, presenting low AMH level is a common exclusion criterion for women to access this treatment in several fertility centers. This often results in more complex and invasive treatments such as IVF.

The objective of this study is to assess the predictive value of AMH for clinical pregnancy in non-infertile population undergoing ds-IUI. Determining this would allow clinicians to establish a more accurate prognosis of IUI cycles and optimize the indication of assisted reproductive techniques (ART).

Methods

This multicenter prospective observational study evaluated the correlation between AMH levels and pregnancy rates in non-infertile women undergoing ds-IUI. Participants were

recruited from June 2020 to December 2022 from three centers: Hospital del Mar and Fertty Clinic (Barcelona, Spain) and Women’s Reproductive Medicine Clinic (Viña del Mar, Chile). The study includes women aged 25–42 years undergoing ds-IUI due to partner’s severe oligoasthenoteratozoospermia, female partner or single status, who were eligible for the study. Patients with a BMI ≥ 30 kg/m², ovarian cysts, endometriosis, or ovulation dysfunction were excluded. In all participants, baseline measures included the following: age (years), pregnancy history, AMH (ng/mL), cycle day-2–5 FSH (IU/L), and cycle day-2–5 AFC by transvaginal ultrasound (TVUS). Patients underwent ovulation induction with low doses of gonadotropins (from 37.5 to 75 IU/day) from the second to the fifth day of the cycle until the follicles reached a diameter of 17 to 20 mm. Follicle growth was monitored by transvaginal ultrasound (TVUS) every 2–3 days, and ds-IUI was performed 36 h after triggering ovulation with subcutaneous injection of 250 µg of HCG (Ovitrelle®, Merck). Skilled gynecologists specialized in reproductive endocrinology and infertility from each center managed patient care and performed the ds-IUIs. Patients repeated subsequent ds-IUI cycles until achieving a live birth or up to 4 cycles when IVF was indicated.

In all cases, serum AMH levels were determined using the commercial automated immunoassay Elecsys® test on a Cobas measurement system by Roche Diagnostics. This test offers a measurement interval of 0.01–23 ng/mL and an inter-day imprecision of $< 5\%$, which is remarkably more accurate than preceding ELISA tests.

Sperm for the Spanish centers was supplied by the CEFER Reproduction Institute sperm bank (Spain), while at Women’s Reproductive Medicine Clinic, it was obtained from the National Sperm Bank of Chile via California Cryobank (USA).

Per each complete ds-IUI cycle, the total number of follicles reaching at least 17 mm in diameter on the trigger day and clinical pregnancy rate were registered. Reproductive outcomes were compared between women with AMH ≥ 1.1 ng/mL and < 1.1 ng/mL. The main outcome measure was the cumulative clinical pregnancy rate after up to 4 consecutive ds-IUI. Clinical pregnancy was defined according to the latest version of the international ART terminology consensus [41].

Statistical analysis

Participant demographics, clinical characteristics, and outcomes were summarized using descriptive statistics. Quantitative variables were reported as means and range or standard deviation (SD).

Cumulative clinical pregnancy rates of patients presenting AMH ≥ 1.1 and < 1.1 ng/mL were represented using Kaplan–Meier, and both curves were compared by means

of the log-rank test or the model of Cox regression. A sub-analysis was also conducted comparing pregnancy rates with AMH ≥ 1.1 and < 1.1 ng/mL in patients in different age groups using the Chi-square test. Statistical significance was established for p -value < 0.05 .

Multivariate logistic regression analysis was performed, including age, BMI, FSH, AFC, and AMH, and correlation coefficients, adjusted odds ratio (OR) with 95% CI, and receiver operating characteristic (ROC) curve analysis were estimated.

T -student test was performed to assess differences between patients who achieved clinical pregnancy in a ds-IUI cycle and those who did not.

The STATA software package version 18.0 (SPSS, Chicago, IL) was used for statistical analysis. Statistical significance was set at $p < 0.05$.

Ethics

This project was approved by the Institutional Review Board and Ethics Committee at Hospital del Mar in Barcelona (Spain) (IRB Protocol ID 2020/9445) and registered at ClinicalTrials.gov (ID NCT06263192).

Neither the data collection, its analysis, nor its results implied any change in the clinical management of ds-IUI for the patients included in the study.

Results

A total of 458 ds-IUI cycles were performed among 245 patients, of whom 108 (44.08%) achieved a clinical pregnancy within 4 ds-IUI cycles. Patient baseline characteristics are shown in Table 1.

Noteworthy, out of the 108 clinical pregnancies achieved through ds-IUI, 91 occurred within the first two ds-IUI cycles (84.2%), with 65 of them occurring after the first ds-IUI attempt (60.2%). The number of clinical pregnancies remarkably decreased after the third and fourth cycles of ds-IUI (12 cases and 5 pregnancies, respectively).

Patients who achieved clinical pregnancy did not exhibit statistically significant differences in AMH levels compared to those who did not become pregnant (Fig. 1), nor did they show differences in other parameters such as age, BMI, FSH, and AFC (Table 2).

The cumulative clinical pregnancy rates for women with AMH ≥ 1.1 and < 1.1 ng/mL are presented through the Kaplan–Meier estimator (Fig. 2). The log-rank test (Mantel–Cox) shows no statistically significant differences in cumulative clinical pregnancy rate between both groups (1.06; p -value 0.302). Sub-analyses of patients in different age groups with AMH ≥ 1.1 ng/mL and < 1.1 ng/mL revealed similar findings,

Table 1 Description of baseline patient characteristics

Patients (n)	245
ds-IUI cycles (n)	458
Age (years)	34.28 $\pm$ 3.86
BMI (kg/m ²)	25.01 $\pm$ 4.26
FSH (IU/L)	7.23 $\pm$ 3.03
AFC (n)	13.23 $\pm$ 7.06
AMH (ng/mL)	2.6 $\pm$ 2.09
Monofollicular cycles (n)	353
Bifollicular cycles (n)	105
1st ds-IUI cycle (n)	245
2nd ds-IUI cycle (n)	123
3rd ds-IUI cycle (n)	57
4th ds-IUI cycle (n)	34

Values expressed as total number (n) or as mean $\pm$ SD

ds-IUI donor sperm intrauterine insemination, *BMI* body mass index, *FSH* follicle-stimulating hormone, *AFC* antral follicle count, *AMH* anti-Müllerian hormone

with no significant differences in pregnancy rates (Supplementary Table 1).

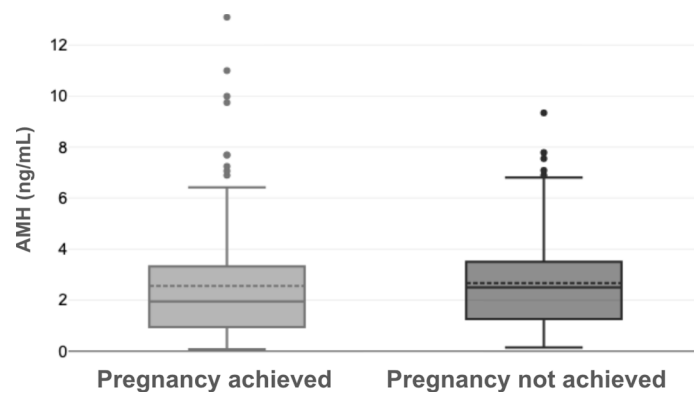
Pearson correlation determined that there was a high positive correlation between AFC and AMH ($r = 0.67$; p -value < 0.001).

Logistic regression analysis examining the influence of age, BMI, FSH, AFC, and AMH on cumulative clinical pregnancy rates is presented in Table 3. The comprehensive model was reliable, being significantly correlated to pregnancy outcomes in the study population ($\chi^2 = 12.45$, p -value 0.029).

ROC curve analyses for AMH and AFC predicting ds-IUI pregnancy outcomes demonstrate areas under the curve (AUC) of 0.554 and 0.562, respectively (Fig. 3 and Supplemental Fig. 1), indicating that using AMH or AFC to predict ds-IUI success in non-infertile women would not provide accurate guidance. Additional ROC curve analyses revealed that neither age, FSH, nor BMI predicts pregnancy following ds-IUI in the study population (Supplemental Figs. 2, 3, 4).

The rates of clinical pregnancy and treatment failure in women with AMH ≥ 1.1 ng/mL were 45.1% and 54.8%, respectively. In contrast, these rates were 40.6% and 59.3% in women with AMH < 1.1 ng/mL. Logistic regression analysis examining the influence of serum AMH on pregnancy rates showed that AMH ≥ 1.1 ng/mL is not a definitive predictive factor for clinical pregnancy following ds-IUI in non-infertile women (OR 0.83; 0.46–1.51) (Table 4).

Fig. 1 Association between AMH and cumulative clinical pregnancy outcome after up to 4 ds-IUI



p-value=0.62.

AMH= Anti-Müllerian hormone; ds-IUI= donor sperm intrauterine insemination.

Table 2 Differences in clinical parameters among patients who achieved pregnancy after up to 4 ds-IUI compared to those who did not

	Pregnancy (n = 108)	No Pregnancy (n = 137)	p-value
Age (years)	33.78 ± 3.85	34.67 ± 3.83	0.057
BMI (kg/m ²)	25.12 ± 4.15	24.93 ± 4.35	0.768
FSH (UI/L)	7.02 ± 2.54	7.41 ± 3.41	0.48
AFC (n)	14.22 ± 7.7	12.42 ± 6.42	0.071
AMH (ng/mL)	2.67 ± 1.83	2.55 ± 2.28	0.649

Values expressed as mean ± SD

ds-IUI donor sperm intrauterine insemination, BMI body mass index, FSH follicle-stimulating hormone, AFC antral follicle count, AMH anti-Müllerian hormone

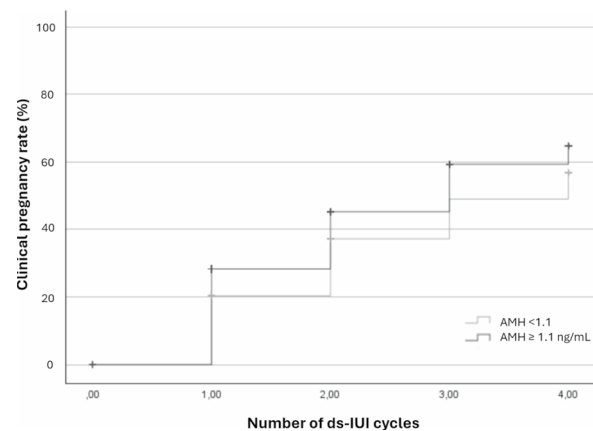
Discussion

This multicenter study showed for the first time that AMH levels do not predict cumulative pregnancy rates following multiple ds-IUI cycles in non-infertile women. Additionally, we found that ovarian reserve markers were comparable between non-infertile women who achieved pregnancy following ds-IUI and those who did not.

Our comprehensive logistic regression model was globally significant, indicating that the variables of age, BMI, FSH, AFC, and AMH have a collective impact on the probability of pregnancy. However, none of the studied variables proved to be an independent predictor of cumulative clinical pregnancy rate in non-infertile women undergoing ds-IUI. This result may be due to several reasons, including the size of the sample or the variability of the data. While we identified a correlation between AMH and AFC in our study cohort, we observed a non-significant trend suggesting higher AFC, but not AMH, in women who obtained

pregnancy compared to those who did not. This contrast may be attributed to inter-observer variations in AFC measurements or perhaps to a potentially higher incidence of favorable bifollicular cycles in patients with higher AFC prior to IUI. Nonetheless, no significant differences in pregnancy outcomes based on ovarian reserve were found, and therefore, none of these plausible hypothetical effects seem remarkable, if present.

The selection of women without anatomical-functional ovarian abnormalities or diagnosis of female infertility along with the use of donor semen allowed us to adequately assess the effect of ovarian reserve on the probability of pregnancy after IUI in non-infertile populations. The prospective nature of the study provided a longitudinal perspective for cumulative effects of exposures, controlled data collection, and the



Log-rank test (Mantel-Cox) = 1.06; p-value 0.302. AMH, anti-Müllerian hormone; ds-IUI, donor sperm intrauterine insemination

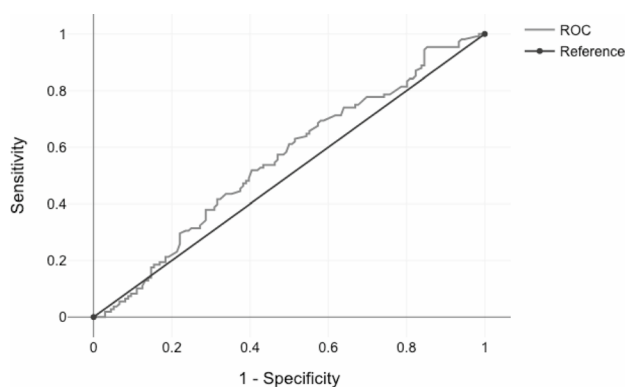
Fig. 2 Cumulative clinical pregnancy rate up to 4 ds-IUI in women with serum AMH levels ≥ 1.1 and < 1.1 ng/mL

Table 3 Logistic regression analysis examining the association between patient characteristics and cumulative clinical pregnancy outcome

	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Age (years)	0.94	0.88–1.00	0.059	0.87	0.75–1.01	0.068
BMI (kg/m ²)	1.01	0.94–1.08	0.767	1.11	0.98–1.25	0.102
FSH (UI/L)	0.96	0.85–1.08	0.478	1.19	0.96–1.46	0.107
AFC (n)	1.04	1.00–1.08	0.074	1.07	0.98–1.17	0.142
AMH (ng/ml)	1.03	0.91–1.16	0.648	0.77	0.53–1.12	0.177

OR, odds ratio; 95% CI, 95% confidence interval

BMI body mass index, FSH follicle-stimulating hormone, AFC antral follicle count, AMH anti-Müllerian hormone, ds-IUI donor sperm intrauterine insemination



AUC= 0.554

ROC= Receiving Operating Characteristic; AUC= Area Under the Curve.

AMH= Anti-Müllerian hormone; ds-IUI= donor sperm intrauterine insemination.

Fig. 3 ROC curve analysis of AMH for cumulative clinical pregnancy rate after up to 4 ds-IUI

ability to measure incidence and multiple outcomes, without

Table 4 Cumulative pregnancy outcome after up to 4 ds-IUI in patients with AMH ≥ 1.1 ng/mL vs AMH < 1.1 ng/mL

	AMH ≥ 1.1 ng/mL (n = 186)	AMH < 1.1 ng/mL (n = 59)	OR (95% CI, p-value)
No pregnancy	102	35	0.83 (0.46–1.51, 0.546)
Pregnancy	84	24	

OR, odds ratio; 95% CI, 95% confidence interval

AMH anti-Müllerian hormone, ds-IUI donor sperm intrauterine insemination

recall bias from participants. Being performed at centers in different continents, the study included patients from different ethnic backgrounds and socioeconomic levels, granting robustness and a greater external validity.

Limitations of the study included the potential influence of undiagnosed polycystic ovary syndrome (PCOS) in women with exceptionally high AMH values [42]. However,

this effect seems minimal, if any, given the exclusion of patients with menstrual irregularities and the presence of 11 participants with AFC > 25 , and only 4 among them > 30 . Another limitation is the limited representation of women with low AMH levels (< 1.1 ng/mL, 43 patients; < 0.5 ng/mL, 15 patients), which may be attributed to the general practice in our centers of not offering IUI to women with low ovarian reserve or those over the age of 42. In addition, the variability in length and total dosage of rFSH exposure before ds-IUI could have influenced the outcomes, although this seems unlikely. Only exposure to excessively high gonadotropin levels has been reported to decrease oocyte quality and pregnancy likelihood with IVF treatments [43–45], but low daily doses were used in all cases in our study.

There is still extensive controversy regarding the relationship between ovarian reserve and fertility, while the association between AMH levels and success rates in natural conception and IUI varies greatly across published studies. Although no studies assessed cumulative pregnancy after ds-IUI in non-infertile population to date, some authors have reported poor predictive value of AMH for natural pregnancy and IUI outcome [12, 28–34], in line with our findings. This is also supported by the recent meta-analysis by Lin et al., which included 11 studies ($n = 4388$ women) and was aimed to study the utility of AMH in predicting pregnancy. The authors found low AMH levels not to be associated with reduced fertility following IUI in different age groups [39], demonstrating the limited capability of AMH to predict fertility when no COS is needed. Yet, a few authors reported better pregnancy rates after IUI in patients with high AMH levels [3, 34–37], and worse outcomes in patients with low AMH levels [38]. However, these works present several limitations. Many only consider the first attempt of IUI and are heterogeneous in its methods, lacking accurate control of confounding variables, especially regarding the study populations, which include male factor or different infertility diagnoses and/or treatment indications. In comparison, our study presents less risk of bias by being prospectively monitored and strictly including women not older than 42 years, without female infertility factors and using

sperm from donors for their IUIs. Additionally, in most studies, low AMH levels were strongly associated with advanced and very advanced maternal age; hence, the poorer pregnancy rates could have been due to age and not necessarily to AMH. In fact, advanced maternal age is an established independent negative prognostic factor for clinical pregnancy and live birth [46, 47], including the following IUI [48]. While our results did not demonstrate significantly higher cumulative clinical pregnancy rates in younger patients, it is noteworthy that the women who conceived following ds-IUI tended to be younger ($p=0.057$). Hence, increasing our sample size could potentially lead to achieving statistical significance.

On the other hand, diminished ovarian reserve (DOR) does not necessarily correlate with poor reproductive outcomes, despite the numerous controversial theories attempting to explain possible oocyte quality impairment associated with DOR [49–51]. These hypotheses suggest potential underlying mechanisms such as ovulation of higher-quality oocytes earlier in life, decreased ovarian support for folliculogenesis during IVF, and reduced euploidy rates in DOR. Yet, these theories remain unproven and are currently debated, with our findings not supporting them. Instead, extensive research suggests that coexisting factors with DOR, rather than the condition itself, impact oocyte performance and embryo quality. Extensive studies by the POSEIDON group and others show how reproductive outcomes are not directly affected by low ovarian reserve but by a range of possible coexisting factors [52–55]. Even young women who have undergone chemotherapy, experiencing DOR due to a gonadotoxic insult, seem to maintain age-appropriate oocyte competence [26, 56]. Therefore, current evidence does not support the existence of specific biochemical or molecular mechanisms in DOR compromising oocyte quality.

Our study emphasizes the inappropriateness of directly inferring a poor pregnancy prognosis to women with low ovarian reserve and therefore automatically dismissing the potential effectiveness of IUI in selected cases, indicating IVF at the outset given its high success rates in fertility clinics. In fact, DOR is a criterion for exclusion for access to IUI in many public programs over the world. However, in practice, many other factors must be taken into account when indicating ART techniques on an individual basis. IVF presents greater reproductive efficiency per cycle than IUI in infertile and elderly maternal populations and has the advantage of being able to freeze additional embryos. However, non-infertile women younger than 38–40 years of age with a male, female, or single infertile partner can benefit from starting ART with IUIs regardless of their ovarian reserve, as these treatments are less complex, less invasive, and less expensive. As these are essentially monofollicular cycles, the prognosis of this technique will depend on

oocyte quality, and therefore presenting low AMH should not be used as an exclusion criterion for non-infertile women seeking ds-IUI. Indeed, conversely, it could be argued that in women with a low ovarian reserve (AFC 2–3 or poor response criteria), the indication for IUI becomes more advisable because IVF would offer little probability of obtaining additional embryos for freezing, providing limited added benefit. Especially in younger patients without female infertility factors, whose oocyte quality is anticipated to be high, IUI should not be dismissed solely based on DOR since their outcomes may be comparable to those with normal ovarian reserve.

Further studies are essential to validate our findings, ensuring a comprehensive interpretation of ovarian markers and a consequent accurate prognosis and indications of ART in each clinical case. Moreover, notably, prospects for a novel trend in ART centered around oocyte-based approaches are emerging [57]. It seems crucial to investigate the influence of aging and molecular environment on oocyte quality, potentially being the main predictor for pregnancy success in the absence of COS. While clinicians should consider the results of this study when indicating ds-IUI, we believe that a deeper understanding of the mechanisms underlying oocyte competence will enhance overall reproductive outcomes in the future.

Conclusions

AMH is not a reliable predictor of pregnancy in non-infertile women undergoing ds-IUI. Even women with significantly low ovarian reserve can achieve successful outcomes after ds-IUI, which may be primarily influenced by oocyte quality. The findings of this multicenter study support the idea that low AMH levels should not limit access of non-infertile women to ds-IUI.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10815-024-03188-5>.

Acknowledgements We thank Ana Badia, nurse and clinical coordinator, for her patient work and technical assistance.

Author contribution MAC conceived the idea and directed the study. SGL participated in the study design as well as in the research plan and coordination, collected data, and wrote the manuscript. JMS and JSA collected data, participated in the literature review, performed statistics, and prepared the figures. MPO and ARC collected data. All authors had access to the data in the study and take responsibility for its integrity. All authors made significant contributions to this manuscript, reviewed its final version, and approved of this submission.

Data Availability Original data of this study is available upon request to the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

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