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Original Article

The role of serum AMH and FF AMH in predicting pregnancy outcome in the fresh cycle of IVF/ICSI: a meta-analysis

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Abstract: Purpose: This meta-analysis tries to find and confirm the true prognostic value of serum AMH and the follicle fluid AMH (FF AMH) on the outcome of ART. Method: We identified all studies published by March 2014 with data related to in vitro fertilization", "intracytoplasmic sperm injection", "assisted reproductive technology" and "antimullerian hormone" in Pubmed database. Studies were included if 2 × 2 tables for outcomes of pregnancy in IVF patients in relation to AMH could be constructed or studies which used T-tests to compare clinical indexes including AMH in pregnant and non-pregnant women. And all the patients were less than 46 years old. Results: A total of 26 studies could be used for this meta-analysis. Of these articles 22 studies could be constructed 2 × 2 tables, with 15 for predicting pregnancy and 7 for non-pregnancy. 11 studies used the analysis of T-test, with 7 articles were duplicated. And of the 11 articles, 8 were for the analysis of serum AMH in prediction of pregnancy, 3 were for FF AMH. Because of heterogeneity among studies, calculation of a summary point estimate for sensitivity and specificity was not possible. For the analysis of serum AMH on non-pregnancy, the heterogeneity was moderate (I-squared of 65.9%), the curves indicated positive find (the AUROC is 0.73, 95% CI is 0.69-0.77.). In the T-test group of serum AMH, the DOR for women with pregnancy outcome was 0.232 (95% confidence interval (CI): 0.034-0.43), with less heterogeneity (I-squared of 45.1%). Unfortunately, the predictive value of FF AMH on pregnancy is still unclear because of large heterogeneity (I-squared of 90.5%). Conclusion: Serum AMH, as an independent parameter, can predict pregnancy outcome after assisted conception and the positive correlation with serum AMH and non-pregnancy should not be ignored either. The predictive value of FF AMH on pregnancy is still unclear.

Keywords: Anti-Mullerian hormone, Pregnancy, IVF, ICSI, meta-analysis

Introduction

According to WHO, infertility will become the third disease following tumor and cardiovascular disease. In recent years, as the global human fertility decreased, which may be caused by the quick pace of life, environmental pollution, the change of diet structure and increasing giving birth age of woman, many couples need to get pregnancy with the help of assisted reproductive technology. Considering the high cost and the possible complications of ART, exploring some parameters which could predict the outcome of ART is of great value, the uncertainty of the outcome of ART procedures can also be minimized. Although some evidences show that age is the primary determinant of in vitro fertilization (IVF) success [1, 2], the relationship between a woman's chronological age and her reproductive capacity is highly variable [3]. In addition, some traditional parameters including biochemical and ultrasonographic markers such as FSH, estradiol (E2), inhibin B (INH-B), antral follicle count (AFC), and ovarian volumes, have been proved to have their own limits. The biochemical values are usually influenced by the menstrual cycle and have limited use for predicting poor and high responders. And the accuracy of ultrasonographic markers are usually affected by interobserver variation [4-7].

Anti-Müllerian hormone (AMH), a dimeric glycoprotein belonging to the transforming growth factor-β (TGF-β) family, is produced by fetal Sertoli cells at the time of testicular differentia-

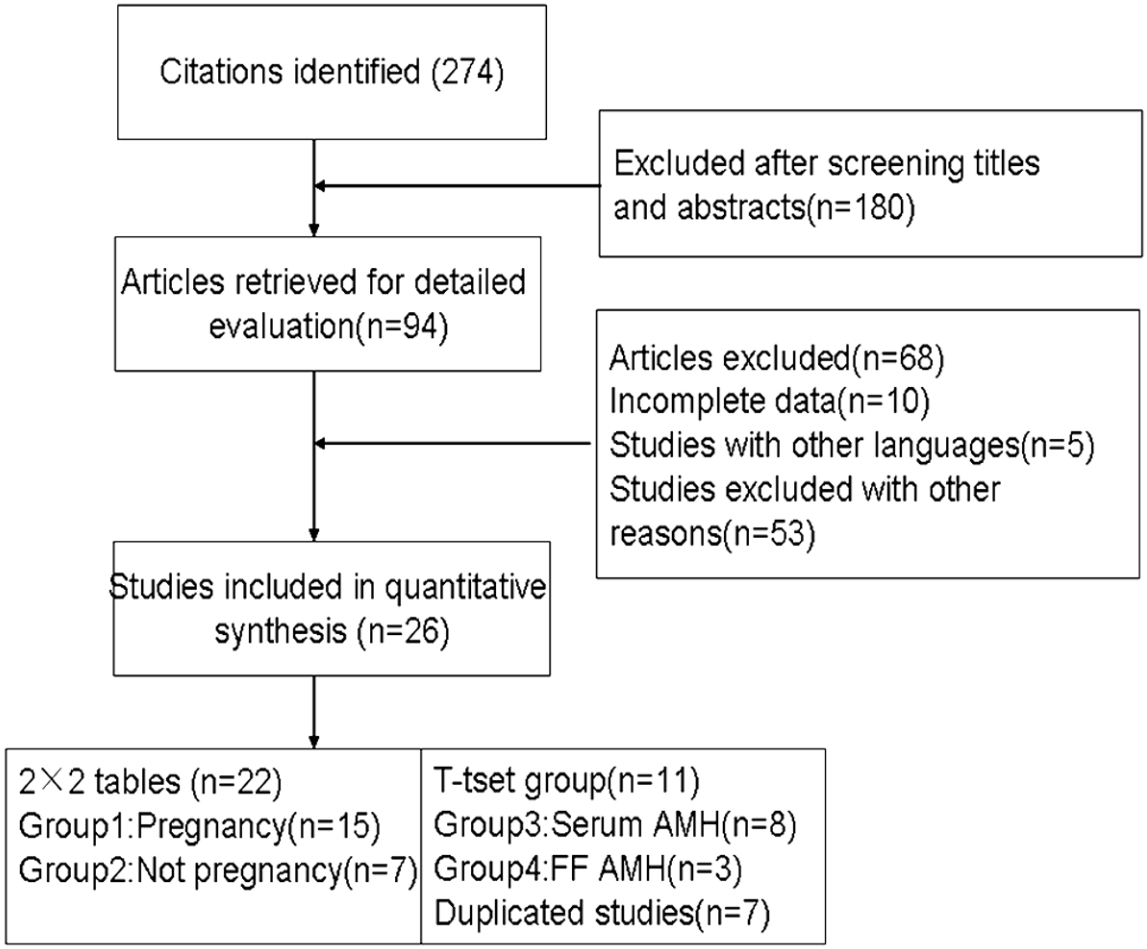

Figure 1. Flow chart of study selection in review of the effect of AMH on prediction of the outcome of IVF/ICSI.

tion, and induces regression of the Mullerian ducts. In women, it is secreted by granulosa cells within preantral and early antral follicles, < 6 mm in diameter [8]. AMH is barely detectable at birth, and its level peaks at puberty and steadily decreases until menopause when its level becomes undetectable [9]. Recently, AMH was studied as a new marker in ART areas. The results of some studies suggested that AMH was an accurate marker for the occurrence of poor response to ovarian hyperstimulation with gonadotropins in IVF [10, 11]. Whereas the vast majority of studies have found that AMH is a superior marker to parameters such as age, day-3 FSH, estradiol or inhibin B levels for predicting ovarian response, and its predictive value was similar to antral follicle count [12]. Furthermore, several studies have revealed significant positive correlation between AMH concentrations and pregnancy rate [13], ongoing pregnancy rate [14] and live birth rate [15-17]. However the results from the other studies [18, 19] indicated that the predictive value for serum AMH in relation to clinical pregnancy rate, ongoing pregnancy rate and live birth rate is controversial [20-22]. There are some studies compare serum AMH and follicle fluid AMH (FF AMH) on the predictive value of pregnancy rate, and the results are variable [23-25]. Wen-Qin Lin [25] etal found that AMH parameters were correlated with good quality embryos and blastocysts, but only FF AMH showed a significant correlation with LBR and CPR. Yukio Hattori [24] concluded that elevated AMH levels in either the serum or follicular fluid appeared to be predictive of clinical pregnancy.

The present review focuses on the role of AMH in the prediction of outcome of IVF/ICSI treatment in the infertile couples of child-bearing age, tries to confirm the prognostic value of serum AMH on the outcome of ART, and assess-

Table 1. Characteristics of the included studies for meta-analysis

Group 1									
author	year	country	design	region	Measurement	COH	cases	Preg	Non
Elgindy EA [47]	2008	Egypt	prospective	Africa	Beckman-Coulter	long luteal	29	12	17
Sahmay S [48]	2013	Turkey	prospective	Asia	DSL-ELISA	long luteal	150	51	99
Kaya C [45]	2010	Turkey	prospective	Asia	DSL-ELISA	long luteal	80	38	42
Lin WQ [25]	2013	china	prospective	Asia	Beckman-Coulter	long luteal	76	47	29
Xi W [49]	2012	china	prospective	Asia	Beckman-Coulter	long luteal	164	93	71
Irez T [50]	2011	Turkey	prospective	Asia	DSL-ELISA	long luteal	209	58	151
Choi MH [13]	2011	Korea	prospective	Asia	Beckman-Coulter	all	360	101	259
Capkin SI [51]	2012	Turkey	prospective	Asia	DSL-ELISA	long luteal	43	14	29
Penarrubia J [27]	2005	Spain	prospective	Europe	Immunotech-Coulter	all	60	27	33
Gnoth C [52]	2008	Germany	prospective	Europe	DSL-ELISA	long luteal	119	56	63
Nisan BA [53]	2012	UK	retrospective	Europe	DSL-ELISA	long luteal	820	267	553
Arce JC [54]	2013	UK	prospective	Europe	Beckman-Coulter	all	749	208	541
Reichman DE [55]	2014	America	retrospective	North America	Beckman-Coulter	all	2060	936	1124
Barad DH [56]	2009	America	prospective	North America	DSL-ELISA	long luteal	76	21	55
Brodin T [57]	2013	America	prospective	North America	DSL-ELISA	long luteal	1230	337	893
Group 2									
author	year	country	design	region	Measurement	COH	cases	Preg	Non
Honnma H [14]	2013	Japan	retrospective	Asia	Beckman-Coulter	all	1043	317	726
Smeenk JM [58]	2007	The Netherlands	prospective	Europe	Immunotech-Coulter	long luteal	80	40	40
Eldar-Geva T [30]	2005	Israel	prospective	Asina	Immunotech-Coulter	long luteal	56	26	30
van Rooij IA [59]	2002	Netherlands	prospective	Europe	Immunotech-Coulter	long luteal	106	79	27
Ebner T [60]	2006	Austria	prospective	Europe	Beckman-Coulter	all	132	68	64
Kwee J [61]	2008	Netherlands	prospective	Europe	DSL-ELISA	all	104	80	24
Lekamge DN [62]	2007	South Australia	retrospective	Oceania	Beckman-Coulter	long luteal	126	36	90
Group 3									
author	year	country	design	region	Measurement	COH I	cases	Preg	Non
Hattori Y [24]	2013	JAPAN	prospective	Asia	Beckman-Coulter,	long luteal	58	26	32
Wunder DM [63]	2008	Switzerland	prospective	Europe	Beckman-Coulter	long luteal	240	58	182
Smeenk JM [58]	2007	The Netherlands	prospective	Europe	Beckman-Coulter	long luteal	80	40	40
Wu CH [64]	2009	China Taiwan	prospective	Asia	Bechman-Caulter	GnRH antagonist	60	26	34
Sahmay S [19]	2012	Turkey	prospective	Asia	DSL-ELISA	long luteal	189	47	142
Lin WQ [25]	2013	china	prospective	Asia	Bechman-Caulter	long luteal	76	47	29
Eldar-Geva T [30]	2005	Israel	prospective	Asia	Bechman-Caulter	long luteal	56	26	30
Sahmay S [48]	2013	Turkey	Prospective	Asia	DSL-ELISA	long luteal	150	51	99
Group 4									
author	year	country	design	region	Measurement	COH	cases	Preg	Non
Hattori Y [24]	2013	JAPAN	prospective	Asia	Beckman-Coulter	long luteal	58	26	32
Wunder DM [63]	2008	Switzerland	prospective	Europe	Beckman-Coulter	long luteal	240	58	182
Lin WQ [25]	2013	china	prospective	Asia	Beckman-Coulter	long luteal	76	47	29

Group 1: The selected studies of the pregnancy prediction value of serum AMH and all the studies could construct 2 × 2 tables; Group 2: The selected studies of the non-pregnancy prediction value of serum AMH and all the studies could construct 2 × 2 tables; Group 3: The selected studies of the pregnancy prediction value of serum AMH with the analysis way of T-test; Group 4: The selected studies of the pregnancy prediction value of FF AMH with the analysis way of T-test. long luteal: Pituitary suppression with a GnRH agonist which begains in the mid-luteal phase of the previous cycle(long GnRH-agonist down-regulation). GnRH antagonist: For GnRH antagonist–based cycles. all: The COH protocols inlcuding "long" ,"short" and "GnRH antagonis" protocols. COH: the protocol of controlled ovarian hyperstimulation.

es the predictive value of FF AMH on pregnancy rate of IVF/ICSI treatment.

Materials and methods

Search strategy and selection criteria

We retrieved Pubmed database using a broad combination of search terms that included "in vitro fertilization/IVF", "intracytoplasmic sperm injection/ICSI", "assisted reproductive technology/ART", in combination with "antimullerian hormone", "mullerian inhibiting substance", "pregnancy", "live birth", "ongoing pregnancy". All publications appeared before March 2014. Furthermore, we reviewed reference lists in the retrieved articles. Because this review used only published data from the literature, no approval from an institutional review board was required.

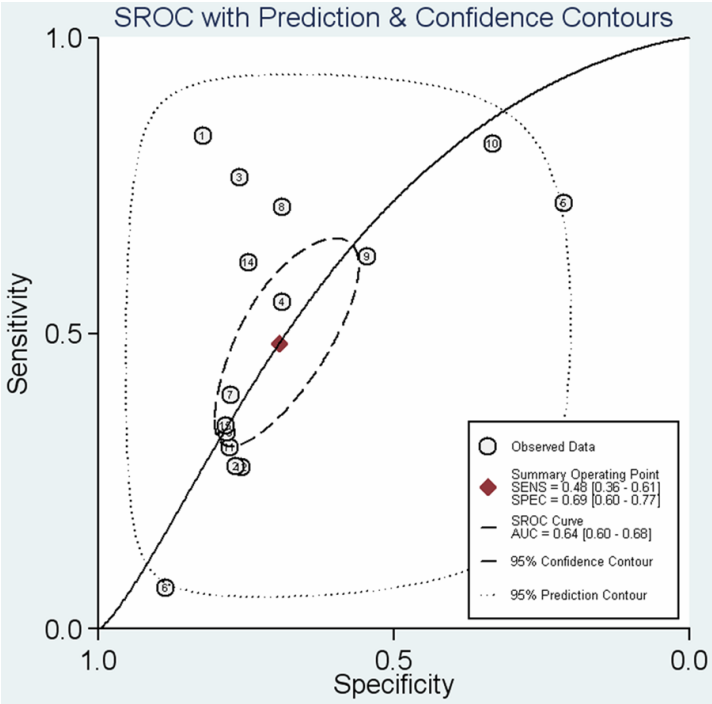

Figure 2. Accuracy of serum AMH on pregnancy prediction in pregnancy group. Summary receiver operating characteristic curve (SROC) of AMH in the prediction of pregnancy after IVF/ICSI with 95% confidence region, 95% prediction region and diagonal line of no discrimination. The area under the curve (AUC) is 0.64 (CI 0.60-0.68).

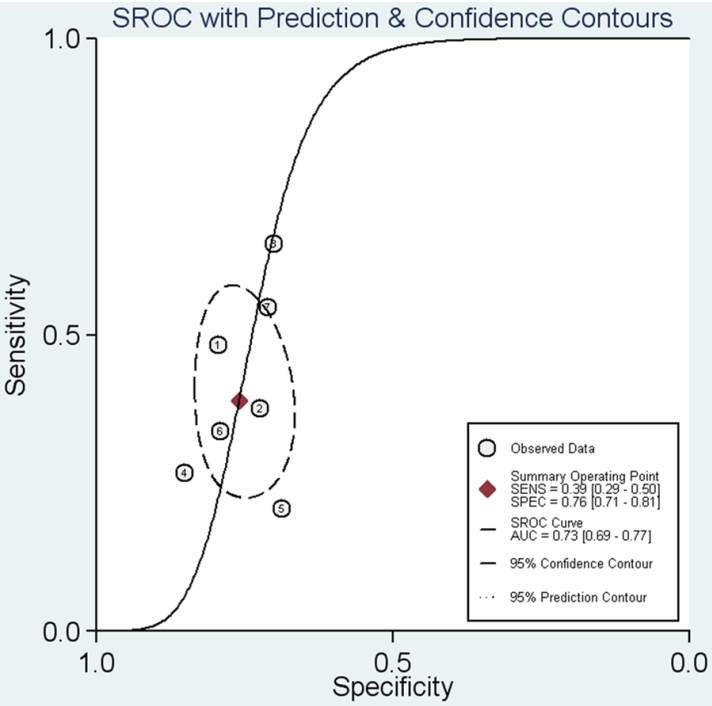

Figure 3. Accuracy of serum AMH on non-pregnancy prediction in not-pregnancy group. Summary receiver operating characteristic curve (SROC) of AMH in the prediction of non-pregnancy after IVF/ICSI with 95% confidence region, 95% prediction region and diagonal line of no discrimination. The area under the curve (AUC) is 0.73 (CI 0.69-0.77).

In this study pregnancy was defined as clinic pregnancy, ongoing pregnancy. Clinic pregnancy was defined as the visualization of a gestational sac with vaginal ultrasound in gestational week > 7. Ongoing pregnancy was defined as the presence of fetal cardiac activity beyond 12 weeks of gestation. A multiple pregnancy was regarded as one pregnancy.

The selection Criteria included if 1) the article was about value of AMH for predicting the IVF outcomes, pregnancy, or ongoing pregnancy. 2) the patients were all ≤ 46 years of age; [26] 3) It was able to construct 2 × 2 tables, when there was a certain cut-off which was related to the outcome of pregnancy or the study used T-test to compare clinical indexes including AMH in pregnant and non-pregnant women. Because of language barrier, only studies published in English or Chinese were included for further analysis. We excluded studies that were not published as full report; studies that were case reports; studies with incomplete data.

Independent assessment

Two investigators (L.N Yao and W Zhang) independently reviewed all the articles, and data were checked by other investigators. The two investigators were blinded to identify information from each study, and judged the inclusion and exclusion of the study. Authors, publication year, study location, types of treatment, numbers of pregnancy women and non-pregnancy women, and other related information were extracted. The concordance rate between the two investigators was 96%. Discrepancies were resolved by consensus and the other researchers (W.Q Lin and H Li).

Statistical analysis

We first constructed the 2 × 2 tables from the selected articles, and cal-

culated sensitivity, specificity, true positive (TP), false positive (FP), true negative (TN), false negative (FN). Heterogeneity of the studies was tested by means of the I-squared measure. The summary ROC curve, sensitivity, specificity, positive and negative likelihood ratio of AMH for predicting pregnancy was generated if homogeneity for AMH could not be rejected. This was conducted by fitting a two-level mixed logistic regression model. In case of heterogeneity, logistic regression and subgroups analysis were used to evaluate whether the study characteristics were associated with the discriminatory capacity. If the study characteristics was not found significant impact on the difference of the test, A Spearman correlation coefficient between sensitivity and specificity was calculated. And in case of a negative correlation (defined by a correlation coefficient of _0.5 or less) a summary ROC curve was estimated, assuming that the Heterogeneity was from the use of different threshold levels.

For the studies which used the analysis of T-test to compare clinical indexes including AMH in pregnant and non-pregnant women, we pooled the numbers of pregnancy women and not-pregnancy women, the mean level and sd (Standard deviation) of AMH in the two groups. And using random (I-V heterogeneity) model with the statistic way of Cohen to combine effect size. The test of heterogeneity was similar to the above way.

Results

We identified 274 study reports from the systematic search. After excluding articles based on the title or abstract, 94 articles were assessed fully for eligibility. After articles reviewed for detailed evaluation, only 26 study databases could be used for our analysis (**Figure 1**). All studies were divided into four groups (Group 1: The selected studies of the pregnancy prediction value of serum AMH and all the studies could construct 2 × 2 tables; Group 2: The selected studies of the non-pregnancy prediction value of serum AMH and all the studies could construct 2 × 2 tables; Group 3: The selected studies of the pregnancy prediction value of serum AMH with the analysis way of T-test.; Group 4: The selected studies of the pregnancy prediction value of FF AMH with the analysis way of T-test.). The characteristics of the included studies were listed in **Table 1**. In the data which could construct 2 × 2 tables, 1647 women were suitable for not-pregnancy analysis, of these 646 (39.2%) had pregnancy. And 6225 women could be used for the analysis of pregnancy prediction, of these 2266 women (36.4%) obtained pregnancy. In the T-test group, there were 909 women who were suitable for pregnancy analysis of serum AMH, and 321 (35.3%) had pregnancy; 374 women were suitable for pregnancy analysis of FF AMH, of these 131 (35%) women had pregnancy.

The predictive value of serum AMH on pregnancy

In Group 1, the sensitivity varies between 7% and 83% and the specificity between 21% and 89%, with the I-squared of 99%. The sources of heterogeneity including characteristics of the study population, variations in the study design, differences of statistical methods are all evaluated. The logistic regression analysis shows that none of these factors recorded has statistically significant impact on the reported predictive performance of AMH. The Spearman correlation coefficient for sensitivity and specificity is -0.45, the *P* value is 0.08, and the heterogeneity is not caused by threshold effect. A plot of sensitivity-specificity points in an ROC space is shown in **Figure 2**. The AUROC is 0.64, 95% CI is 0.6-0.68. The adjusted for serum AMH positive likelihood ratio is 2.0 and negative likelihood ratio is 0.75. The positive post-probability is 47% and the negative post-probability is 30% if the Pre-probability is 36% (**Figure 4A**). The *P* value of publication bias is 0.255.

Group 3 included 8 studies, the I-squared is 45.1%, the heterogeneity is less, the *P* value of publication bias is 0.289. The result showed that serum AMH was a good predictive parameter to predict pregnancy outcome of IVF or ICSI ($P < 0.05$). Forest plot of diagnostic odds ratio (DOR) of 8 studies is shown in **Figure 5**.

The predictive value of serum AMH on not-pregnancy

There are 7 articles which conform to our criteria in Group 2. The sensitivity is between 21% and 65% and the specificity is between 69% and 85%, and the heterogeneity is moderate (I-squared of 65.9%) The AUROC is 0.73, 95% CI is 0.69-0.77. The publication bias shows no significance ($P = 0.242$). The logistic regression analysis does not show that the study charac-

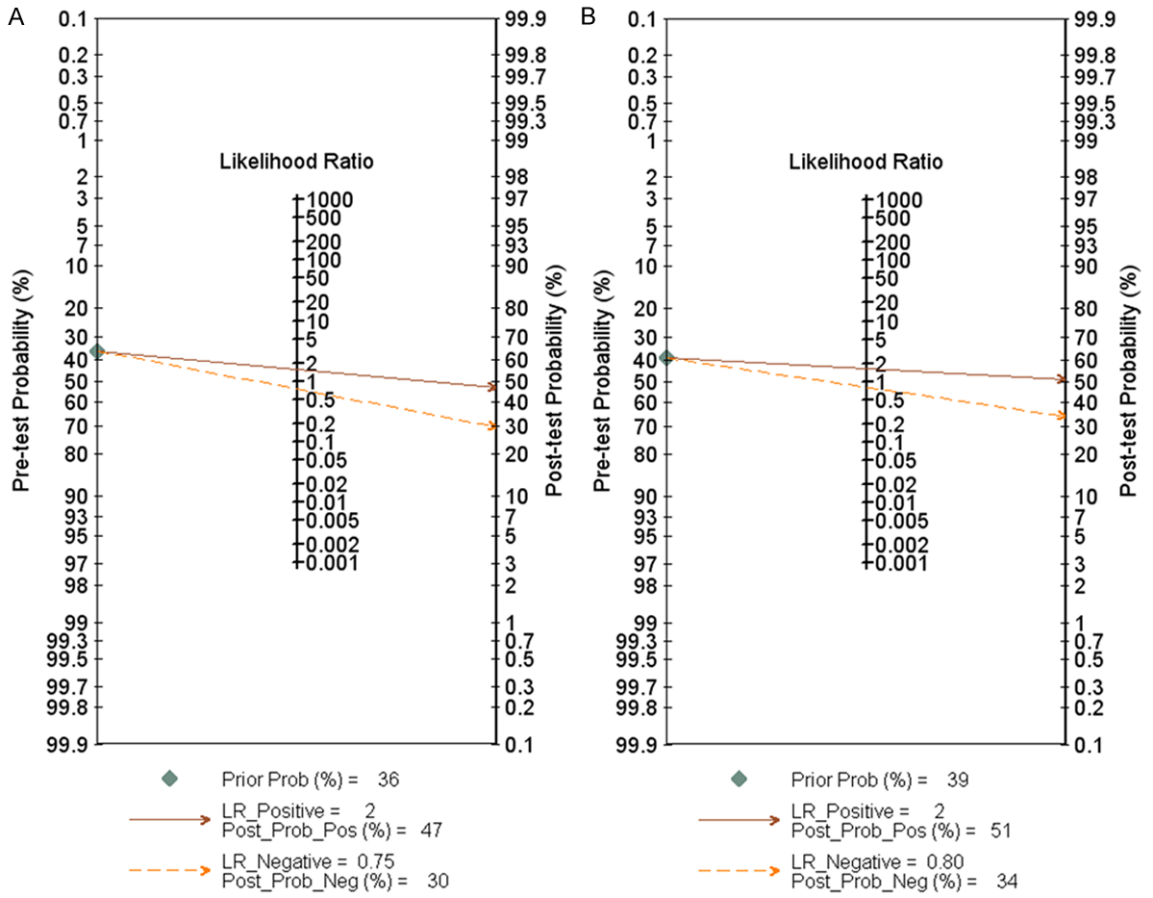

Figure 4. Post-test probability. Occurrence of antimullerian hormone (AMH) results within a specified likelihood ratio (LR) range and the concomitant posttest probabilities of pregnancy and nonpregnancy, given a prevalence of pregnancy of 36% and nonpregnancy of 39%.

teristics had a statistically significant impact on the reported predictive performance of serum AMH. The Spearman correlation coefficient for sensitivity and specificity is -0.14, the *P* value is 0.78. The threshold effect is not obvious. A plot of sensitivity-specificity points in an ROC space is shown in **Figure 3**. The adjusted for serum AMH positive likelihood ratio is 2.0 and negative likelihood ratio is 0.8. The positive post-probability is 51% and the negative post-probability is 34% if the pre-probability is 39% (**Figure 4B**).

The predictive value of FF AMH on pregnancy

Group 4 includes 3 studies for assessing the value of FF AMH on predicting pregnancy. The value of I-squared is 90.5%. Forest plot of diagnostic odds ratio (DOR) of 3 studies is shown in **Figure 6**. And the *P* value of publication bias is 0.637.

Discussion

AMH has been identified by many researchers as a predictive parameter of ovarian response [10, 27, 28]. Serum AMH has become a standard determination to evaluate the ovarian reserve. But whether AMH has predictive value in IVF/ICSI cycles is still uncertain. Several studies had found some positive association between circulating concentrations of AMH and fertilization rate, embryo quality and pregnancy outcome [29-31] in IVF/ICSI cycles.

One study [29] evaluated 109 women (< 42 years old) and demonstrated that day 3 serum AMH level and IVF outcome were strongly associated, and higher AMH concentrations were associated with a higher clinical pregnancy rate. But a recent research [19] detected that serum AMH, FSH, and AFC cannot predict clinical pregnancy in IVF patients under 40. There are also some studies with the way of meta-

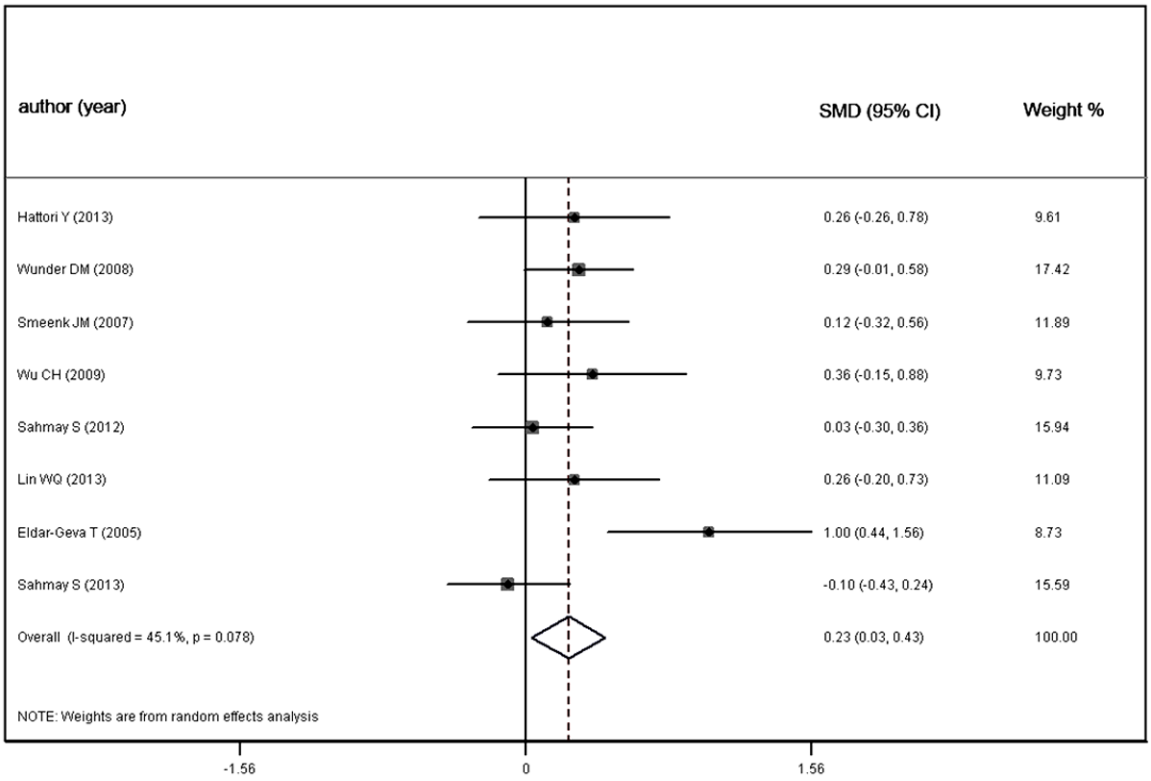

Figure 5. Forest plot of diagnostic odds ratio (DOR) of serum AMH. Forest plot of diagnostic odds ratio (DOR) of 8 studies which use the analysis way of T-test to explore the pregnancy predictive value of serum AMH in the cycles of IVF/ICSI.

analysis which hope to find the correlation between AMH and the outcome of IVF/ICSI. One showed that AMH was able to predict extremes in ovarian response to controlled ovarian hyperstimulation but could not predict pregnancy after ART treatment. And its future clinical role may be in the individualization of ART stimulation protocols [32]. Our meta-analysis tries to explore the predictive value of serum AMH on pregnancy and non-pregnancy in the fresh cycles of IVF/ICSI. In 2 × 2 tables group we find that serum AMH has a certain value to predict the outcome of IVF/ICSI. The AUROC of pregnancy prediction is 0.69, and the AUROC of non-pregnancy prediction is 0.73. But because of the large heterogeneity (I-squared of 99% and 65.9%), the accuracy of the results is less. Fortunately, in Group 3, Serum AMH was proved to be a good predictive parameter to predict pregnancy outcome of IVF/ICSI ($P < 0.05$), and the heterogeneity is less (I-squared of 45.1%).

Besides, the present study use the way of meta-analysis for the first time to identify the role of FF AMH in predicting the outcome of IVF/ICSI. Our previous report showed that among the parameters including serum AMH, FF AMH, FSH, luteinizing hormone (LH) and antral follicle count (AFC), only FF AMH showed a significant correlation with LBR and CPR [25]. A recent research of Bindu N Mehta [33] et al showed that FF AMH was a plausible biochemical indicator of functional viability of oocyte in conventional IVF cycles. Clinical pregnancy rates and embryo implantation rates were significantly higher when patients with follicles containing high AMH concentration [34]. But CHEN Xin et al [23] found that AMH level in the serum and follicle fluid on the day of oocyte retrieval was predictive of the treatment outcome of controlled ovarian hyperstimulation in POCS patients but not of pregnancy outcomes after IVF-ET. This present study finds that FF AMH is not correlated with the pregnancy outcome of IVF/ICSI. Unfortunately, the heterogeneity of the pooled studies is significant, and the numbers of incorporated studies and the sample size is small, which may affect the accuracy of the result.

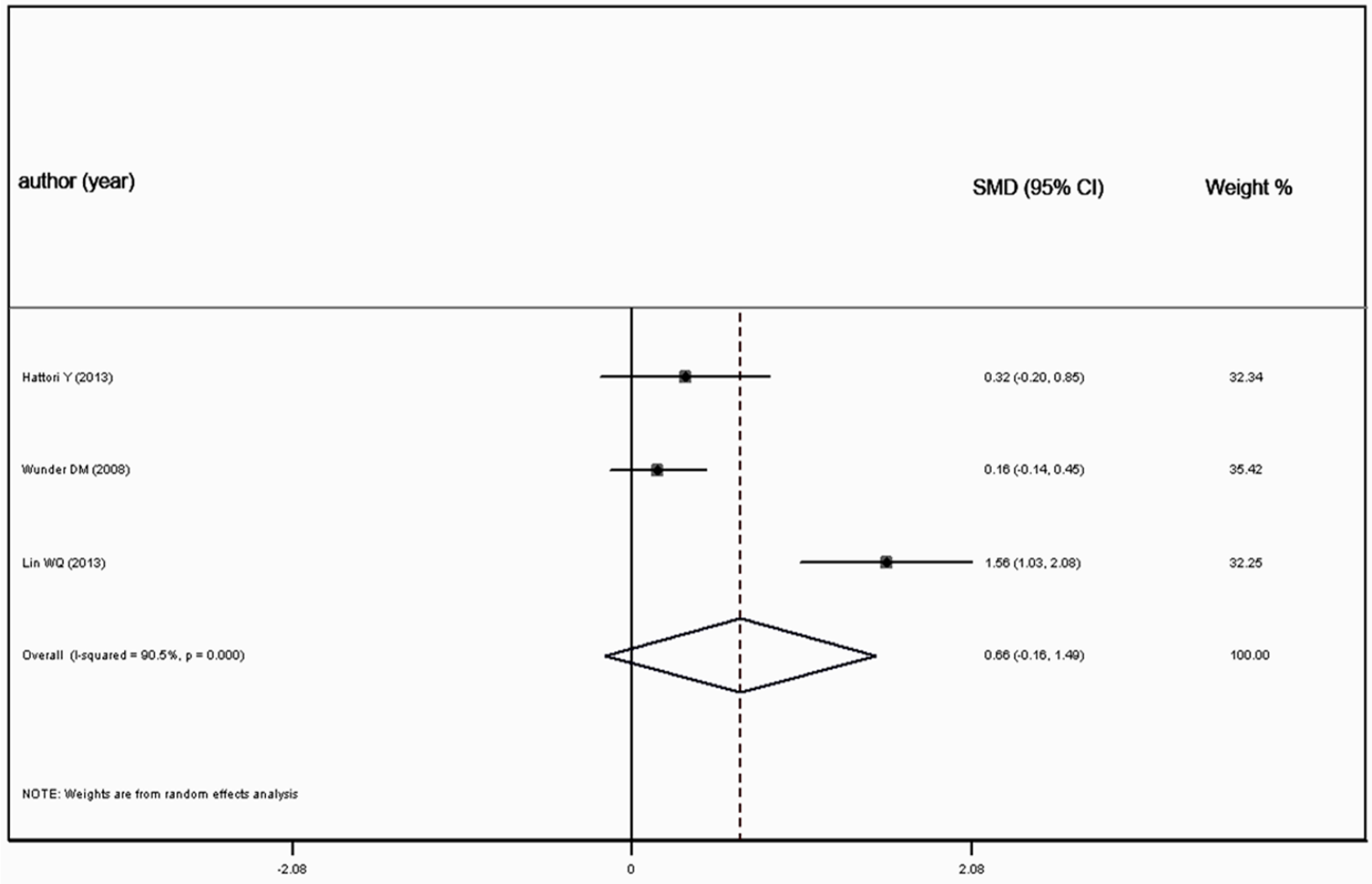

Figure 6. Forest plot of DOR of FF AMH. Forest plot of diagnostic odds ratio (DOR) of 3 studies which use the analysis way of T-test to explore the pregnancy prediction value of FF AMH in the cycles of IVF/ICSI.

Clinical application and limitation

Predicting chances of pregnancy after an IVF cycle can help to prevent overtreatment. Although various models have been developed for the prediction of pregnancy after IVF, there is no consensus to pinpoint which predictor is the most clinically relevant and on what factors one should base the decision to start treatment or not. A meta-analysis [35] used to show that female age, duration of subfertility, baseline FSH and number of oocytes, all reflecting ovarian function, are predictors of pregnancy after IVF. van Loendersloot et al [36] recently published a study which construct a prediction model including thirteen variables. For all cycles, these were female age, duration of subfertility, previous ongoing pregnancy, male subfertility, diminished ovarian reserve, endometriosis, basal FSH and number of failed IVF cycles. After the first cycle: fertilization, number of embryos, mean morphological score per Day 3 embryo, presence of 8-cell embryos on Day 3 and presence of morulae on Day 3 were also included.

AMH is closely related to the ovarian reserve. Reductions in serum AMH due to ovarian aging reflects not only a reduction in the size of the primordial follicle pool but also an increasing rate of per-follicle granulosa cell apoptosis, which would be expected to reduce the per-follicle production of AMH and diminish oocyte quality. A study of Hiroyuki Honnma et al [14] with large number of cases showed that high serum AMH could be predictive of the presence of high-quality embryos on D3 and could potentially improve the rates of embryo development to the blastocyst stage, (single) blastocyst transfer, and pregnancy. AMH as a member of future predictive model should be considered. Stamatina Iliodromit [37] et al did a meta- analysis and found that AMH adds some value in predicting live birth, and this is independent of age or AMH assay, although its predictive accuracy is poor and should not be over-interpreted.

The present meta-analysis takes serum AMH and FF AMH as the predictive variables, and tries to examine whether AMH is a predictor of pregnancy in women undergoing IVF/ICSI. The results show that there is some value of serum AMH in predicting the pregnancy outcome of IVF/ICSI. Although the heterogeneity is large in Group1 and moderate in Group 2 (I-squared of 99% and 65.9%), the heterogeneity of Group 3 is less (I-squared of 45.1%). This makes the accuracy of the conclusion believable. The pity is that it is hard to calculate the cut-off value of AMH and we could not get the sensitivity or specificity of serum AMH because of the large heterogeneity. And because the adjusted positive likelihood ratio of serum AMH is 2.0 and negative likelihood ratio is 0.75, serum AMH alone is hard to alter a clinical decision according the research of Jaeschke et al [38].

The studies about FF AMH as a predictor of the pregnancy outcome of IVF/ICSI are comparatively fewer. The present meta-analysis finds a negative correlation of FF AMH with the outcome of IVF/ICSI, but the heterogeneity (I-squared of 90.5%) is too larger and it make the accuracy of this analysis become uncertain. Besides the sample of FF AMH is usually collected on the day of OPU, and prediction of pregnancy on the OPU day may be too little and too late since the IVF cycle has been to the end. Anyhow, this meta-analysis may show some light of AMH as a member of predictive model in predicting the outcome of IVF/ICSI.

The limitation of our study could not be ignored either. Although we have tried many ways such as limiting age range and using different analysis to reduce the heterogeneity, the result is still not much satisfactory. Bleil ME et al [39] find that African American women may have lower AMH levels at younger ages but experience less reduction in AMH with advancing age, and Latina and Chinese women compared with white women may have lower AMH levels, marking a lower ovarian reserve and a possibly increased risk for earlier menopause. Their study may indirectly give us some information that different races may bring some bias.

In addition, because of the lack of an international AMH standard, heterogeneity of the measurement of AMH may also contribute to the noted discrepancies. The main measurements in our study are Beckman-Coulter, Immunotech-Coulter (IOT) and DSL-ELISA Kit (Diagnostic Systems Laboratories). Some studies [40, 41] showed that the regression equations comparing DSL to Gen II assays (Beckman-Coulter) in two different studies appeared more similar. In contrast, as the test standards differed from those in the DSL assay, in-house and indepen-

dent external evaluation suggested that AMH values would be approximately 40% higher when measured using the Gen II assay as compared with the DSL assay [42]. Both IOT and DSL also differed in their pairs of monoclonal antibodies and in standardization, so they did not give comparable values for quantitation of AMH [43, 44]. Unifying the measurement method of AMH and getting a uniform standard of AMH may help us reduce the bias and find a cut-off value of AMH to predict the pregnancy outcome of IVF/ICSI.

Moreover, the design of pooled studies, sample sizes, PCOS and potential matrix effects may all produce heterogeneity. For example, some studies [24, 45] found that the significantly high level of AMH in PCOS patients was not only because of the large number of small antral follicles, but also the high level of FF AMH in the preovulatory follicles. It suggested that there may exist abnormal secretion of AMH in PCOS patients. Unfortunately, we do not exclude the PCOS patients, and the samples of pooled studies are not very even. The logistic regression analysis shows that none of these characteristics including the region of the study population, the study design, the measurement of AMH and the protocols of controlled ovarian hyperstimulation have statistically significant impact on the accuracy of our results, and we fail to find the source of the heterogeneity and lose it.

The future

The more research of AMH, the role of AMH becomes much more be understood. AMH as a predictor of ovary reserve has become a consensus in recent years. But the pathway of AMH activity has not been completely understood. It is believed that AMH participate in the regulation of release from the primordial follicle pool, hence arranging the pace at which follicles reenter meiosis and growth, and the rate of set down of the primordial follicle pool. In the PCOS patient, the relations between AMH and LH, high level of androgen, total cholesterol, insulin resistance and BMI still need more studies to confirm. For AMH's predictive role of pregnancy outcome in the cycles of IVF/ICSI, the mechanism is still limited in its predictive role of ovarian reserve. Getting pregnancy needs many steps, and there are many confounders. Whether AMH are correlated with the quality of oocytes, embryos, blastocysts, and other confounders also need further verification. Besides, serum AMH is often referred to a larger normal range in every age stage [46], the cut-off value of AMH as a predictor of pregnancy outcome in IVF/ICSI is still unclear, and it may help the clinicians better identify patients who may have much higher probability of pregnancy.

Furthermore, uniting AMH and other parameters as predictive models of pregnancy outcome in IVF/ICS is also worth to be considered more.

Conclusion

In summary, this meta-analysis tries to assess the role of serum AMH in predicting the pregnancy outcome of IVF/ICSI. The result reveals that there is positive correlation between serum AMH and pregnancy. The positive correlation with serum AMH and non-pregnancy should not be ignored either. Unfortunately, the predictive value of FF AMH on pregnancy is still unclear because of large heterogeneity. This meta-analysis indicates the potential role of AMH as a predictor of pregnancy in IVF/ICSI. For conforming the real predictive role of AMH in IVF/ICSI, reducing and limiting bias in the greatest degree should be concerned in the future.

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Disclosure of conflict of interest

None.

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References

[1] Templeton A, Morris JK, Parslow W. Factors that affect outcome of in-vitro fertilisation treatment. Lancet 1996; 348: 1402-1406.

[2] Hunault CC, Eijkemans MJ, Pieters MH, Habbema JD, Fauser BC, Macklon NS. A prediction model for selecting patients undergoing in vitro fertilization for elective single embryo transfer. Fertil Steril 2002; 77: 725-732.
[3] de Bruin JP, Dorland M, Spek ER, Posthuma G, van Haaften M, Looman CW, te Velde ER. Age-related changes in the ultrastructure of the resting follicle pool in human ovaries. Biol Reprod 2004; 70: 419-424.
[4] Bukulmez O, Arici A. Assessment of ovarian reserve. Curr Opin Obstet Gynecol 2004; 16: 231-237.
[5] Sills ES, Alper MM, Walsh AP. Ovarian reserve screening in infertility: practical applications and theoretical directions for research. Eur J Obstet Gynecol Reprod Biol 2009; 146: 30-36.
[6] Al-Azemi M, Killick SR, Duffy S, Pye C, Refaat B, Hill N, Ledger W. Multi-marker assessment of ovarian reserve predicts oocyte yield after ovulation induction. Hum Reprod 2011; 26: 414-422.
[7] Gleicher N, Weghofer A, Barad DH. Defining ovarian reserve to better understand ovarian aging. Reprod Biol Endocrinol 2011; 9: 23.
[8] Weenen C, Laven JS, Von Bergh AR, Cranfield M, Groome NP, Visser JA, Kramer P, Fauser BC, Themmen AP. Anti-Mullerian hormone expression pattern in the human ovary: potential implications for initial and cyclic follicle recruitment. Mol Hum Reprod 2004; 10: 77-83.
[9] Mulders AG, Laven JS, Eijkemans MJ, de Jong FH, Themmen AP, Fauser BC. Changes in anti-Mullerian hormone serum concentrations over time suggest delayed ovarian ageing in normogonadotrophic anovulatory infertility. Hum Reprod 2004; 19: 2036-2042.
[10] Fanchin R, Mendez Lozano DH, Louafi N, Achour-Frydman N, Frydman R, Taieb J. Dynamics of serum anti-Mullerian hormone levels during the luteal phase of controlled ovarian hyperstimulation. Hum Reprod 2005; 20: 747-751.
[11] Patrelli TS, Gizzo S, Sianesi N, Levati L, Pezzuto A, Ferrari B, Bacchi Modena A. Anti-Mullerian hormone serum values and ovarian reserve: can it predict a decrease in fertility after ovarian stimulation by ART cycles? PLoS One 2012; 7: e44571.
[12] La Marca A, Sighinolfi G, Radi D, Argento C, Baraldi E, Artenisio AC, Stabile G, Volpe A. Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update 2010; 16: 113-130.
[13] Choi MH, Yoo JH, Kim HO, Cha SH, Park CW, Yang KM, Song IO, Koong MK, Kang IS. Serum anti-Mullerian hormone levels as a predictor of the ovarian response and IVF outcomes. Clin Exp Reprod Med 2011; 38: 153-158.
[14] Honnma H, Baba T, Sasaki M, Hashiba Y, Oguri H, Fukunaga T, Endo T, Asada Y. Serum anti-Mullerian hormone levels affect the rate of ongoing pregnancy after in vitro fertilization. Reprod Sci 2013; 20: 51-59.
[15] Nelson SM, Yates RW, Fleming R. Serum anti-Mullerian hormone and FSH: prediction of live birth and extremes of response in stimulated cycles--implications for individualization of therapy. Hum Reprod 2007; 22: 2414-2421.
[16] Gleicher N, Weghofer A, Barad DH. Anti-Mullerian hormone (AMH) defines, independent of age, low versus good live-birth chances in women with severely diminished ovarian reserve. Fertil Steril 2010; 94: 2824-2827.
[17] La Marca A, Nelson SM, Sighinolfi G, Manno M, Baraldi E, Roli L, Xella S, Marsella T, Tagliasacchi D, D'Amico R, Volpe A. Anti-Mullerian hormone-based prediction model for a live birth in assisted reproduction. Reprod Biomed Online 2011; 22: 341-349.
[18] Wang JG, Douglas NC, Nakhuda GS, Choi JM, Park SJ, Thornton MH, Guarnaccia MM, Sauer MV. The association between anti-Mullerian hormone and IVF pregnancy outcomes is influenced by age. Reprod Biomed Online 2010; 21: 757-761.
[19] Sahmay S, Demirayak G, Guralp O, Ocal P, Senturk LM, Oral E, Irez T. Serum anti-mullerian hormone, follicle stimulating hormone and antral follicle count measurement cannot predict pregnancy rates in IVF/ICSI cycles. J Assist Reprod Genet 2012; 29: 589-595.
[20] Guerif F, Lemseffer M, Couet M, Gervereau O, Ract V, Royere D. Serum antimullerian hormone is not predictive of oocyte quality in vitro fertilization. Ann Endocrinol (Paris) 2009; 70: 230-234.
[21] Riggs R, Kimble T, Oehninger S, Bocca S, Zhao Y, Leader B, Stadtmauer L. Anti-Mullerian hormone serum levels predict response to controlled ovarian hyperstimulation but not embryo quality or pregnancy outcome in oocyte donation. Fertil Steril 2011; 95: 410-412.
[22] Mutlu MF, Erdem M, Erdem A, Yildiz S, Mutlu I, Arisoy O, Oktem M. Antral follicle count determines poor ovarian response better than anti-Mullerian hormone but age is the only predictor for live birth in in vitro fertilization cycles. J Assist Reprod Genet2013; 30: 657-665.
[23] Chen X, Yin M, Ye D, He Y, Chen S. [Predictive value of anti-Mullerian hormone levels in serum and follicle fluid for IVF-ET outcomes in patients with polycystic ovarian syndrome]. Nan Fang Yi Ke Da Xue Xue Bao 2013; 33: 546-549.
[24] Hattori Y, Sato T, Okada H, Saito C, Sugiura-Ogasawara M. Comparison of follicular fluid and serum anti-Mullerian hormone levels as predictors of the outcome of assisted repro-

ductive treatment. Eur J Obstet Gynecol Reprod Biol 2013; 169: 252-256.
[25] Lin WQ, Yao LN, Zhang DX, Zhang W, Yang XJ, Yu R. The predictive value of anti-Mullerian hormone on embryo quality, blastocyst development, and pregnancy rate following in vitro fertilization-embryo transfer (IVF-ET). J Assist Reprod Genet 2013; 30: 649-655.
[26] Rasgon N, Shelton S, Halbreich U. Perimenopausal mental disorders: epidemiology and phenomenology. CNS Spectr 2005; 10: 471-478.
[27] Penarrubia J, Fabregues F, Manau D, Creus M, Casals G, Casamitjana R, Carmona F, Vanrell JA, Balasch J. Basal and stimulation day 5 anti-Mullerian hormone serum concentrations as predictors of ovarian response and pregnancy in assisted reproductive technology cycles stimulated with gonadotropin-releasing hormone agonist–gonadotropin treatment. Hum Reprod 2005; 20: 915-922.
[28] Nardo LG, Gelbaya TA, Wilkinson H, Roberts SA, Yates A, Pemberton P, Laing I. Circulating basal anti-Mullerian hormone levels as predictor of ovarian response in women undergoing ovarian stimulation for in vitro fertilization. Fertil Steril 2009; 92: 1586-1593.
[29] Hazout A, Bouchard P, Seifer DB, Aussage P, Junca AM, Cohen-Bacrie P. Serum antimullerian hormone/mullerian-inhibiting substance appears to be a more discriminatory marker of assisted reproductive technology outcome than follicle-stimulating hormone, inhibin B, or estradiol. Fertil Steril 2004; 82: 1323-1329.
[30] Eldar-Geva T, Ben-Chetrit A, Spitz IM, Rabinowitz R, Markowitz E, Mimoni T, Gal M, Zylber-Haran E, Margalioth EJ. Dynamic assays of inhibin B, anti-Mullerian hormone and estradiol following FSH stimulation and ovarian ultrasonography as predictors of IVF outcome. Hum Reprod 2005; 20: 3178-3183.
[31] Majumder K, Gelbaya TA, Laing I, Nardo LG. The use of anti-Mullerian hormone and antral follicle count to predict the potential of oocytes and embryos. Eur J Obstet Gynecol Reprod Biol 2010; 150: 166-170.
[32] Broer SL, Mol B, Dolleman M, Fauser BC, Broekmans FJ. The role of anti-Mullerian hormone assessment in assisted reproductive technology outcome. Curr Opin Obstet Gynecol 2010; 22: 193-201.
[33] Mehta BN, Chimote MN, Chimote NN, Nath NM, Chimote NM. Follicular-fluid anti-Mullerian hormone (FF AMH) is a plausible biochemical indicator of functional viability of oocyte in conventional in vitro fertilization (IVF) cycles. J Hum Reprod Sci 2013; 6: 99-105.
[34] Fanchin R, Mendez Lozano DH, Frydman N, Gougeon A, di Clemente N, Frydman R, Taieb J. Anti-Mullerian hormone concentrations in the follicular fluid of the preovulatory follicle are predictive of the implantation potential of the ensuing embryo obtained by in vitro fertilization. J Clin Endocrinol Metab 2007; 92: 1796-1802.
[35] van Loendersloot LL, van Wely M, Limpens J, Bossuyt PM, Repping S, van der Veen F. Predictive factors in in vitro fertilization (IVF): a systematic review and meta-analysis. Hum Reprod Update 2010; 16: 577-589.
[36] van Loendersloot LL, van Wely M, Repping S, Bossuyt PM, van der Veen F. Individualized decision-making in IVF: calculating the chances of pregnancy. Hum Reprod 2013; 28: 2972-2980.
[37] Iliodromiti S, Kelsey TW, Wu O, Anderson RA, Nelson SM. The predictive accuracy of anti-Mullerian hormone for live birth after assisted conception: a systematic review and meta-analysis of the literature. Hum Reprod Update 2014; 20: 560-570.
[38] Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. JAMA 1994; 271: 703-707.
[39] Bleil ME, Gregorich SE, Adler NE, Sternfeld B, Rosen MP, Cedars MI. Race/ethnic disparities in reproductive age: an examination of ovarian reserve estimates across four race/ethnic groups of healthy, regularly cycling women. Fertil Steril 2014; 101: 199-207.
[40] Nelson SM, La Marca A. The journey from the old to the new AMH assay: how to avoid getting lost in the values. Reprod Biomed Online 2011; 23: 411-420.
[41] Li HW, Ng EH, Wong BP, Anderson RA, Ho PC, Yeung WS. Correlation between three assay systems for anti-Mullerian hormone (AMH) determination. J Assist Reprod Genet 2012; 29: 1443-1446.
[42] Wallace AM, Faye SA, Fleming R, Nelson SM. A multicentre evaluation of the new Beckman Coulter anti-Mullerian hormone immunoassay (AMH Gen II). Ann Clin Biochem 2011; 48: 370-373.
[43] Freour T, Mirallie S, Bach-Ngohou K, Denis M, Barriere P, Masson D. Measurement of serum anti-Mullerian hormone by Beckman Coulter ELISA and DSL ELISA: comparison and relevance in assisted reproduction technology (ART). Clin Chim Acta 2007; 375: 162-164.
[44] Taieb J, Belville C, Coussieu C, Guibourdenche J, Picard JY, Di clemente N. [Two immunoassays for antimullerian hormone measurement: analytical and clinical performances]. Ann Biol Clin (Paris) 2008; 66: 537-547.
[45] Kaya C, Pabuccu R, Satiroglu H. Serum antimullerian hormone concentrations on day 3 of

the in vitro fertilization stimulation cycle are predictive of the fertilization, implantation, and pregnancy in polycystic ovary syndrome patients undergoing assisted reproduction. Fertil Steril 2010; 94: 2202-2207.

[46] Shebl O, Ebner T, Sir A, Schreier-Lechner E, Mayer RB, Tews G, Sommergruber M. Age-related distribution of basal serum AMH level in women of reproductive age and a presumably healthy cohort. Fertil Steril 2011; 95: 832-834.

[47] Elgindy EA, El-Haieg DO, El-Sebaey A. Anti-Mullerian hormone: correlation of early follicular, ovulatory and midluteal levels with ovarian response and cycle outcome in intracytoplasmic sperm injection patients. Fertil Steril 2008; 89: 1670-1676.

[48] Sahmay S, Guralp O, Aydogan B, Cepni I, Oral E, Irez T. Anti-Mullerian hormone and polycystic ovary syndrome: assessment of the clinical pregnancy rates in in vitro fertilization patients. Gynecol Endocrinol 2013; 29: 440-443.

[49] Xi W, Gong F, Lu G. Correlation of serum Anti-Mullerian hormone concentrations on day 3 of the in vitro fertilization stimulation cycle with assisted reproduction outcome in polycystic ovary syndrome patients. J Assist Reprod Genet 2012; 29: 397-402.

[50] Irez T, Ocal P, Guralp O, Cetin M, Aydogan B, Sahmay S. Different serum anti-Mullerian hormone concentrations are associated with oocyte quality, embryo development parameters and IVF-ICSI outcomes. Arch Gynecol Obstet 2011; 284: 1295-1301.

[51] Capkin SI, Ozyer S, Karayalcin R, Moraloglu O, Ozcan S, Ugur M. Serum and follicular fluid Anti-Mullerian hormone concentrations at the time of follicle puncture and reproductive outcome. J Turk Ger Gynecol Assoc 2012; 13: 21-26.

[52] Gnoth C, Schuring AN, Friol K, Tigges J, Mallmann P, Godehardt E. Relevance of anti-Mullerian hormone measurement in a routine IVF program. Hum Reprod 2008; 23: 1359-1365.

[53] Nisan BA, Zhiliaeva EP. [The international experience of involvement of state and private sectors in reformation of health care]. Probl Sotsialnoi Gig Zdravookhranenniiai Istor Med 2012; 47-49.

[54] Arce JC, La Marca A, Mirner Klein B, Nyboe Andersen A, Fleming R. Antimullerian hormone in gonadotropin releasing-hormone antagonist cycles: prediction of ovarian response and cumulative treatment outcome in good-prognosis patients. Fertil Steril 2013; 99: 1644-1653.

[55] Reichman DE, Goldschlag D, Rosenwaks Z. Value of antimullerian hormone as a prognostic indicator of in vitro fertilization outcome. Fertil Steril 2014; 101: 1012-1018, e1011.

[56] Barad DH, Weghofer A, Gleicher N. Comparing anti-Mullerian hormone (AMH) and follicle-stimulating hormone (FSH) as predictors of ovarian function. Fertil Steril 2009; 91 Suppl 4: 1553-1555.

[57] Brodin T, Hadziosmanovic N, Berglund L, Olovsson M, Holte J. Antimullerian hormone levels are strongly associated with live-birth rates after assisted reproduction. J Clin Endocrinol Metab 2013; 98: 1107-1114.

[58] Smeenk JM, Sweep FC, Zielhuis GA, Kremer JA, Thomas CM, Braat DD. Antimullerian hormone predicts ovarian responsiveness, but not embryo quality or pregnancy, after in vitro fertilization or intracyoplasmic sperm injection. Fertil Steril 2007; 87: 223-226.

[59] van Rooij IA, Broekmans FJ, te Velde ER, Fauser BC, Bancsi LF, de Jong FH, Themmen AP. Serum anti-Mullerian hormone levels: a novel measure of ovarian reserve. Hum Reprod 2002; 17: 3065-3071.

[60] Ebner T, Sommergruber M, Moser M, Shebl O, Schreier-Lechner E, Tews G. Basal level of anti-Mullerian hormone is associated with oocyte quality in stimulated cycles. Hum Reprod 2006; 21: 2022-2026.

[61] Kwee J, Schats R, McDonnell J, Themmen A, de Jong F, Lambalk C. Evaluation of anti-Mullerian hormone as a test for the prediction of ovarian reserve. Fertil Steril 2008; 90: 737-743.

[62] Lekamge DN, Barry M, Kolo M, Lane M, Gilchrist RB, Tremellen KP. Anti-Mullerian hormone as a predictor of IVF outcome. Reprod Biomed Online 2007; 14: 602-610.

[63] Wunder DM, Guibourdenche J, Birkhauser MH, Bersinger NA. Anti-Mullerian hormone and inhibin B as predictors of pregnancy after treatment by in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril 2008; 90: 2203-2210.

[64] Wu CH, Chen YC, Wu HH, Yang JG, Chang YJ, Tsai HD. Serum anti-Mullerian hormone predicts ovarian response and cycle outcome in IVF patients. J Assist Reprod Genet 2009; 26: 383-389.