Predictive Value of AMH on Spontaneous Abortion: Systematic Review and Meta-analysis

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Research Article

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Abstract

Objective: To systematically evaluate the predictive value of anti-Mullerian hormone (AMH) in relation to spontaneous abortion (SA), taking into consideration the variables of age and conception mode.

Methods: We searched electronic database including PubMed, Embase, and The Cochrane Library databases for original researches that reported the relationship between AMH and SA, and four tables of diagnostic tests could be extracted.

Results: We included 15 qualifying studies, which demonstrated a significant relationship between shoulder meta shoulder on receiver operating characteristic (ROC) curve and the Spearman correlation coefficient of 0.800, with a p-value of 0.000. These findings indicates the existence of threshold effect. When fitting the summary receiver operating characteristic (SROC) curve, the resulting area under the curve (AUC) is determined to be 0.5263, while the Q index is calculated to be 0.5197. The study found that the sensitivity and specificity of AMH in predicting SA were 0.14 (95% CI: 0.13 – 0.15) and 0.81 (95% CI: 0.80 – 0.82), respectively. Based on the subgroup analysis conducted on age, it was found that the AUC for fitting the SROC curve in the younger group was determined to be 0.5514. Additionally, the Q index for this subgroup was calculated to be 0.5386. The AUC in the senior cohort was determined to be 0.5080, whereas the Q index was calculated to be 0.5060. Determining the method of conception, the heterogeneity subgroup analysis revealed that the odds ratio (OR) for natural conception was 1.78 (95% CI: 1.12 – 2.84), with a p-value greater than 0.05. The SROC curve for assisted reproductive technology is shown to be 0.5005, whereas the Q index is calculated to be 0.5004. The AUC by the International Union for Immunology (IUI) turns out to be 0.8214, while the Q index is measured to be 0.7553. The SROC curve was determined to be 0.5452, while the Q index yielded a value of 0.5339. The sensitivity analysis results demonstrate the robustness of the analysis findings. The Deeks funnel diagram does not appear to indicate any apparent presence of publishing bias.

Conclusions: The prognostic significance of serum AMH level for SA is not readily apparent. In the stratified study examining the relationship between age and conception mode, it was determined that AMH did not exhibit a strong predictive capacity for SA. Furthermore, it was concluded that a solitary instance of low AMH levels cannot be relied upon as a reliable indicator for assessing the likelihood of experiencing SA.

Introduction

Women's childbearing age is significantly impacted by urbanization, industrialization, and the growing awareness of gender equality[1]. Both the percentage of women working in social work and their earnings from that labor are rising. Postponing parenthood can help women in the labor market earn more money[2]. Therefore, in order to avoid the negative impact of childbearing on income, women tend to choose to postpone the age of first childbearing[3]. With the increase of age, women's fertility declines and the risk of miscarriage increases[4]. The decline of female fertility mostly stems from a reduction in both the quantity and quality of oocytes. AMH is a biomarker for estimating the number of eggs a woman has in her ovaries and predict how well she would respond to ovarian stimulation. AMH levels below 0.5 - 1.1 ng/ml suggest a decline in ovarian reserve function. However, more research is needed to determine if it can be reliably employed as a prognostic marker for clinical evaluation of SA[5]. The study conducted by Pils et al confirmed a correlation between a greater biological age with a lower AMH level and early pregnancy loss[6].Lyttle SB et al. colleagues discovered a correlation between higher levels of AMH and a reduced risk of abortion. Additionally, they observed that women with strongly diminished ovarian reserve function (AMH≤0.4 ng/mL) had an abortion rate more than double that of women with AMH≥1 ng/mL[7]. A retrospective investigation conducted by Cornille AS et al. assessed the prognostic significance of AMH level and age in relation to early abortion. The findings indicate that both AMH level and age are robust predictors of early pregnancy loss[8]. Nevertheless, there is a discrepancy in the findings about the prognostic significance of AMH as a potential indicator of SA. In their study, Ashley W. Tiegs et al.[9] discovered that there is no discernible distinction in either individual cycles or overall reproductive outcomes between patients with low AMH levels (< 1.0 ng/mL) and those with normal AMH levels (≥1.0 ng/mL) during intrauterine insemination (IUI). This finding holds true even after accounting for variations in IUI treatment strategy, the number of dominant follicles, and the patient's body mass index. The research primarily centers on the association between AMH and abortion within the context of assisted reproductive technology. However, there is a scarcity of prospective research on women who conceive naturally, which leads to a deviation in the assessment of AMH and raises doubts about the effectiveness of serum AMH as a predictor of SA. This systematic review and meta-analysis aimed to consolidate conflicting research to investigate the prognostic significance of AMH for SA in patients undergoing spontaneous pregnancy and assisted ART.

Method

The meta-analysis in this systematic review adhered to the PRISM standards and utilized the public de-identification data. As a result, this work was exempted from requiring permission from the institutional review committee[10].

Search strategy

Conduct a comprehensive search on PubMed, Embase, and The Cochrane Library to investigate the correlation between AMH and SA. Additionally, retrieve four tables containing diagnostic test results. The deadline for the search is December 2022. There are no limitations on the language used to search for materials. The technique of amalgamating subject terms with unrestricted terms is employed for information retrieval. The specified search terms are as follows:

1. Abortions OR Spontaneous OR Spontaneous Abortions OR Spontaneous Abortion OR Early Pregnancy Loss OR Early Pregnancy Losses OR Loss, Early Pregnancy OR Losses, Early Pregnancy OR Pregnancy Loss, Early OR Pregnancy Losses, Early OR Miscarriage OR Miscarriages OR Abortion, Tubal OR Abortions, Tubal OR Tubal Abortion OR Tubal Abortions

2. Anti-Mullerian hormone OR Anti Mullerian Hormone OR Mullerian-Inhibiting Factor OR Mullerian Inhibiting Factor OR Anti-Mullerian Factor OR Anti Mullerian Factor OR Mullerian-Inhibitory Substance OR Mullerian Inhibitory Substance OR Mullerian Inhibiting Hormone OR Mullerian Inhibiting Substance OR Mullerian Regression Factor OR Mullerian-Inhibiting Hormone OR Anti-Muellerian Hormone OR Anti Muellerian Hormone OR Hormone, Anti-Muellerian OR Antimullerian Hormone

Inclusion criteria

1. The research design employed either prospective or retrospective methods to investigate the correlation between AMH and SA. (2) The study included women who were conceived by ART or spontaneously, and the abortion rate was recorded for each group of women.(3) Obtain and document the serum AMH values for all participants, and establish a threshold value to distinguish between low and normal levels of AMH. This will allow for the classification of people into a low level group and a non-low level group based on their AMH levels.(4) In order to participate in the study, it is essential to possess sufficient data to create a 2×2 four-grid table that is mandated by the diagnostic test. This table should include the counts of subjects falling into the categories of true positive (TP), true negative (TN), false positive (FP), and false negative (FN) under the specified cutoff value. Alternatively, the sensitivity, specificity, number of cases, and report display can be provided. (5) Only the most recent studies with the greatest sample sizes will be included if multiple studies utilize the same or overlapping demographic data. (6) If the patients are identical, this meta-analysis can incorporate many trials with varying amounts of AMH.

Exclusion criteria

1. The data is insufficient, and it remains unfeasible to construct a four-grid dataset either from the original text or by contacting the author. (2) The objective of experimental research differs. (3) The records exhibit inconsistency in their categories, encompassing conference minutes, reviews, remarks, and animal experimental research, among others.

Data extraction and quality evaluation

Two evaluators independently reviewed the literature based on predetermined criteria for inclusion and exclusion. They assessed the quality of the included literature using the evaluation criteria of QUADAS for diagnostic accuracy studies. They also collected and cross-checked the data. If there is a disagreement, the two sides engage in negotiations to resolve the issue or seek the input of a third party. The retrieved data comprises fundamental literature material, research classifications, the AMH cut-off value (with a conversion formula of 1ng/mL=7.14 pmol/L), the AMH determination method, the number of true positives, false positives, true negatives, and false negatives, among other details[11].

Statistical analysis

The meta-analysis utilized Meta-DiSc 1.4 software, revman5.3 software, and STATA 17.0 software, as indicated by the analysis. Heterogeneity in diagnostic tests is often attributed to the threshold effect, which is a significant factor[12]. The ROC curve is generated using Meta-DiSc 1.4 software. The Spearman correlation coefficient is computed between the logarithm of sensitivity and the logarithm of (1-specificity) to assess the presence of a threshold effect. If a distribution plan follows a "shoulder-to-arm" pattern and the Spearman correlation coefficient shows a significant positive correlation ($P < 0.05$), it suggests the presence of a threshold effect[13]. Compute the area under the SROC curve, the AUC and the Q index if a threshold effect is present. If a threshold effect is absent, the calculation involves determining the area under the SROC curve, the AUC and the Q index. Additionally, the combined values of sensitivity, specificity, negative likelihood ratio, positive likelihood ratio, and diagnostic odds ratio are computed. The Chi-square test was employed to assess the presence of heterogeneity, excluding the threshold effect. Additionally, the I^2 statistic was used to quantify the extent of heterogeneity. The significance criterion for the meta-analysis test is α=0.05 [14]. To further investigate the predictive significance of AMH on spontaneous abortion based on age stratification, the study population was separated into two groups: a young group and an old group, with an age boundary of 35. Meta-analysis was conducted separately for each group. Heterogeneity analysis was conducted based on the conception mode of the individuals to see if there are variations in the risk of SA between natural conception and assisted reproductive technology methods such as intrauterine insemination, fresh embryo transfer, frozen embryo transfer, etc. Utilizing the STATA 17.0 program to generate a Deeks funnel plot for the purpose of assessing the presence of publication bias. Conducting a sensitivity study to determine the robustness of the evaluation results.

Document retrieval results

A comprehensive search was conducted on PubMed, The Cochrane Library, Embase, and Web of Science databases, resulting in a total of 774 publications. After eliminating duplicate articles, 477 articles were retained. After a meticulous examination of the themes and abstracts, a total of 71 documents were initially selected. Out of these, 38 documents were either conference abstracts or their original text could not be located. Additionally, 3 papers were reviews, and 15 documents did not have 2×2 four-grid tables that could be extracted. Finally, 15 original documents were included (Fig.1).

Basic characteristics and quality evaluation of included research

The 15 studies were categorized into two groups based on the level of AMH: the low-level group and the normal group. The analysis incorporated two prospective investigations and 13 retrospective cohort studies. Out of the total, 5 documents analyze the topics in various age cohorts with a threshold of 35 years, while 2 documents specifically examine young females below the age of 35. Furthermore, among the publications, one focused exclusively on natural pregnancy, another addressed both natural pregnancy and ART, while the remaining 13 articles exclusively explored ART. Specifically, these 13 studies comprised 9 cases of intrauterine insemination (IUI) and 10 cases of embryo transfers, consisting of 9 fresh embryos and 2 frozen embryos(Table 1).

We employed the Quadras-2 tool, which was supplied by Revman5.3, to assess the caliber of the literature that was included. The scale comprises four components: case selection, trials to be evaluated, gold standard, and case flow and progress. Each component of the question has three possible answers: Yes, No, or Uncertainty. If all the responses to the significant inquiries in this section are affirmative, they can be classified as having a low bias risk. Conversely, if the responses are negative or unclear, it suggests the potential for bias. Unclear signifies that there is insufficient information available from the original literature to evaluate the significant inquiries(Fig. 2).

Table 1 Summary of the characteristics of the included studies.

Author (year), country	Age range	Design	Characteristics of included subjects	Natural conception/ART	AMH examine			
					AMH assay	AMH threshold	TP	FP
Lyttle Schumacher et al(2018)America	30-44	Prospective cohort study	Enrolled women between the ages of 30 and 44 years who were trying to conceive naturally.	Natural conception	Ul-trasensitive AMH ELISA	1ng/mL	24	48
Liu et al (2022)China	20-46	retrospective cohort study	2246 infertile women who underwent their first in vitro fertilization/intracy-toplasmic sperm injection (IVF/ICSI) treatment in the reproductive centre of Tianjin Central Hospital of Gyne-cology Obstetrics	IVF/ICSI with ET	ELISA	1.6ng/mL	60	185
Semih Kaleli et al(2022)Turkey	20-39	retrospective study	The study was carried out on a total of 770 cycles of 362women in an infertility cohort that consisted of 75 women with DOR treated by 153 cycles and 287 women without DOR treated by 617 cycles.	IUI	ELISA	1.2ng/ml	1	16
Dai et al (2020)China	>36	retrospective study	The patients included in this study who received IVF/ ICSI/ET treatment in the reproductive centre of Changzhou Maternal and Health Care Hospital contributed a total of 492 IVF/ICSI cycles (from January 2017 to July 2020) and these IVF cycles-contributed 292 ET cycles.	IVF/ICSI/ET	-	1.1ng/ml	11	24
Stylianos Vagios et al(2021)America	-	retrospective study	All cycles derived from women who underwent ovarian stimulation with gonadotropins coupled with an IUI at Massachusetts General Hospital Fertility Center between November 2007 and March 2019 were evaluated for inclusion in the study	IUI	-	0.7ng/ml	11	26
Alison Richards et al (2021)Britain	36.9 ± 3.8	retrospective study	all single, fresh embryo transfers had an AMH less than 25 pmol/l between 1	IVF/ICSI	-	0.76ng/mL(5.4pmol/l)	45	64

			January 2010 and 31 December 2016 was undertaken					
Tiegs et al (2020)America	20-35	retrospective cohort study	all subfertile couples with female patients <35 years of age undergoing IUI cycles at a single large infertility center between 2001 and 2018. Both natural and stimulated cycles followed by IUI were included.	IUI	electrochemiluminescence immunoassay	1ng/mL	19	66
Zhang et al (2019)China	20–51	single-center retrospective cohort study	women who underwent their first IVF cycles. Of 9431 women, 7283 women of reproductive age were young (< 35 yr), and the other 2148 were at an advanced age (≥35 yr).	IVF	ELISA	1.32ng/ml/0.62ng/ml	176	119
Catherine et al(2019)Australia	-	prospective cohort study	Recurrent embryonic miscarriage patients attending a RM clinic between June 2008 and May 2014 were included.	spontaneously or by ART	DSL AMH generation II method	1.4ng/ml(10pmol/L)	29	37
LI et al (2018)China	18–40	retrospective analysis	A total of 828 non-polycystic ovary patients that underwent their first frozen-thawed embryo transfers in our center between January 2010 and January 2015 were recruited in this retrospective analysis.	FET	ELISA	1.4ng/ml	21	45
Bruno Tarasconi et al(2017)Brazil	19-45	Cohort study	A total of 1,060 patients who attained a clinical pregnancy after IVF-ET	IVF-ET	ELISA	1.60 ng/mL	45	107
Nigel Pereira et al (2016)America	<35	retrospective cohort study	All fresh IVF cycles initiated at the Ronald O Perelman and Claudia Cohen Center for Reproductive Medicine between January 2010 and July 2013 resulting in ET	fresh IVF-ET	ELISA	1ng/mL	27	195

			were analyzed for potential inclusion.					
Lin et al (2014)Taiwan	≤35	Retrospective cohort study	70 young women (< 35 years of age) with low level of serum AMH (< 2 ng/ml) and 104 young women with level of serum AMH (≥ 2 ng/ml) who underwent IVF/ICSI cycles between January 2011 and November 2012 were enrolled.	ART-ET	enzymatically-amplified two-site immunoassay	2ng/ml	4	49
Lekamge et al (2007)South Australia	19-41	retrospective observational study	The present study measured baseline concentrations of serum AMH and FSH, and AFC from 126 women undergoing IVF treatment	IVF	ELISA	1.96ng/ml(14 pmol/l)	5	12
Keane et al (2017)Australia	22–48	Retrospective cohort study	This retrospective study conducted at PIVET Medical Centre examined pregnancy and birth outcomes of 1425 IVF treatment cycles with AFC and AMH measurements along with a fresh transfer, from a total of 3505 initiated cycles conducted over a period of approximately 7.5 years	IVF-ET	ELISA	0.7ng/ml(4.9 pmol/L)	24	48

Results

Eleven articles are evenly distributed over the ROC curve, and the Spearman correlation coefficient is 0.800, with a p-value of 0.000, indicating the presence of a threshold effect. The SROC curve was fitted, resulting in an AUC of 0.5263 and a Q index of 0.5197 (Fig. 3A). The predictive accuracy of AMH in determining the occurrence of SA is characterized by a sensitivity of 0.14 (95% CI: 0.13 ~ 0.15) (Fig. 3B) and a specificity of 0.81 (95% CI: 0.80 ~ 0.82)(Fig. 3C).

Subgroup analysis carried out based on age, and a total of 7 studies included participants from the younger group(n=8321)[9][15][16][17][18][19][20]. The AUC of SROC curve is 0.5514, and the Q index is 0.5386 (Fig. 4B). The elderly group was included in 5 studies(n=3899)[15, 16, 18,20].The AUC of SROC curve is 0.5080, and the Q index is 0.5060 (Fig. 4B).

Two studies on natural pregnancy were conducted, and the heterogeneity subgroup analysis was performed based on the method of conception(n=548)[7] [15], OR=1.78(1.12 , 2.84), $P > 0.05$(Fig. 5A). There are 14 studies on assisted reproductive technology(n=15748) [9, 15-27]. The AUC under SROC curve is 0.5005 and the Q index is 0.5004 (Fig. 5B).Among them, there are 3 IUI studies(n=1039) [16, 17, 23], the AUC under SROC curve is 0.8214, and the Q index is 0.7553 (Fig. 5C). There are 11 studies on embryo transfer (n=14709)[15, 17-22, 24-27]. The AUC under SROC curve is 0.5452 and the Q index is 0.5339 (Fig. 5D).

Sensitivity analysis

Sensitivity analysis was used to assess the influence of a single study on this meta-analysis by reducing each article one at a time. The combined DOR remained generally stable after excluding any number of papers, indicating that the study's conclusions about the predictive power of AMH for ovarian reactivity and clinical pregnancy rate were not overly influenced by any one study (Table 2).

Publish biased assessment

Deeks' funnel plot shows that all points are basically symmetrically distributed on both sides of the tropic of cancer, and Deeks' test is P=0.87, suggesting that the included literature has no obvious publication bias (Figure 6).

Table 2 Sensitivity analysis.

Literature	DOR	95%CI
Lyttle Schumacher, B.M	1.33	1.12 to 1.59
Liu, X	1.38	1.14 to 1.67
Kaleli, S	1.36	1.15 to 1.62
Dai, X. L	1.38	1.16 to 1.64
Vagios, S	1.33	1.12 to 1.58
Richardson, A	1.40	1.17 to 1.67
Tiegs, A. W	1.39	1.17 to 1.66
Catherine D	1.37	1.14 to 1.64
Li, X. L	1.31	1.11 to 1.54
Tarasconi, B	1.29	1.10 to 1.52
Pereira, N	1.40	1.18 to 1.66
Lin, P. Y	1.36	1.14 to 1.62
Lekamge, D. N	1.35	1.13 to 1.60
Keane, K	1.31	1.11 to 1.54
Zhang, B. Q	1.38	1.13 to 1.69
Zhang, B. Q	1.35	1.13 to 1.62

Discussion

Delay in childbearing age and declining fertility have become increasingly prominent issues. One of the more challenging issues in reproductive health is the irreversible loss in female fertility,which is a key element influencing SA. The risk of SA after pregnancy increases as women age because their ovaries generate fewer collected follicles, lower-quality eggs, and a reduced capacity to produce high-quality oocytes. Age of the female has a substantial link with the likelihood of abortion and is an independent risk factor impacting fertility and pregnancy outcome. Women between the ages of 20 and 29 have the lowest abortion risk, accounting for 12%, while women over 45 have the highest risk,accounting for 65%. The age-related rise in trisomy frequency is thought to be the cause of this association[21]. It is discovered that abnormalities in the embryonic chromosome account for at least half of early SA cases, with older women more likely to have these abnormalities[22][23].The most frequent reason for abortions is trisomy in the embryo. While the risk of other trisomies typically rises rapidly around the age of 35, the risk of trisomy 16 increases linearly from 20 to 40 [28].Around the age of 35, women's natural fertility starts to wane, and infertility typically sets in many years before menstruation totally stops. The loss of natural fertility brought on by postponing childbearing cannot be made up for by ART, despite the fact that it can assist certain couples with infertility issues. It is well accepted that ovarian reserve function may be a good indicator of future fertility and that oocyte quality appears to decrease with age. According to studies conducted on IVF oocytes, the rate of oocyte aneuploidy rises with age. In women under 35, the rate is modest (10%), but it rises to 30% at age 40, 40% at age 43, and 100% in women over 45 [24].To reflect the function of the ovarian reserve, one can use an ovarian reserve test, an ultrasonic measurement, and basic hormone levels. AMH inhibits the early stages of follicular development and is generated by granulosa cells found in preantral and tiny antral follicles. Research has demonstrated that AMH is more sensitive and responsive in the early stages of ovarian function decline, and that it can accurately reflect the number of follicles in non-gonadotropin-dependent stages. It also exhibits good stability throughout the menstrual cycle and across weeks, and it is largely unaffected by objective factors like patients and testers[25].The AMH index of women varies with age; the serum AMH level peaks in adolescence, between the ages of 23 and 25. After that, the level declines with age, declining by roughly 5.6% annually until the menopausal women's AMH level falls or becomes virtually undetectable, which may indicate a shifting correlation between the serum AMH level and ovarian reserve function. In addition to pathogenic variables including genetics, immunology, iatrogenic factors such pelvic surgery, radiation, and chemotherapy, as well as unhealthy lifestyle choices like smoking, ovarian reserve function may decline physically with age.According to Zhang Chunxiao et al. 's[26] literature review, there is a strong positive correlation between the amount of ovarian reactivity and the number of recovered oocytes and the change in serum AMH level. Serum AMH levels with a critical value of 3.21ng/ml had a 94% sensitivity for determining a patient's poor ovarian reactivity, an 88% specificity for diagnosis, and an area under the ROC curve of approximately 0.947.According to findings from other studies, ovarian reserve function can be more accurately determined by AMH level than by FSH index when 8.1 pmol/L is used as the crucial threshold[27]. According to a study, the median amount of serum AMH is 22 pmol/L, while normal values for French women of reproductive age in the first trimester are approximately 2.42 ng/mL[28, 29]. This discrepancy may be caused by race, which should be considered when interpreting AMH value. The age-related drop of Chinese women is even more pronounced than that of European women, with a decrease of 30% and 45% for women aged 28 and 80, respectively, despite the fact that the peak

level of AMH in Chinese women at 25 is higher than in European women[30]. Furthermore, compared to white women, African-American women appear to have lower serum AMH levels, but their age dependence diminishes[31, 32]. AMH was revealed to have a role in the process of threatening abortion as evidenced by the dropping blood AMH level in these patients and the subsequent decrease in its expression level with the occurrence of pregnancy failure. The increase of AMH expression may promote the expression of endothelial tissue factor, enhance the recruitment of neutrophils, and further promote the formation of threatened abortion in early pregnancy[33]. Whether an AMH level has prognostic significance for SA is still up for debate. Certain writers have demonstrated a connection between pregnancy loss and low AMH levels. For example, in 2017, Pils et al.[6] confirmed that 62% of women with very early abortion showed low AMH level (≤1 ng/mL). A meta-analysis [34] found that low AMH (< 1.1 ng/ml, RR 3.66, 95% CI 2.1-6.4, P<0.001) significantly increased the risk of miscarriage in the first trimester of pregnancy. Serum AMH could be a useful indicator for estimating the likelihood of an early abortion. According to Bruno et al. [18], patients with lower serum AMH levels had a significantly higher abortion rate. The Box-Tidwell test also confirmed that the abortion rate was present in all age groups and that the impact of AMH on the rate (OR 0.92, 95% CI 0.87-0.98) was unaffected by age (OR 1.08, 95% CI 1.03-1.12). It was discovered in Keane[27] that patients with low AMH levels had the highest abortion rates, and that age dependence rose. The incidence of abortions increased with age. Some authors, on the other hand, contend that there is no clear connection between AMH and miscarriage. A meta-analysis, for instance, found that while AMH level can predict ovarian responsiveness in controlled ovarian hyperstimulation, it cannot increase the incidence of pregnancy or live births. This was determined by reevaluating 20 randomized controlled studies[35]. According to Zarek et al. [36] clinical abortion following a spontaneous conception is unrelated to serum AMH levels. Although AMH concentration is thought to have a function in SA, this investigation found no correlation between clinical pregnancy loss and low (< 1.0 ng/mL) or high (> 3.5 ng/mL) levels of AMH. Thus, more research is required to determine the predictive usefulness of blood AMH level in SA.

Through the creation of a diagnostic experiment AMH could not be used as an effective biological index to predict whether abortion occurred, but it could be used as a screening index for healthy individuals, and a normal level of AMH had a low risk of abortion, according to a meta-analysis of this study's data on the sensitivity and specificity of AMH in predicting spontaneous abortion, which were 0.14 (0.13-0.15) and 0.81 (0.80-0.82). This is in line with the findings of Semih's research [16], which examined the pregnancy outcome of IUI cycles and discovered that there was no variation in the abortion rate across all AMH levels or between women under 35 and those over 35. After IUI, ovulation induction and pregnancy cannot be predicted by female age or AMH. AMH should not be utilized as a measure of oocyte quality, according to Dai et al. [22], who also believe that the hormone has a limited impact in predicting the development potential of embryos in vitro but no role in predicting the development potential of embryos in vivo. In a similar vein, women with AMH < 5.41 pmol/L and women with AMH ≥5.41 pmol/l showed no discernible difference in the rate of biochemical pregnancy or abortion (41.3% vs. 41.6%, *P*=0.809) in the trial conducted by Alison Richards et al. [23].

The primary cause of study heterogeneity is the threshold effect, which is brought about by various articles' use of distinct diagnostic cutoff values. The updating of test technology and diagnostic technique iterations can lead to changes in the diagnostic cutoff value of the same reagent, conversely, various reagents can detect the same diagnostic test. As a result, it is unavoidable that different publications would have varied diagnostic criteria. As a result, before doing any data analysis, we determine whether a threshold effect exists between the studies. There is currently no agreed-upon threshold for low AMH levels in clinical settings, despite the fact that AMH is frequently utilized to indicate ovarian reserve and forecast ovarian stimulation response. Research indicates that a threshold AMH value of 1.211 ng/mL would be a fair middle ground for differentiating between women with normal ovarian function and those with dysfunctional ovarian reserves[37]. There was a threshold effect among the various studies in this meta-analysis since the included articles established different low AMH level cut-offs (0.7-2 ng/mL) and used different AMH detection reagents. As a result, we use the SROC approach to thoroughly assess the evaluation test's prediction accuracy. This study approach is more accurate since it considers the possibility that the diagnostic efficacy may be impacted by the various AMH cut-off values chosen by various studies. The threshold effect study revealed a Spearman correlation coefficient of 0.800, p=0.000, indicating that varying thresholds were the primary cause of the variability of spontaneous abortion in AMH. Certain research employ the best threshold rather than predetermining it, which could lead to an accuracy inaccuracy in the predictions. According to some research, the SA rate is highest (IRR, 2.1 95% CI 1.1, 3.9) when the outcome of the abortion is at the extreme value of AMH level, that is, AMH is below the 10th percentile (0.4 ng/mL). Additionally, Lyttle et al. [21] showed that among women under 35, those with AMH < 0.4 ng/ml had a 2.3-fold increased incidence of abortion compared to women with AMH ≥1 ng/mL. However, we are unable to conduct a meta-analysis and assess the connection between abnormally low AMH and SA because of the paucity of original research on additional stratification of low AMH level.

Heterogeneity can result from the threshold effect as well as from the selection of various populations and variations in the caliber of the investigation. Age-stratified subgroup analysis yields essentially identical results, with no discernible good predictive value. In order to fit the SROC curve, the young group was included in the study. The Q index was 0.5386, the AUC was less than 0.6, and the AUC was 0.5514. As a result, it is thought that AMH has no prognostic value for spontaneous abortions in young women. A low serum AMH level does not guarantee a poor pregnancy result for young women. It is not sufficient to demonstrate that the quality of follicles influences the result of pregnancy, rather, the low AMH level may represent a decline in follicles and have some bearing on the pregnancy rate. The AMH level is typically at a normal level, indicating that some older women still have great fertility possibilities in terms of ovarian function reserve, and that their pregnancy outcome and fertility potential are good. The physiological characteristics of older women determine the deficiency of ovarian function itself. However, the AMH has no valid prognostic value in this group, and the computed AUC and Q index for older women in this research are 0.5080 and 0.5060, respectively. According to Dai et al. [22], AMH should not be utilized to determine the quality of oocytes in older women. Regardless of age, AMH level cannot be utilized as a reliable indicator to predict SA in this trial. The outcomes of earlier research on the predictive significance of AMH for pregnancy following in vitro fertilization and embryo transfer support it. Although ovarian reserve and reaction do not influence the expected ability of a particular embryo, it is thought that a low AMH level is preferable to low egg quality. Despite this, there is some clinical utility for using low AMH levels as a routine screening tool for women undergoing reproductive treatment[38, 39]. Normal ovulation and high-quality oocytes may be more important in SA than the quantity of ovarian reserves.

One of the main challenges to fertility nowadays is the deterioration of ovarian reserve function. To achieve conception in patients with reproductive needs, ART such as artificial insemination, in vitro fertilization-embryo transfer, and its offshoots are required. With all forms of assisted reproductive technologies,

the quality of follicles and their ability to form high-quality embryos vary, and after women take ovulation-promoting drugs, their ovarian responsiveness varies due to differences in ovarian reserve function. These variations also affect the final pregnancy rate and pregnancy outcome. Prior research has indicated that the causes of SA during an assisted reproductive technology pregnancy are numerous and varied, with a rate of approximately 10~20% both domestically and internationally. The factors could include the age of the expectant mothers, the amount of medication used to induce ovulation, ovarian function, embryonic chromosomes, and more[40, 41]. As a result, by integrating naturally pregnant women and doing prospective experimental research, it can more accurately reflect the association between AMH and SA. However, gathering data on naturally pregnant patients in a clinic and maintaining follow-up might be challenging. Furthermore, there was an increase in the percentage of pregnant women with lower AMH levels, and the majority of the literature that was retrieved concentrated on examining the predictive role of AMH in SA incidence in women on antidepressant therapy. The total DOR value of the natural conception study was 1.78 (95%: 1.12, 2.84), and the chance of SA at low AMH level was 1.78 times higher than that at normal or high AMH level, according to the heterogeneity subgroup analysis of conception mode. In patients with natural conception, low AMH may be associated with the development of SA; further experimental research is required to confirm this. According to the SROC curve fitted by ART's conception, AUC is less than 0.6, Q index is 0.5004, and AUC is 0.5005. It is believed that there is no prognostic value for spontaneous abortions caused by ART in AMH. The IUI research exhibits a good prediction value, as seen by its AUC under the SROC curve of 0.8214 and Q index of 0.7553. On the other hand, the area AUC under the SROC curve fitted by embryo transfer is 0.5452 and the Q index is 0.5339, indicating no predictive value. It is believed that the serum AMH level has no bearing on the quality of oocytes, has little bearing on the potential for embryonic development in vivo, and has no bearing on the clinical pregnancy outcome of in vitro fertilization. This is based on the correlation between ART and spontaneous abortion. On the other hand, AMH measurement reflects the ovarian reserve function of patients prior to ovulation induction cycle, but it cannot predict the occurrence of SA. Consequently, it is not advised to regularly check for AMH in order to forecast SA.

In conclusion, a low level of AMH is not regarded as a predictor of SA for screening purposes in order to prevent overtreatment, nor can it be used as a basis for predicting the risk of SA. In diagnosing ovarian status, however, AMH is more useful than estrogen level. It also somewhat reflects women's fertility and may be a useful guide for helping women conceive, creating customized ovulation promotion plans in clinics, minimizing ovarian overstimulation, and lessening the financial burden on patients. Larger-scale epidemiological and clinical investigations are required to further validate the aforementioned conclusions because of the limitations in the amount and quality of included studies.

Declarations

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Author contributions RY, DL, CL, and XH wrote the manuscript. XF took charge of the examination and modification of articles. RY, DL, and CL revised the manuscript.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there are no conflicts of interest.

Ethical approval No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication.

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Figures

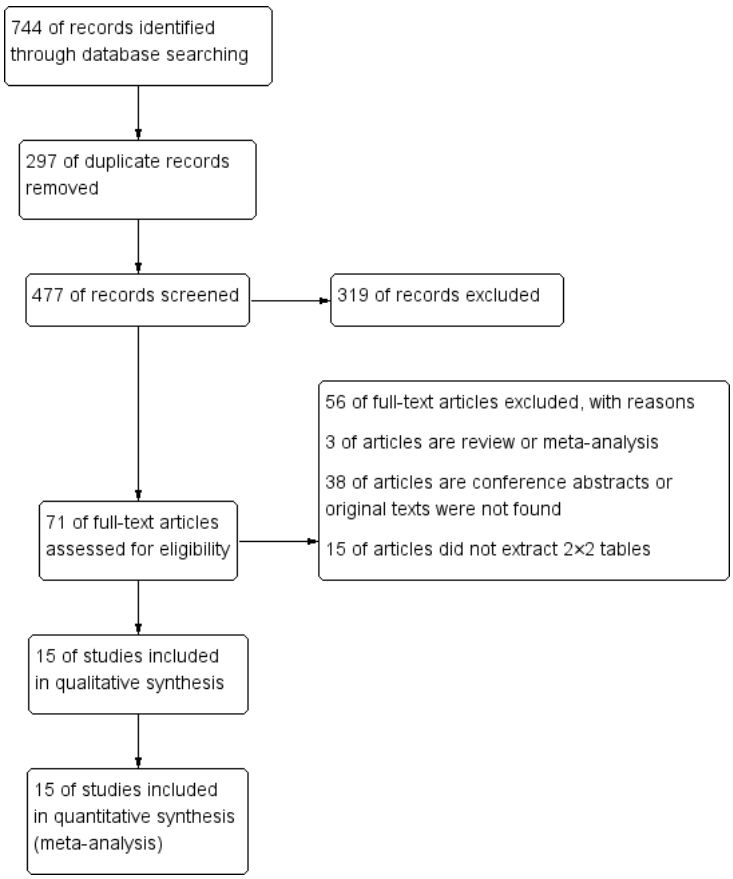

Figure 1

Flow chart of study identification and inclusion.

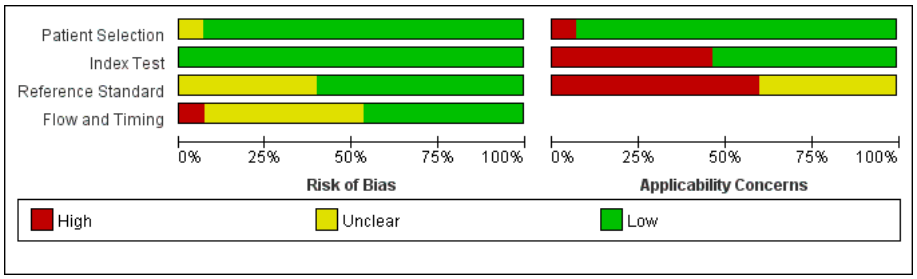

Figure 2

QUADAS criteria for included studies.

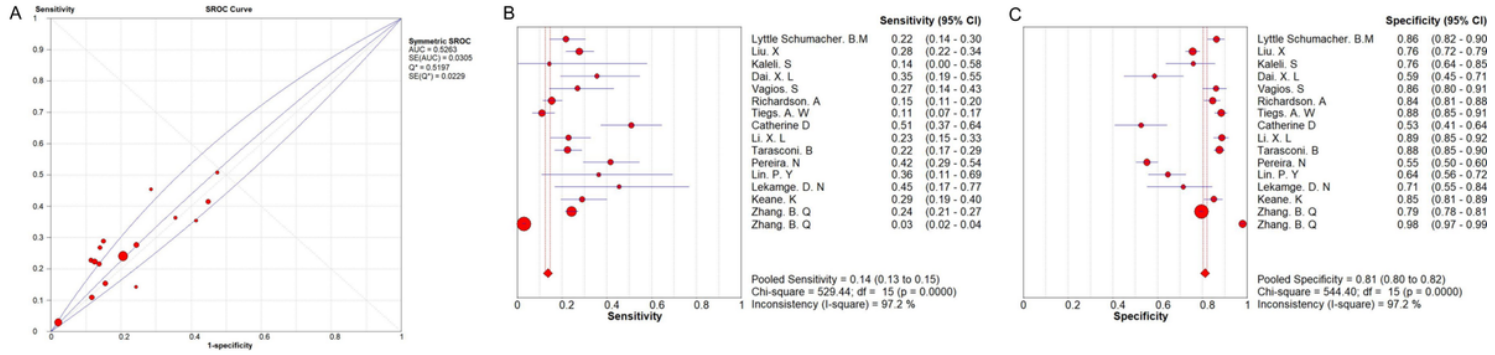

Figure 3

Receiver operating curve analysis of AMH for prediction of SA.(A), AMH predicts SROC curve of SA,Sensitivity (B) and specificity (C) of AMH to SA prediction forest map.

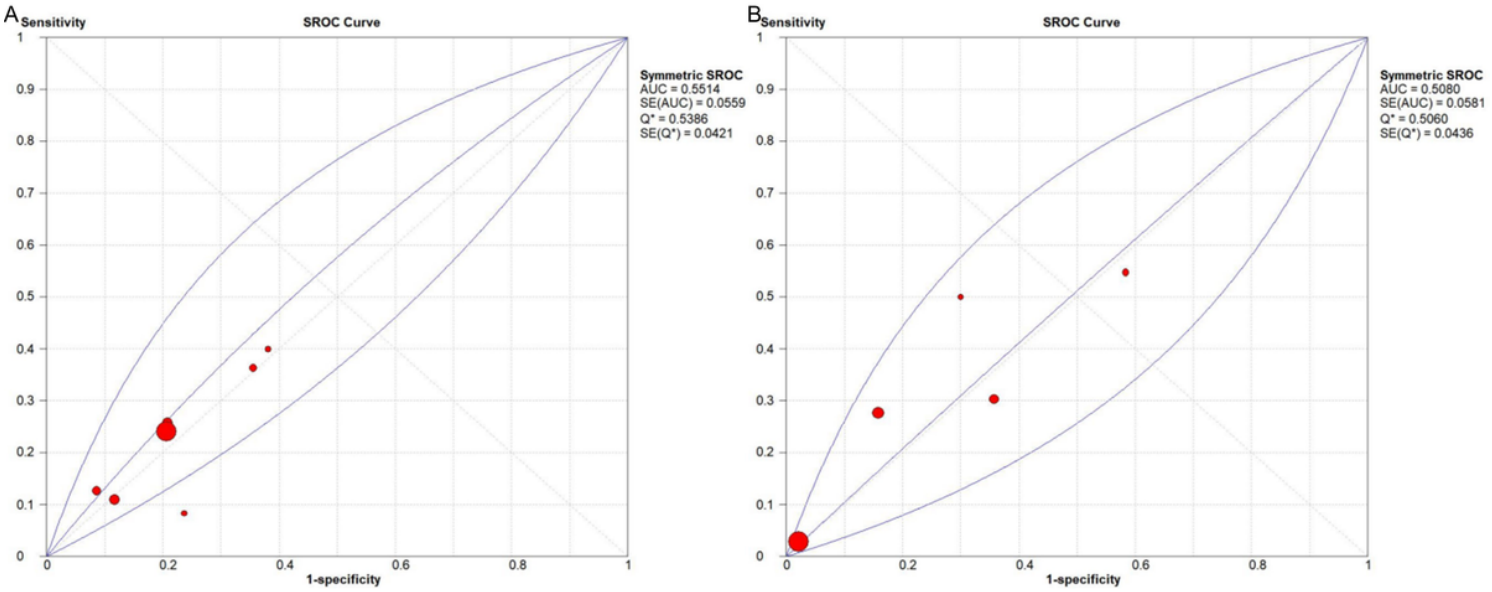

Figure 4

The influence of age on AMH's prediction of SA. (A) The young group AMH predicts the SROC curve of SA. (B) The old group AMH predicts the SROC curve of SA.

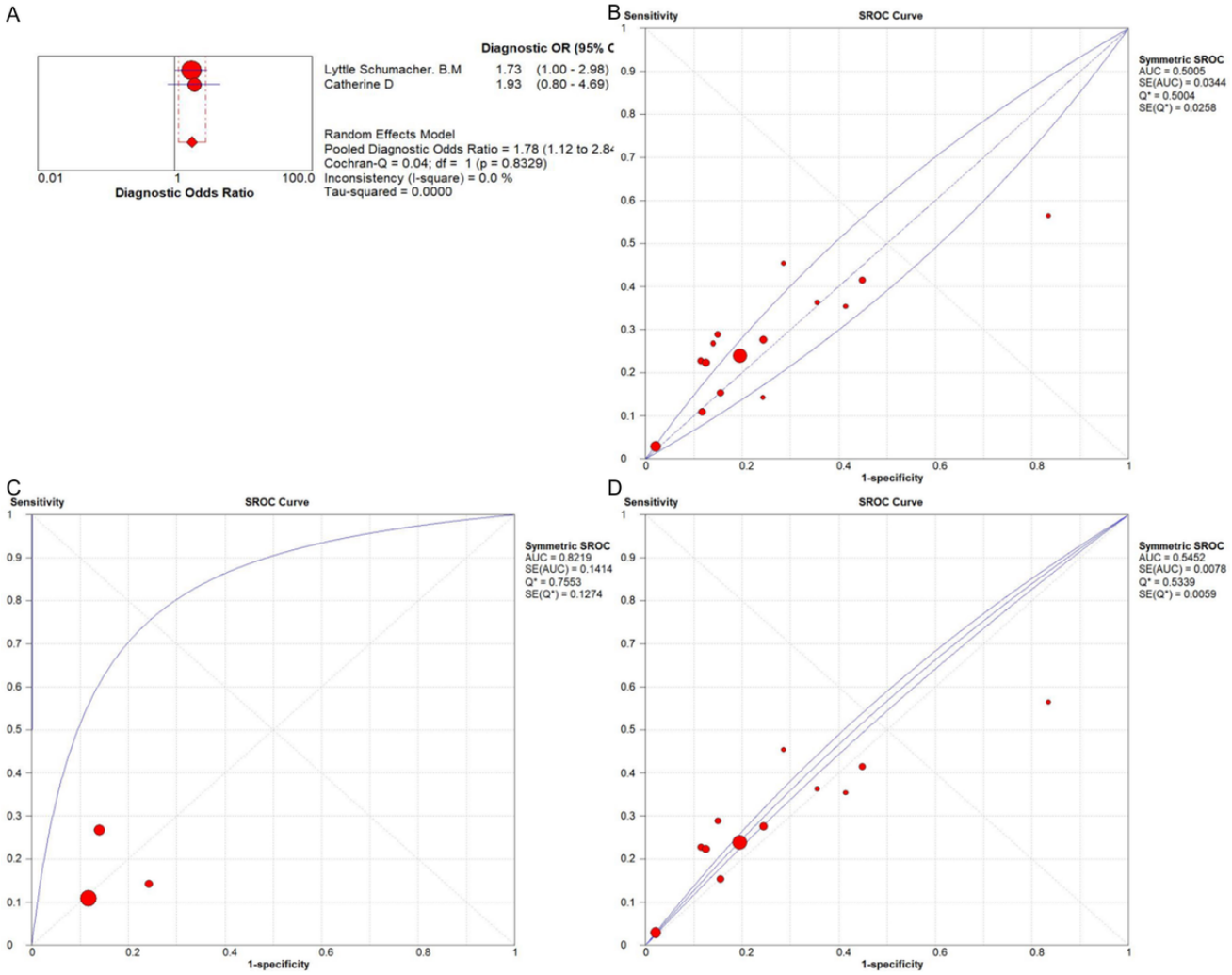

Figure 5

Effect of conception mode on AMH predicting SA. (A) DOR value of SA in naturally pregnant women is predicted by AMH. (B) The SROC curve of AMH predicting SA in ART group. (C) The SROC curve of AMH predicting SA in IUI group.(D)The SROC curve of AMH predicting SA in IUI group.

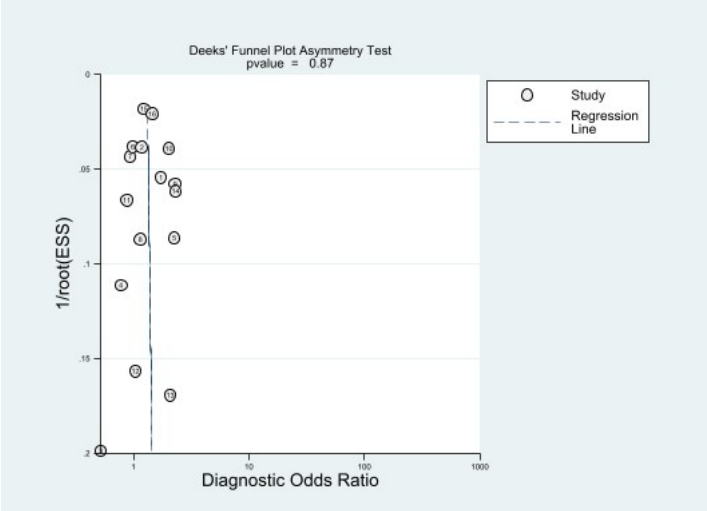

Figure 6

Publish the Deeks funnel chart of bias risk.