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Is diminished ovarian reserve a risk factor for miscarriage? Results of a systematic review and meta-analysis

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BACKGROUND: Anti-Müllerian hormone (AMH) serum concentration and antral follicle count (AFC), as measured by transvaginal ultrasonography, accurately reflect the antral follicle pool. However, AMH and AFC association with fertility surrogates (i.e. age at menopause, probability of conceiving naturally and ART success rate) is questioned. Miscarriage is often considered an alternative measure of reproductive capacity. Nonetheless, the impact of diminished ovarian reserve (DOR) on miscarriage incidence remains an understudied and unresolved issue.

OBJECTIVE AND RATIONALE: The aim of this systematic review and meta-analysis was to elucidate associations between DOR and miscarriage risk, both in women who conceived naturally and in those who achieved pregnancy through ART.

SEARCH METHODS: Relevant studies were identified by a systematic search in PubMed, MEDLINE, Embase and Scopus, from database inception to 1 March 2021. Studies were included only if all the following conditions were met: DOR was defined using serum AMH concentration or AFC; miscarriage rate was reported separately for different groups of women categorized according to the AMH and/or AFC level;

authors reported either the rate of intrauterine pregnancy loss before 22 weeks of gestation or enough data were available to calculate it.

OUTCOMES: From a total of 347 publications initially identified, 16 studies were included. Pooled results from 13 retrospective studies focusing on ART pregnancies showed a significantly higher rate of miscarriage in women with a low AMH, as compared to women with a medium or high serum AMH concentration (12 042 women, random effects model, odds ratio (OR) 1.35; 95% CI, 1.10–1.66; $P = 0.004$; $I^2 = 50\%$). The only prospective study on ART pregnancies failed to show any association (61 women, risk ratio (RR) 2.95; 95% CI, 0.66–3.18; $P = 0.16$). Data from two prospective studies, which included naturally conceived pregnancies, showed a significantly increased miscarriage risk for women with low serum AMH. However, these data could not undergo meta-analysis owing to differing study designs. Using three retrospective studies, we observed an association between low AFC and miscarriage incidence (three retrospective studies on ART pregnancies, random effects model, OR 1.81; 95% CI, 1.02–3.21; $P = 0.04$; $I^2 = 64\%$).

WIDER IMPLICATIONS: Our meta-analysis findings suggest that within the DOR patient subgroup, serum AMH and AFC biomarker levels may correlate with both the quantitative and qualitative aspects of ovarian reserve. However, owing to study limitations, the aetiology of this effect remains unclear and we are unable to define a causal relationship between DOR and increased miscarriage or to provide clinical recommendations based on this information. However, if confirmed by future well-designed studies, these findings would be profoundly informative for guiding women in family planning decisions.

Key words: diminished ovarian reserve / anti-Müllerian hormone / antral follicle count / miscarriage / ART / natural conception

Introduction

Oocyte and follicular pools decline with age (Broekmans *et al.*, 2009). The quantity of oocytes that a woman possesses at a particular time in her life is commonly known as 'ovarian reserve' (Practice Committee of the American Society for Reproductive Medicine, 2015; Steiner *et al.*, 2017; Tal and Seifer, 2017). Ovarian senescence is characterized by a depletion of oocyte quality over time, which corresponds to a reduction in the likelihood of a fertilized oocyte resulting in a live birth (Practice Committee of the American Society for Reproductive Medicine, 2020).

Since the late 1980s several tests, including blood biomarkers and ovarian imaging, have been proposed to more accurately assess the ovarian reserve (Practice Committee of the American Society for Reproductive Medicine, 2015; Tal and Seifer, 2017). Among all proposed ovarian reserve tests (ORTs), serum anti-Müllerian hormone (AMH) concentration and antral follicle count (AFC), defined as the sum of antral follicles in both ovaries as measured by transvaginal ultrasonography during early follicular phase, are regarded to have the best predictive value for ovarian reserve (Practice Committee of the American Society for Reproductive Medicine, 2015; Tal and Seifer, 2017).

Experimental models further suggest that AFC and AMH accurately predict antral follicle pool size, which is also an indirect reflection of remaining primordial follicles (Broer *et al.*, 2014).

However, accurately assessing oocyte quality remains exceedingly difficult. While ORTs have been proposed as a possible solution (Steiner *et al.*, 2017), overlapping age effects on both the residual ovarian reserve and oocyte quality hamper definitive conclusions. As expected, disentangling the independent impact of ovarian reserve remains challenging. In an attempt to clarify this impact, authors have generally relied on several outcomes including age at menopause, IVF success rate, cumulative probability of conception after 6 and 12 cycles, and time to pregnancy (TTP). Depmann *et al.* (2017a)in an individual patient data meta-analysis demonstrated the capacity of AMH for predicting age at menopause and, thus, the end of natural fertility. However, individual age at menopause predictions showed poor accuracy, particularly when predicting early menopause (i.e. $\leq$45 years). As concluded by the authors themselves, clinical application of these findings is problematic Depmann *et al.* (2017a). In IVF, AMH and AFC are used to predict reproductive success measures, including importantly the ovarian response to gonadotrophins. AMH and AFC measurements during IVF are beneficial for individualizing stimulation protocols during controlled ovarian stimulation (COS).

However, few published studies have demonstrated an association of AMH and AFC with pregnancy and, particularly, live-birth rates (Brodin *et al.*, 2013). Critically, the reliability of this study model is likely hampered by differences in oocyte/embryo availability, which itself is considered a predictor of IVF outcome (Drakopoulos *et al.*, 2016; Tarasconi *et al.*, 2017). Prospective studies designed to determine the extent to which ovarian reserve biomarkers can accurately reflect the probability of conceiving naturally have so far failed to demonstrate an association (Hagen *et al.*, 2012; Zarek *et al.*, 2015; Depmann *et al.*, 2017a,b; Steiner *et al.*, 2017). Nested case–control studies derived from cohorts of pregnant women found identical serum AMH concentrations among subfertile and fertile women (as based on the TTP) and a comparable proportion of subjects with low serum AMH levels between the two groups (Streuli *et al.*, 2014; Somigliana *et al.*, 2015).

Fecundity, however, is defined by the capacity to reproduce, which includes not only the ability conceive but also to carry a foetus to viability (Steiner *et al.*, 2017). Within this context, miscarriage rate has been proposed as a possible measure of reproductive capacity (Lyttle Schumacher *et al.*, 2018). Reduced oocyte quality is thought to be the result of meiotic errors, which is considered the leading cause of embryo aneuploidy and, as a consequence, miscarriage (Kim, 2017; Peuranpää *et al.*, 2020).

Unfortunately, few studies have been designed to specifically assess miscarriage risk in women with diminished ovarian reserve (DOR) (Lyttle Schumacher *et al.*, 2018; Peuranpää *et al.*, 2020). Most available data come from studies investigating how ovarian reserve impacts ART outcomes, including the incidence of miscarriage, defined as the spontaneous loss of an intrauterine pregnancy prior to 22 complete weeks of gestation (Zegers-Hochschild *et al.*, 2017). In the present systematic review and meta-analysis, we combine these often neglected data and data from *ad hoc* studies to elucidate the association between DOR, as defined by serum AMH level and/or AFC, and miscarriage risk.

Methods

This literature overview was reported according to the PRISMA guidelines for systematic reviews (Moher *et al.*, 2009; Deeks *et al.*, 2018) and the meta-analysis was conducted according to the MOOSE guidelines (Stroup *et al.*, 2000). Since published de-identified data were used, this study was exempt from institutional review board approval. A protocol for this systematic review and meta-analysis has been registered at PROSPERO (ID number: CRD42021225487).

Sources and study selection

The present systematic review and meta-analysis was restricted to published research articles that reported data relevant to the association between ORTs level and risk of miscarriage. We systematically searched PubMed, MEDLINE, Embase and Scopus, from database inception to 1 March 2021. Searches were limited to studies in humans and were conducted using the following terms: 'AMH' OR 'anti-Müllerian hormone' OR 'AFC' OR 'antral follicle count' OR 'diminished ovarian reserve' AND 'miscarriage' OR 'abortion' OR 'pregnancy loss'.

Studies were included only if: DOR was defined using serum AMH concentration or AFC; miscarriage rate was reported separately for different groups of women categorized according to ORTs levels; the authors reported either the miscarriage rate, as defined as an intrauterine pregnancy loss occurring before 22 weeks of gestation, or there was enough data to calculate it. The loss of an intrauterine anembryonic pregnancy was considered consistent with the accepted definition of miscarriage (Zegers-Hochschild *et al.*, 2017). Studies that generically reported pregnancy loss, defined as pregnancy that failed to result in live birth (i.e., pre-embryonic or embryonic loss, foetal loss, stillbirth, ectopic, or pregnancy of unknown location), were excluded. Studies were excluded if the authors calculated the numerator of the miscarriage rate by adding the number of intrauterine pregnancy losses to the number of pregnancies of unknown location and of biochemical pregnancies. Studies were also excluded if these data were not independently extractable.

The association between DOR and recurrent miscarriage was not investigated because it has already been well described in a recent meta-analysis study (Bunnewell *et al.*, 2020).

Published randomized controlled trials (RCTs) and cohort and case control studies were all eligible for inclusion. All pertinent articles were retrieved and respective reference lists were systematically reviewed to identify additional reports for inclusion in the meta-analysis. Moreover, review articles and meta-analyses that focused on the association between ovarian reserve and ART outcome or natural conception were consulted and their reference lists searched for potential additional studies. No attempt was made to identify unpublished studies.

Two authors (A.B. and P.E.L.S.) independently performed an initial screening of every article's title and abstract. Studies were excluded if they were deemed irrelevant by both the observers. If there was ambiguity or uncertainty for inclusion, studies were discussed at group meetings with the other authors (E.S. and F.C.). Reports were classified according to the study design into RCTs, case–control studies, prospective and retrospective cohort studies.

Risk of bias and quality assessment

Two authors (A.B. and E.S.) independently assessed the included studies for risks of bias using the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies (Wells *et al.*, 2009) and the Cochrane 'Risk of bias' assessment tool for RCTs (Higgins *et al.*, 2019). The authors also graded the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Atkins *et al.*, 2004). Quality of evidence was downgraded by one level for serious concerns and by two levels for very serious concerns for risk of bias, inconsistency, indirectness, imprecision and publication bias.

Data extraction and analysis

Two authors (A.B. and F.C.) independently evaluated all articles and extrapolated the data on standardized forms. A final abstraction form was compiled from the two evaluation forms after a discussion with the remaining authors resolved any reviewer discrepancies.

For every study, the year of publication, location, study design, characteristics of the included subjects, mode of conception (natural or ART conception), and ORTs assessed (serum AMH and/or AFC) were recorded.

Miscarriage risk estimates were calculated for all four of the following comparisons: women with low serum AMH concentration/AFC versus women with medium or high serum AMH concentration/AFC; women with low serum AMH concentration/AFC versus women with medium serum AMH concentration/AFC; women with low serum AMH concentration/AFC versus women with high serum AMH concentration/AFC; women with medium serum AMH concentration/AFC versus women with high serum AMH concentration/AFC.

Women were included in the low, medium and high ORTs level group based on the criteria used in the original studies. To account for possible confounders, sub-analyses were conducted (i.e. splitting studies based on the age of included subjects and serum AMH cutoffs considered for defining DOR).

The risk estimate for miscarriage was expressed using a risk ratio (RR) with 95% CI for prospective, and odds ratio (OR) with 95% CI for retrospective, studies.

The inconsistency of the studies' results was measured using Cochrane Q and the I^2 statistic (Higgins *et al.*, 2019). Risk estimates were combined in a meta-analysis using a fixed effects model when the heterogeneity found among the studies was absent to moderate ($0\% \leq I^2 < 30\%$). When heterogeneity was moderate, substantial, or considerable ($I^2 \geq 30\%$), the DerSimonian and Laird method was used (DerSimonian and Laird 1986; DerSimonian and Kacker, 2007) for a random-effects model (Egger *et al.*, 2001). All analyses were performed using Review Manager (RevMan) [Computer program], Version 5.4, The Cochrane Collaboration, 2020.

Results

Results of search and description of studies

Figure 1 summarizes the process of literature identification and selection of studies (Moher *et al.*, 2009). Our literature searches yielded 347 studies, of which 22 duplicates were removed. After a review of

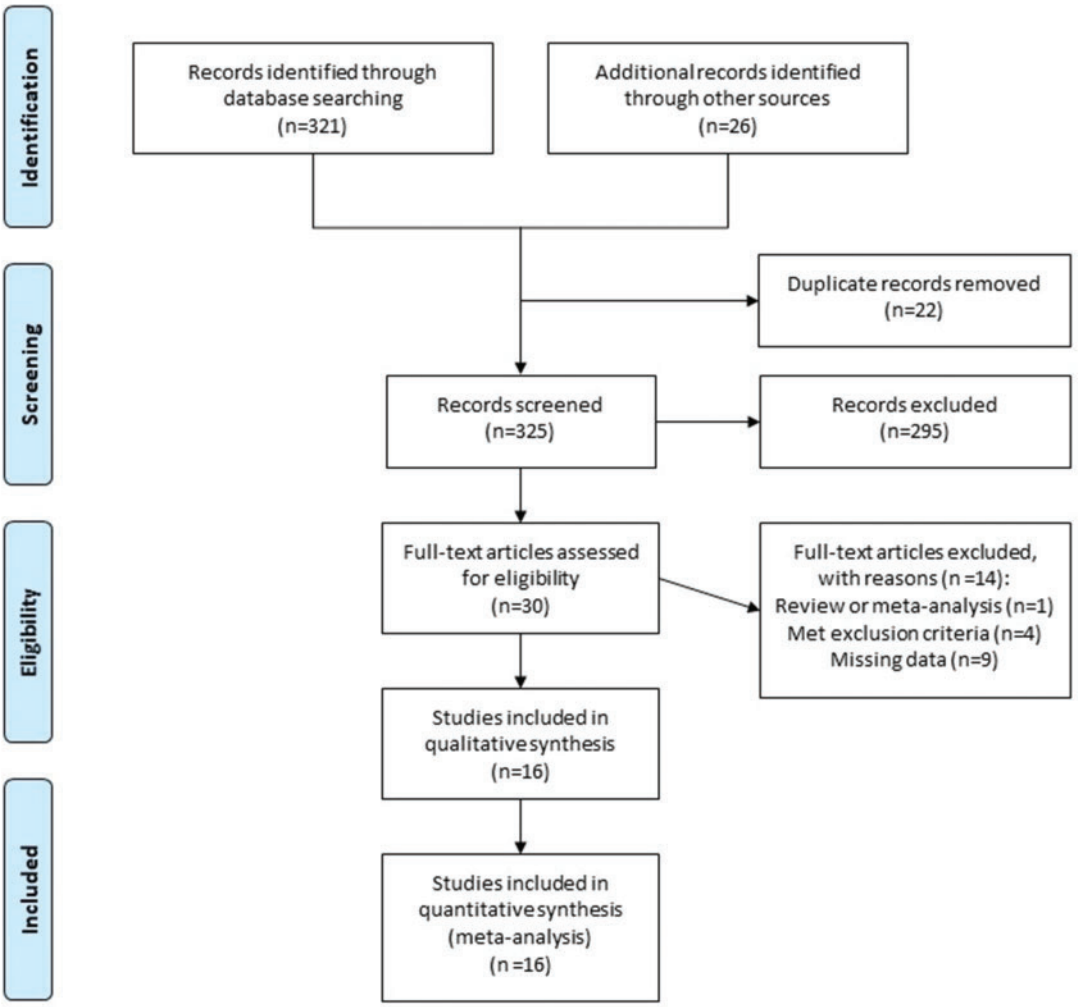

Figure 1. Selection of studies for a systematic review and meta-analysis of diminished ovarian reserve as a risk factor for miscarriage.

the titles and abstracts, 30 studies were identified as potentially eligible for inclusion. After a full review, we excluded one systematic review and meta-analysis (Bunnewell *et al.*, 2020), nine studies because the reported data being insufficient to extract numerator and denominator values for calculating miscarriage rates (Holte *et al.*, 2011; Fridén *et al.*, 2011; Brodin *et al.*, 2013; Arce *et al.*, 2014; van Tilborg *et al.*, 2017; Li *et al.*, 2018; Sjaarda *et al.*, 2018; Shi *et al.*, 2019; Tiegs *et al.*, 2020), three studies because pregnancy loss was defined as pregnancy that failed to result in live birth (Zarek *et al.*, 2016; Bishop *et al.*, 2017; Moreau *et al.*, 2019), and one study because exact AMH cutoffs were not extractable (Tremellen and Kolo, 2010).

Data relevant to the association between ovarian reserve and miscarriage were extracted from the remaining 16 articles (Lekamge *et al.*, 2007; Lan *et al.*, 2013; Szafarowska *et al.*, 2014; Pereira *et al.*, 2016; Keane *et al.*, 2017; Tarasconi *et al.*, 2017; Chang *et al.*, 2018; Lyttle Schumacher *et al.*, 2018; Levi-Setti *et al.*, 2019; Preaubert *et al.*, 2019; Zhang *et al.*, 2019; Abdullah *et al.*, 2020; Dai *et al.*, 2020; Kostrzewa *et al.*, 2020; Peuranpää *et al.*, 2020; Cornille *et al.*, 2021). Of these, two were prospective cohort studies and focused on natural conception, 1 was an RCT and 13 were retrospective cohort studies and reported data about outcomes of pregnancies achieved through ART (i.e. IVF (including classical IVF and ICSI) or IUI). Characteristics of all included studies are reported in Table I.

Cutoff values for defining low, medium and high serum AMH concentration and AFC

Cutoffs for defining low serum AMH concentration varied from 0.5 ng/ml (Preaubert *et al.*, 2019) to 1.96 ng/ml (Lekamge *et al.*, 2007). In most studies it was set to 1 or 1.1 ng/ml (Szafarowska *et al.*, 2014; Pereira *et al.*, 2016; Chang *et al.*, 2018; Lyttle Schumacher *et al.*, 2018; Dai *et al.*, 2020; Kostrzewa *et al.*, 2020; Peuranpää *et al.*, 2020). The cutoff for defining a high serum AMH concentration varied from 2.0 (Peuranpää et al., 2020) to 5.60 ng/ml (Tarasconi *et al.*, 2017).

Table I Characteristics of the 16 included studies.

Study	Country	Design	Characteristics of included subjects	Natural conception/ART	ORT/s assessed	Low AMH serum concentration cutoffs [a]	Medium AMH serum concentration cutoffs [a]	High AMH serum concentration cutoffs [a]	AMH assay	Low AFC cutpoints	Medium AFC cutpoints	High AFC cutpoints	Sub-analysis according to age
Lekamge *et al.* (2007)	Australia	Retrospective cohort study	Patients attending the clinical infertility service of the University of Adelaide. The criteria for inclusion were: (i) first cycle of IVF treatment; and (ii) no evidence of endocrinological disorders. Women with PCOs were excluded	IVF	AMH	≤14 pmol/l (1.96 ng/ml)	>14 pmol/l (1.96 ng/ml)	>14 pmol/l [b] (1.96 ng/ml)	High-sensitivity immunoenzymetric assay (Beckman Coulter, France)	N.R.	N.R.	N.R.	N.R.
Lan *et al.* (2013)	Vietnam	RCT	Women (age <40 years; BMI <28 kg/m^2; early follicular phase FSH < 12 IU/l) randomized to a predefined AMH- or AFC-based r-FSH dosing algorithm in preparation for IVF	IVF	AMH and AFC	<0.7 ng/ml (5 pmol/l)	0.7–2.1 ng/ml (5-15 pmol/l)	>2.1 ng/ml (15 pmol/l)	N.R.	<6	6-15	>15	N.R.
Szafarowska *et al.* (2014)	Poland	Retrospective cohort study	Infertile women (aged 27–44 years) who were diagnosed and treated with ART	ART	AMH	<1 ng/ml (7.14 pmol/l)	1-2.5 ng/ml (7.14-17.85 pmol/l)	>2.5 ng/ml (17.85 pmol/l)	N.R.	N.R.	N.R.	N.R.	N.R.
Pereira *et al.* (2016)	USA	Retrospective cohort study	Patients <35 years of age undergoing fresh IVF who had at least two 8-cell, day-3 embryos transferred with grades 1, 1.5 or 2	IVF	AMH	≤1 ng/ml or ≤0.5 ng/ml (7.14 or 3.57 pmol/l)	>1 ng/ml (7.14 pmol/l)	>1 ng/ml [b] (7.14 pmol/l)	GenII Beckman ELISA assay (Beckman Coulter Inc., CA, USA)	N.R.	N.R.	N.R.	Only women aged < 35 years were included
Keane *et al.* (2017)	Australia	Retrospective cohort study	Women undergoing IVF/ICSI cycles with after AMH/AFC assessment	IVF	AFC and AMH	≤9.9 pmol/L (1.39 ng/ml)	10-19.9 pmol/L (1.40-2.79 ng/ml)	>20.0 pmol/L (2.80 ng/ml)	Beckman Coulter Immunotech AMH Enzyme Immunoassay	<4	5-19	>20	N.R.
Tarasconi *et al.* (2017)	France	Retrospective cohort study	Infertilewomen undergoing IVF-ET. Inclusion criteria were: 1) absence of family history of genetic disorders, congenital malformation, or recurrent pregnancy losses for both partners; and 2) absence of uterine abnormalities and/or malformations	IVF	AMH	0.08–1.60 ng/ml (0.57-11.42 pmol/l)	1.61–5.59 ng/ml (11.50-39.91 pmol/l)	5.60–35.00 ng/ml (39.98-249,9 pmol/l)	AMH Gen II ELISA assay (Beckman Coulter)	N.R.	N.R.	N.R.	The following age groups were analyzed separetely: ≤33, 34-36, ≥ 37 years
Chang *et al.* (2018)	China	Retrospective cohort study	Infertile women who received IVF/ICSI in the Reproductive Medicine Research Center of the Affiliated Sixth Hospital of Sun Yat-sen University between January and December 2017	IVF	AMH and AFC	<1.1 ng/ml (7.85 pmol/l)	≥1.1 ng/ml (7.85 pmol/l)	≥1.1 ng/ml [b] (7.85 pmol/l)	N.R.	<6	≥6 [b]	N.A.	Women aged <37 or ≥37 years were separetly analyzed

Continued

Table I Continued

Study	Country	Design	Characteristics of included subjects	Natural conception/ART	ORT/s assessed	Low AMH serum concentration cutoffs [a]	Medium AMH serum concentration cutoffs [a]	High AMH serum concentration cutoffs [a]	AMH assay	Low AFC cutpoints	Medium AFC cutpoints	High AFC cutpoints	Sub-analysis according to age
Lyttle Schumacher *et al.* (2018)	USA	Prospective cohort study	Women between the ages of 30 and 44 years who were trying to conceive naturally. Women were excluded if they reported a history of infertility, PCOs), or endometriosis, had a partner with infertility, were currently breastfeeding, or did not speak English.	NC	AMH	≤0.4 ng/ml or < 1 ng/ml (2.86-7,14 pmol/l)	≥1 ng/ml (7.14 pmol/l)	≥1 ng/ml [b] (7.14 pmol/l)	Ultrasensitive AMH ELISA, Ansh	N.R.	N.R.	N.R.	N.R.
Zhang *et al.* (2019)	China	Retrospective cohort study	Women who underwent their first IVF cycles in Center for Reproductive Medicine, Shandong University, from March 2013 to June 2014.	IVF	AMH	Young (< 35 yr) group: 0.01–1.32 ng/ml (0.07–9.43 pmol/l); Old (≥35 yr) group: 0.01–0.62 ng/ml (0.07-4.43 pmol/l)	Young (<35 yr) group: 1.32–3.99 ng/ml (9.43–28.49 pmol/l); Old (≥35 yr) group: 0.63–2.41 ng/ml (4.50-17,21 pmol/l)	Young (<35 yr) group: 3.99–22.05 ng/ml (28.49–157.44 pmol/l); Old (≥35 yr) group: 2.41–22.05 ng/ml (17.21-157.44 pmol/l)	ELISA (Ansh Labs, Webster, USA)	N.R.	N.R.	N.R.	IVF outcomes for women < and ≥35 years were reported separetly
Preaubert *et al.* (2019)	Canada	Retrospective cohort study	Women aged ≤39 years initiating their first modified natural IVF cycle between 2010 and 2013 at a university-affiliated private IVF centre. PCOs women were excluded.	IVF	AMH	<0.5 ng/ml (3.57 pmol/l)	0.51–2.03 ng/ml (3.64-14.49 pmol/l)	2.04–6.56 ng/ml (14.57-46.84 pmol/l)	AMH Gen II ELISA, Beckman Coulter Inc., Brea, CA, USA	N.R.	N.R.	N.R.	IV F outcomes for women < 35 years were separetely reported
Levi-Setti *et al.* (2019)	Italy	Retrospective cohort study	Women (age ≤44 years and a BMI between 18 and 27 kg/m^2) classified according to the Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number (POSEIDON) stratification system, scheduled for IVF	IVF	AMH and AFC	<1.2 ng/ml (8.57 pmol/l)	≥1.2 ng/ml (8.57 pmol/l)	≥1.2 ng/ml [b] (8.57 pmol/l)	N.R.	<5	≥5 [b]	N.A.	IV F outcomes for women < and > 35 years were separetely reported
Abdullah *et al.* (2020)	China	Retrospective cohort study	Women (aged between 25–40 years) classified according to the Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number (POSEIDON) stratification system, scheduled for IVF	IVF	AMH and AFC	<1.2 ng/ml (8.57 pmol/l)	≥1.2 ng/ml (8.57 pmol/l)	≥1.2 ng/ml [b] (8.57 pmol/l)	N.R.	<5	≥5 [b]	N.A.	IV F outcomes for women < and > 35 years were separetely reported
Dai *et al.* (2020)	China	Retrospective cohort study	Patients who received IVF/ICSI treatment in the reproductive centre of Changzhou Maternal and Health Care Hospital. Only women aged more	IVF	AMH	<1.1 ng/ml (7.85 pmol/l)	≥1.1 ng/ml (7.85 pmol/l)	≥1.1 ng/ml [b] (7.85 pmol/l)	N.R.	N.R.	N.R.	N.R.	Only women aged more than 36 years were included

Continued

Table I Continued

Study	Country	Design	Characteristics of included subjects	Natural conception/ART	ORT/s assessed	Low AMH serum concentration cutoffs [a]	Medium AMH serum concentration cutoffs [a]	High AMH serum concentration cutoffs [a]	AMH assay	Low AFC cutpoints	Medium AFC cutpoints	High AFC cutpoints	Sub-analysis according to age
			than 36 years without a diagnosis of recurrent spontaneous abortion were included										
Peuranpää *et al.* (2020)	Finland	Retrospective cohort study	Women undergoing their first oocyte retrieval for IVF/ICSI who had their serum AMH measured within the preceding 12 months of their ovarian stimulation and who had at least one subsequent ET cycle (fresh or frozen-thawed)	IVF	AMH	<1.0 µg/L (1 ng/ml) (7.14 pmol/l)	1.0–1.9 µg/L (1.0–1.9 ng/ml) (7.14–13.57 pmol/l)	≥2.0 µg/L (2.0 ng/ml) (14.28 pmol/l)	AMH Gen II ELISA, Beckman Coulter, Brea, CA, USA)	N.R.	N.R.	N.R.	N.R.
Kostrzewa *et al.* (2020)	Poland	Prospective cohort study	Women aged 18–34 years in the first trimester of a spontaneous intrauterine pregnancy, either with an embryo or fetus without any cardiac activity by ultrasound examination or with a normal pregnancy	NC	AMH	<1.1 ng/ml (7.85 pmol/l)	1.1–4.5 ng/ml (7.85–32.13 pmol/l)	>4.5 ng/ml (32.13 pmol/l)	Gen II ELISA kit (Beckman Coulter, Warsaw, Poland)	N.R.	N.R.	N.R.	N.R.
Cornille *et al.* (2021)	France	Retrospective cohort study	Women aged 18-37 years, who had completed an IVF or ICSI cycle with fresh ET.Women at risk for recurrent pregnancy loss and those with a history of gonadotoxic treatment were excluded	IVF	AMH	<0.85 ng/ml (6.07 pmol/l)	1.4–4 ng/ml (10–28.56 pmol/l)	N.R.	Electrochemiluminescence (Elecsys, Roche)	N.R.	N.R.	N.R.	Only women aged ≤37 years were included

[a]In parentheses AMH converted values for each study.
[b]miscarriage was not reported for AMH/AFC medium and high groups separately.
RCT, randomized clinical trial; AMH, anti-Müllerian hormone; AFC, antral follicle count; ORT, ovarian reserve test; PCOs, polycystic ovary syndrome; ET, embryo transfer; N.R., not reported; N.A., not applicable.

In seven studies, with data regarding medium and high serum AMH groups, the AMH values are not reported separately (Lekamge et al., 2007; Pereira et al., 2016; Chang et al., 2018; Lyttle Schumacher et al., 2018; Levi-Setti et al., 2019; Abdullah et al., 2020; Dai et al., 2020).

The cutoff value for defining low AFC varied from four (Keane et al., 2017) to six (Lan et al., 2013; Chang et al., 2018). The cutoff for defining high AFC varied from 15 (Lan et al., 2013) to 20 (Keane et al., 2017). In three studies with data regarding medium and high serum AFC groups, AFC values were not reported separately (Chang et al., 2018; Levi-Setti et al., 2019; Abdullah et al., 2020) (Table I).

Risk of bias and quality assessment results

Results obtained from our risk of bias assessment for observational studies are summarized in Table II. Overall, the quality assessment of these eligible studies showed a low risk of bias. Amongst the nine applicable stars assessing the three main categories of selection, comparability and outcomes, the eligible studies received between eight and nine stars. The RCT conducted by Lan et al. was judged at high risk for performance, detection and reporting bias and at low risk for other bias domains (Lan et al., 2013). Funnel plots were generated and following visual evaluation, no apparent publication bias was observed.

A summary of quality of evidence according to the GRADE system is reported in Table III. Owing to the retrospective design of the majority of included studies, the lower boundaries of CIs being close to unity, and the inability to properly adjust for the effect of age, the quality of evidence was between low and very low.

Synthesis of results

Women with low serum AMH concentration/AFC versus women with medium or high serum AMH concentration/AFC

Serum AMH concentration. Thirteen retrospective studies including women who achieved pregnancy through ART were meta-analyzed (Lekamge et al., 2007; Szafarowska et al., 2014; Pereira et al., 2016; Keane et al., 2017; Tarasconi et al., 2017; Chang et al., 2018; Levi-Setti et al., 2019; Preaubert et al., 2019; Zhang et al., 2019; Abdullah et al., 2020; Dai et al., 2020; Peuranpää et al., 2020; Cornille et al., 2021). We observed a significantly higher risk of miscarriage in women with a low serum AMH concentration (random effects model, OR 1.35; 95% CI, 1.10–1.66; P=0.004; I^2=50%) (Fig. 2A) (Table III).

Three prospective studies were also analyzed (Lan et al., 2013; Lyttle Schumacher et al., 2018; Kostrzewa et al., 2020). Lan et al., reported the outcomes of 2, 20 and 39 pregnancies achieved through IVF in the group of women with low (<0.7 ng/ml), medium (0.7–2.1 ng/ml) and high (>2.1 ng/ml) serum AMH concentration, respectively (Lan et al., 2013). We observed no significant differences (RR 2.95; 95% CI, 0.66–3.18; P=0.16) (Lan et al., 2013). Lyttle Schumacher et al. enrolled 533 women between the ages of 30 and 44 years who were trying to conceive naturally. In the first menstrual cycle after enrolment, participants provided a blood sample on the second, third, or fourth menstrual day and serum AMH concentration was assessed. The authors observed that women with DOR (AMH<1 ng/ml) had an increased miscarriage risk when compared with women with an AMH≥ 1 ng/ml (RR 1.57; 95% CI, 1.09–2.28; P=0.02) (Lyttle Schumacher et al., 2018) (Table III). Kostrzewa et al. included 63

Table II Risk of bias and quality assessment.

Cohort studies	Selection				Comparability	Outcome			
	Representativeness of the exposed cohort	*Selection of the non-exposed cohort*	*Ascertainment of exposure*	*Outcome of interest was not present at the start of the study*	*Comparability of cohorts on the basis of the design or analysis*	*Assessment of outcome*	*Was follow-up long enough for outcomes to occur?*	*Adequacy of follow up of cohorts*	*Total score*
Lekamge et al. (2007)	*	*	*	*	*	*	*	*	8
Szafarowska et al. (2014)	*	*	*	*	*	*	*	*	8
Pereira et al. (2016)	*	*	*	*	*	*	*	*	8
Keane et al. (2017)	*	*	*	*	*	*	*	*	8
Tarasconi et al. (2017)	*	*	*	*	*	*	*	*	8
Chang et al. (2018)	*	*	*	*	*	*	*	*	8
Lyttle Schumacher et al. (2018)	*	*	*	*	**	*	*	*	9
Zhang et al. (2019)	*	*	*	*	*	*	*	*	8
Preaubert et al. (2019)	*	*	*	*	*	*	*	*	8
Levi-Setti et al. (2019)	*	*	*	*	*	*	*	*	8
Abdullah et al. (2020)	*	*	*	*	*	*	*	*	8
Dai et al. (2020)	*	*	*	*	*	*	*	*	8
Peuranpää et al. (2020)	*	*	*	*	*	*	*	*	8
Kostrzewa et al. (2020)	*	*	*	*	*	*	*	*	8
Cornille et al. (2021)	*	*	*	*	*	*	*	*	8

Newcastle-Ottawa Quality Assessment Scale: this scale has a scoring system using asterisks based on three domains, including selection of study groups, comparability of groups, and ascertainment of exposure. A maximum of four asterisks could be given to the selection domain, two asterisks to the comparability domain, and three asterisks to the exposure domain. A greater number of asterisks indicates greater quality.

Table III Miscarriage risk estimates according to the serum AMH concentration/AFC: summary of results and quality of evidence.

Comparator	Nr of studies	Studies design	Effect estimate [95% CI]	Quality of evidence (GRADE)
Women with low AMH versus wn with medium or high AMH				
ART conception				
Main analysis	13	Retrospective	OR 1.35 [1.10–1.66]	Low
Subgroup analysis				
Women < 35 years old	5	Retrospective	OR 1.24 [1.06–1.44]	Low
Women ≥ 35 years old	5	Retrospective	OR 1.48 [1.04–2.11]	Low
AMH < 0.7 ng/ml	4	Retrospective	OR 1.63 [1.05–2.53]	Low
Spontaneous conception				
Main analysis				
Lyttle Schumacher *et al.* (2018)	1	Prospective	RR 1.57 [1.09–2.28]	Low
Kostrzewa *et al.* (2020)	1	Prospective	RR 3.66 [2.1–6.4]	Low
Subgroup analysis				
AMH ≤ 0.4 ng/ml versus AMH > 0.4 ng/ml (Lyttle Schumacher *et al.*, 2018)	1	Prospective	RR 2.21 [1.45–3.38]	Low
AMH ≤ 0.4 ng/ml versus AMH ≥ 1 ng/ml (Lyttle Schumacher *et al.*, 2018)	1	Prospective	RR 2.23 [1.46–3.42]	Low
Women with low AFC versus wn with medium or high AFC				
ART conception				
Main analysis	3	Retrospective	OR 1.81 [1.02–3.21]	Low
Subgroup analysis				
Women < 35 years old	2	Retrospective	OR 1.88 [1.03–3.43]	Low
Women ≥ 35 years old	2	Retrospective	OR 1.38 [0.71–2.65]	Low
Women with low AMH versus Wn with medium AMH				
ART conception				
Main analysis	6	Retrospective	OR 1.31 [1.15–1.51]	Low
Subgroup analysis				
Women < 35 years old	2	Retrospective	OR 1.28 [1.07–1.53]	Low
Women ≥ 35 years old	2	Retrospective	OR 1.85 [1.35–2.52]	Low
AMH < 0.7 ng/ml	3	Retrospective	OR 1.91 [1.40–2.60]	Low
Women with low AFC versus wn with medium AFC				
ART conception				
Main analysis				
Keane *et al.* (2017)	1	Retrospective	OR 2.21 [0.76–6.47]	Very low
Women with low AMH versus wn with high AMH				
ART conception				
Main analysis	5	Retrospective	OR 1.26 [1.08–1.47]	Low
Subgroup analysis				
Women < 35 years old	2	Retrospective	OR 1.37 [0.65–2.89]	Low
Women ≥ 35 years old	2	Retrospective	OR 2.05 [1.42–2.95]	Low
AMH < 0.7 ng/ml	3	Retrospective	OR 2.11 [1.53–2.92]	Low
Women with low AFC versus wn with high AFC				
ART conception				
Main analysis				
Keane *et al.* (2017)	1	Retrospective	OR 3.42 [1.13–10.32]	Very low
Women with medium AMH versus wn with high AMH				
ART conception				
Main analysis	5	Retrospective	OR 1.23 [0.89–1.71]	Low
Subgroup analysis				

Continued

Table III Continued

Comparator	Nr of studies	Studies design	Effect estimate [95% CI]	Quality of evidence (GRADE)
Women < 35 years old	2	Retrospective	OR 0.91 [0.77–1.08]	Low
Women ≥ 35 years old	2	Retrospective	OR 1.08 [0.81–1.44]	Low
Women with medium AFC versus wn with high AFC				
ART conception				
Main analysis				
Keane *et al.* (2017)	1	Retrospective	OR 1.71 [1.00–2.92]	Very low

Nr, number; OR, odds ratio; RR, risk ratio; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

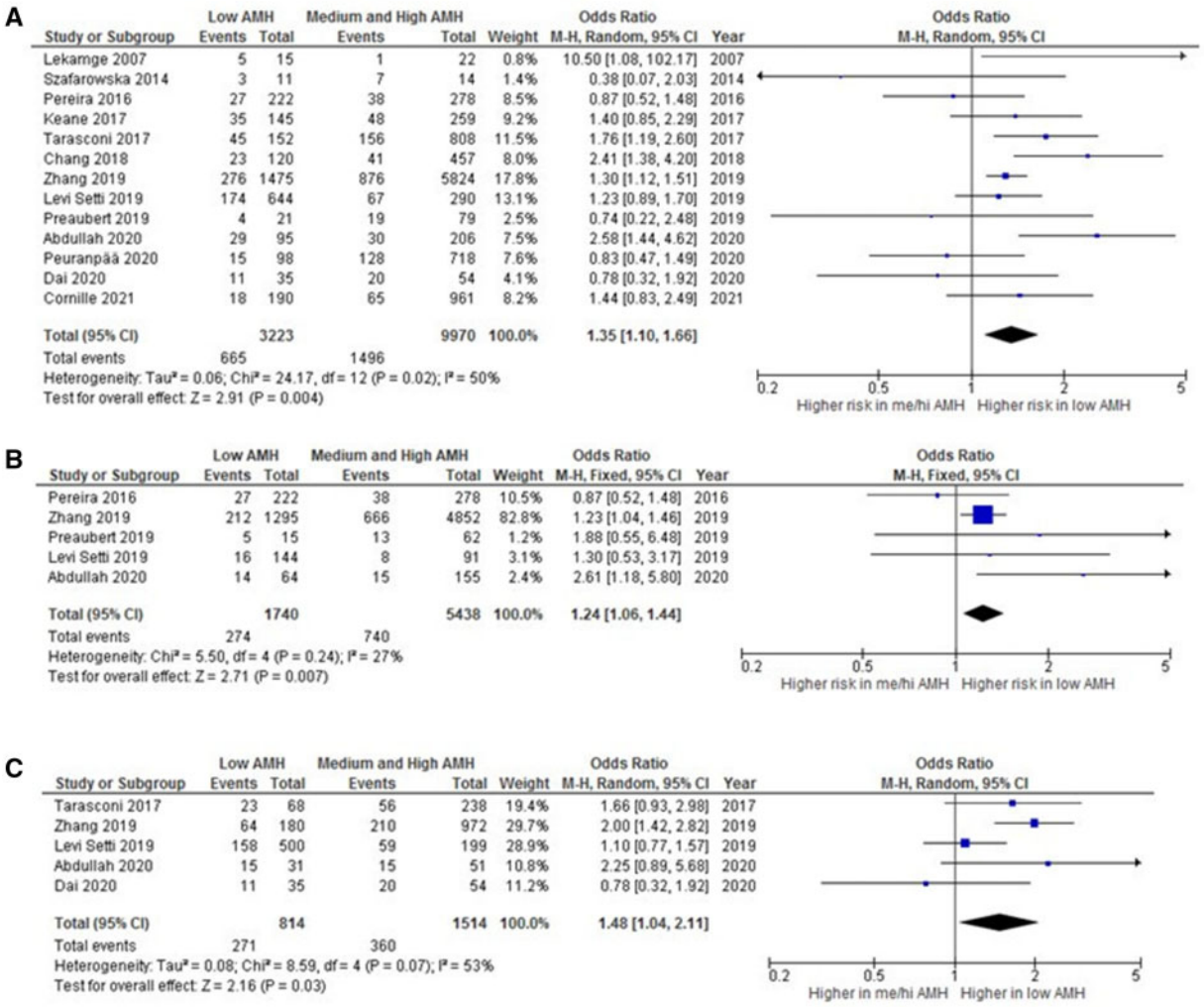

Figure 2. Miscarriage risk estimate according to serum anti-Müllerian hormone concentration. Women with low serum anti-Müllerian hormone (AMH) concentration versus those with medium or high serum AMH concentration. (**A**) Whole cohort. (**B**) Women younger than 35 years. (**C**) Women aged 35 years or older.

women aged 18–34 years with a spontaneous pregnancy at less than 12.6 gestational weeks either with an embryo or foetus without any cardiac activity by ultrasound examination (miscarriage group) or with a normal pregnancy (control group). The authors found a significantly higher risk of pregnancy loss in the first trimester for women with low AMH (<1.1 ng/ml; RR 3.66; 95% CI, 2.1–6.4; $P<0.001$) (Kostrzewa *et al.*, 2020) (Table III). However, these results could not be pooled due to the differing study designs.

Sub-analysis according to subject age. Five retrospective studies provided data for women younger than 35 years old (Pereira *et al.*, 2016; Levi-Setti *et al.*, 2019; Preaubert *et al.*, 2019; Zhang *et al.*, 2019; Abdullah *et al.*, 2020). Pooling of results showed a significantly higher risk of miscarriage in women with a low serum AMH concentration (fixed effects model, OR 1.24; 95% CI, 1.06–1.44; $P=0.007$; $I^2=27\%$) (Fig. 2B) (Table III). Five retrospective studies reported data for women ≥ 35 years (Tarasconi *et al.*, 2017; Levi-Setti *et al.*, 2019; Zhang *et al.*, 2019; Abdullah *et al.*, 2020; Dai *et al.*, 2020). Also, within this subgroup, we observed a significantly increased miscarriage risk for the low serum AMH group (random effects model, OR 1.48; 95% CI, 1.04–2.11; $P=0.03$; $I^2=53\%$) (Fig. 2C) (Table III).

Sub-analysis according to DOR severity. Our meta-analysis was restricted to studies including women with a severely DOR (AMH <0.7 ng/ml) (random effects model, OR 1.63; 95% CI, 1.05–2.53; $P=0.03$; $I^2=47\%$) (Pereira *et al.*, 2016; Keane *et al.*, 2017; Preaubert *et al.*, 2019; Zhang *et al.*, 2019) (Table III). Data published by Lyttle Schumacher *et al.* showed that women with low AMH (≤ 0.4 ng/ml) miscarried at over twice the rate of women with an AMH > 0.4 ng/ml (RR 2.21; 95% CI, 1.45–3.38; $P=0.0002$) and with an AMH ≥ 1 ng/ml (RR 2.23; 95% CI, 1.46–3.42; $P=0.0002$) (Lyttle Schumacher *et al.*, 2018) (Table III).

Antral follicle count. Three retrospective studies including women who achieved pregnancy through ART were meta-analyzed (Keane *et al.*, 2017; Levi-Setti *et al.*, 2019; Abdullah *et al.*, 2020). Pooling of results showed a significantly higher miscarriage risk for women with low AFC (random effects model, OR 1.81; 95% CI, 1.02–3.21; $P=0.04$; $I^2=64\%$) (Fig. 3A) (Table III).

Sub-analysis according to subject age. Two studies provided data for women younger than 35 years and for those aged 35 years or older (Levi-Setti *et al.*, 2019; Abdullah *et al.*, 2020). Meta-analysis showed a higher miscarriage risk for women younger than 35 years old (fixed effects model, OR 1.88; 95% CI, 1.03–3.43; $P=0.04$; $I^2=24\%$) (Fig. 3B) (Table III). We observed no significant risk change for women 35 years or older (random effects model, OR 1.38; 95% CI, 0.71–2.65; $P=0.34$; $I^2=50\%$) (Fig. 3C) (Table III).

Women with low serum AMH concentration/AFC versus women with medium serum AMH concentration/AFC

Serum AMH concentration. We meta-analyzed six retrospective studies that included women who achieved pregnancy through ART (Keane *et al.*, 2017; Tarasconi *et al.*, 2017; Preaubert *et al.*, 2019; Zhang *et al.*, 2019; Peuranpää *et al.*, 2020; Cornille *et al.*, 2021). We observed a significantly higher miscarriage risk in women with low AMH (fixed effects model, OR 1.31; 95% CI, 1.15–1.51; $P<0.0001$; $I^2=3\%$) (Supplementary Fig. S1A) (Table III). Lan *et al.* (2013) reported prospective data for a total of 22 pregnancies, however the calculated risk estimate was not statistically significant (RR 2.50; 95% CI, 0.49–12.89; $P=0.27$).

Sub-analysis according to subject age. Two retrospective studies provided data for women younger than 35 years old (Preaubert *et al.*, 2019; Zhang *et al.*, 2019). Pooling of results showed a significant higher risk of miscarriage in women with a low serum AMH concentration (fixed effects model, OR 1.28; 95% CI, 1.07–1.53; $P=0.006$; $I^2=0\%$) (Table III). Additionally, two retrospective studies reported data for women ≥ 35 years (Tarasconi *et al.*, 2017; Zhang *et al.*, 2019). We observed a significant association between DOR and miscarriage incidence (fixed effects model, OR 1.85; 95% CI, 1.35–2.52; $P=0.0001$; $I^2=0\%$) (Table III).

Sub-analysis according to DOR severity. Two studies focused on women with a severely DOR (AMH cutoff <0.7 ng/ml) (Keane *et al.*, 2017; Preaubert *et al.*, 2019; Zhang *et al.*, 2019). Pooling of results showed a significantly higher miscarriage risk in women with a very low serum AMH (<0.7 ng/ml) (fixed effects model, OR 1.91; 95% CI, 1.40–2.60; $P<0.0001$; $I^2=0\%$) (Table III).

Antral follicle count. Only one study provided sufficient data for comparing miscarriage risk in women with low AFC versus medium AFC. Authors did not observe a significant difference between groups (OR 2.21; 95% CI, 0.76–6.47; $P=0.15$) (Keane *et al.*, 2017) (Table III).

Women with low serum AMH concentration/AFC versus women with high serum AMH concentration/AFCH

Serum AMH concentration. Five retrospective studies including pregnant subjects after ART were meta-analyzed (Keane *et al.*, 2017; Tarasconi *et al.*, 2017; Preaubert *et al.*, 2019; Zhang *et al.*, 2019; Peuranpää *et al.*, 2020). A significantly higher miscarriage risk was observed for women with a low serum AMH (fixed effects model, OR 1.26; 95% CI, 1.08–1.47; $P=0.003$; $I^2=25\%$) (Supplementary Fig. S1B) (Table III).

Sub-analysis according to subject age. Two retrospective studies provided data for women younger than 35 years old. Pooling of results failed to show a significantly different miscarriage risk between groups (OR 1.37; 95% CI, 0.65–2.89; $P=0.41$; $I^2=32\%$) (Preaubert *et al.*, 2019; Zhang *et al.*, 2019) (Table III). Two retrospective studies reported IVF outcomes for women ≥ 35 years old (Tarasconi *et al.*, 2017; Zhang *et al.*, 2019). Meta-analysis of the data showed a significantly higher miscarriage risk for women with DOR (fixed effects model, OR 2.05; 95% CI, 1.42–2.95; $P=0.0001$; $I^2=0\%$) (Table III). Calculated risk estimates using the prospective data provided by Lan *et al.* (2013) resulted in statistically significant association (41 included subjects, RR 3.25; 95% CI, 0.68–15.61; $P=0.14$).

Sub-analysis according to DOR severity. Three studies focused on women with a severely DOR (AMH cutpoint <0.7 ng/ml) (Keane *et al.*, 2017; Preaubert *et al.*, 2019; Zhang *et al.*, 2019). We observed an increased miscarriage risk for women with a very low AMH (<0.7 ng/ml) (fixed effects model, OR 2.11; 95% CI, 1.53–2.92; $P<0.00001$; $I^2=0\%$) (Table III).

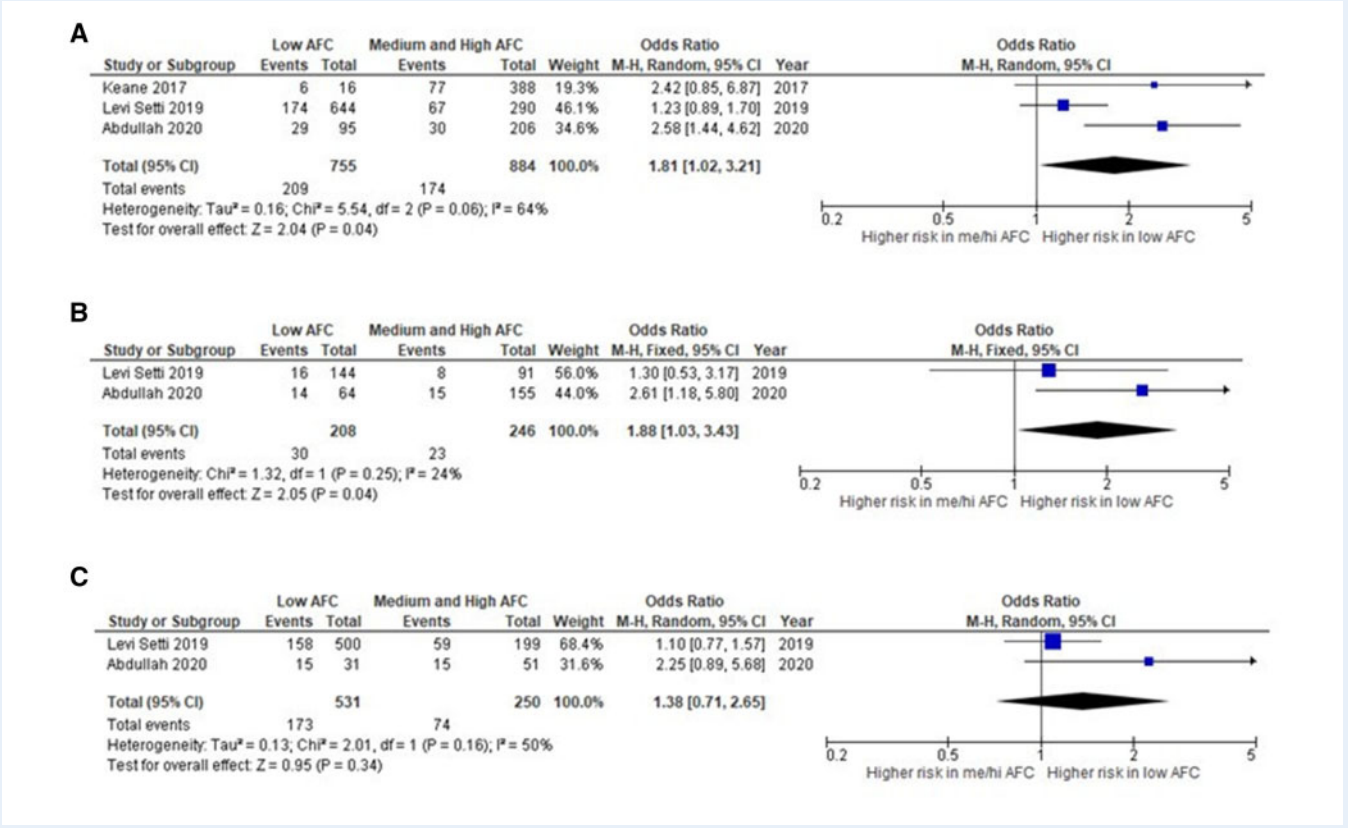

Figure 3. Miscarriage risk estimate according to antral follicle count. Women with low antral follicle count (AFC) versus those with medium or high AFC. (**A**) Whole cohort. (**B**) Women younger than 35 years. (**C**) Women aged 35 years or older.

Antral follicle count. Only one study provided enough data to compare miscarriage risk for women with low AFC versus high AFC (170 included subjects, OR 3.42; 95% CI, 1.13–10.32; P=0.03) (Keane *et al.*, 2017) (Table III).

Women with medium serum AMH concentration/AFC versus women with high serum AMH concentration/AFC

Serum AMH concentration. Five retrospective studies reported miscarriage incidence in women with a medium and a high serum AMH concentration (Keane *et al.*, 2017; Tarasconi *et al.*, 2017; Preaubert *et al.*, 2019; Zhang *et al.*, 2019; Peuranpää *et al.*, 2020). Pooling of these data showed no significant association between serum AMH concentration and miscarriage risk (random effects model, OR 1.23; 95% CI, 0.89–1.71; P=0.23; I^2=63%) (Supplementary Fig. S1C) (Table III). The risk estimate calculated with data provided by Lan *et al.* (2013) showed no significant association (59 included subjects, RR 1.30; 95% CI, 0.41–4.08; P=0.65).

Sub-analysis according to subject age. Our meta-analyses of studies reporting data for women < 35 years old (Preaubert *et al.*, 2019; Zhang *et al.*, 2019) and > 35 years old (Tarasconi *et al.*, 2017; Zhang *et al.*, 2019) failed to show a significant association between serum AMH concentration and miscarriage incidence (fixed effects model, OR 0.91; 95% CI, 0.77–1.08; P=0.28; I^2=28% and fixed effects model, OR 1.08; 95% CI, 0.81–1.44; P=0.60; I^2=6%, respectively) (Table III).

Antral follicle count. Only one study provided sufficient data for comparing miscarriage risk in women with a medium AFC to that of women with a high AFC. Authors did not observe a significantly different risk between groups (388 included subjects, OR 1.71; 95% CI, 1.00–2.92; P=0.05) (Keane *et al.*, 2017) (Table III).

Discussion

Main findings

In the present study, our meta-analysis findings from observational studies that included women who underwent ART are in agreement with those of prospective studies that focused on naturally conceived pregnancies. In fact, synthesis of results in both contexts showed that women with low serum AMH concentrations have an increased risk of miscarriage as compared to those with a medium or high AMH level. Pooling of data from retrospective cohorts also showed a significantly higher miscarriage rate in patients with low AFC. Sub-analyses suggested that the age of included subjects does not influence the association between AMH level and miscarriage risk. On the contrary, after splitting studies that reported outcomes according to AFC level, we observed an increase in miscarriage incidence only in young women (< 35 years old).

We confirmed a significant association between DOR (both when it was defined on the basis of the serum AMH concentration used in the

original studies and when it was defined on the basis of a severely diminished AMH serum concentration (i.e. AMH < 0.7 ng/ml)) and miscarriage when the inclusion in the control group was restricted to women with a medium serum AMH concentration. Interestingly, we also observed no differences in the miscarriage risk between women with a medium serum AMH concentration and those with a high serum AMH concentration. Taken together, our results exclude the possibility that the observed association between low serum AMH concentration and miscarriage risk is actually a reflection of a better reproductive prognosis (i.e. a lower chance of miscarriage) for women with a high serum AMH concentration.

Importantly, sub-analyses showed a slightly higher miscarriage risk in women with a serum AMH concentration < 0.7 ng/ml. An association between a severely reduced serum AMH concentration and miscarriage risk is an intriguing hypothesis that, if confirmed by specifically designed studies, would further strengthen our findings.

In a recent systematic review, Bunnewell *et al.* (2020) highlighted a potential association between DOR (i.e. AMH ≤ 1 ng/ml or AFC ≤ 7) and higher risk of recurrent pregnancy loss (RPL), especially in women with unexplained RPL. Although RPL is a distinct clinical entity, these results are consistent with DOR contributing to the pathophysiology of pregnancy loss. However, while the particular mechanisms involved have yet to be elucidated, currently published evidence does provide enough data to formulate several hypotheses. In a prospective cohort trial, Katz-Jaffe *et al.* demonstrated that, among women undergoing comprehensive chromosome screening after IVF, those with compromised ovarian reserve serum parameters (basal FSH and AMH) had a significantly higher proportion of aneuploid blastocysts than those with normal values (Katz-Jaffe *et al.*, 2013). More recently, Shahine *et al.* showed a higher rate of aneuploid embryos in patients with unexplained RPL and DOR (i.e. cycle Day 3 FSH > 10 UI/ml and/or AMH < 1 ng/ml), when compared to patients with unexplained RPL and normal ovarian reserve testing (Shahine *et al.*, 2016).

However, evidence also exists suggesting the contrary situation. In a recent pivotal prospective study, Steiner *et al.* showed that biomarkers of DOR (i.e. low AMH or high FSH) are not associated with reduced fecundity or a lower probability of conceiving after 6 or 12 cycles of attempting pregnancy (Steiner *et al.*, 2017). Furthermore, in ART populations both live birth rates (LBRs) and embryo euploidy rates within woman's age categories seem not to be influenced by ovarian response to COS (Barash *et al.*, 2017; Irani *et al.*, 2020). These findings partially contradict the above proposed interpretation. In fact, had it been a true aneuploidy problem, we would expect the considered outcomes (i.e. embryo euploidy rate, natural fertility, miscarriage rate and LBR after ART) to be affected in a similar way. Therefore, the available data are intriguing but remain far from definitively defining a causal relation between increased aneuploidy rate and increased miscarriage rate in women with DOR.

Alternative explanations may also be considered but lack robust evidence. In particular, it may be possible that the premature exhaustion of the ovarian reserve reflects some other systematic clinical condition(s) or past exposure(s) that could independently affect ovarian reserve and miscarriage risk. It also may be possible that this association is not exclusively mediated by the oocyte. Furthermore, a common pathogenic insult could affect both the ovary (impairing ovarian reserve formation or accelerating exhaustion) and the uterus (affecting its capacity to receive the embryos). These possibilities would suggest the association between DOR and miscarriage is not causal, but that the two occurrences merely share a common cause. This hypothesis seems plausible, but remains highly speculative and requires specific investigation.

Strengths and limitations

To the best of our knowledge, this is the first systematic review and meta-analysis to examine the impact of ovarian reserve on miscarriage risk. Several limitations should be considered in the interpretation of our results. First, subjects were included in the low, medium and high ORTs level groups, respecting the criteria used in the original studies. Therefore, we were forced to accommodate an overlap in serum AMH concentrations. In order to mitigate this overlap, we conducted a sub-analysis including only subjects with a severe reduction of ovarian reserve (i.e. AMH < 0.7 ng/ml). This allowed us to limit the overlap (at least for the comparison between women with DOR and women with medium or high ovarian reserve) to a serum AMH value not exceeding 0.2 ng/ml.

A second limitation is that the different techniques used to assess serum AMH concentration might diminish the direct comparison of the studies' findings. Indeed, discrepancies between AMH values detected using different assays have been demonstrated (Magnusson *et al.*, 2017). Different sample storage and handling conditions could also influence test results (Broer *et al.*, 2014; Dewailly *et al.*, 2014). To overcome this weakness, studies are urgently need that are conducted according to international laboratory guidelines and that include reference preparations (Broer *et al.*, 2014).

A third limitation is that a considerable proportion of data comes from one study only (Zhang *et al.*, 2019). This may cause this study's results to significantly influence our present meta-analysis. We addressed this possibility by excluding data from this study and repeating our analysis. Our principal association was not altered, even after removal of this data.

A fourth limitation is that female age is the most reliable predictor of miscarriage and may act as a possible effect modifier, limiting the strength of evidence. Unfortunately, in the majority of our included studies, the mean (± SD) age of women is not reported separately for each AMH/AFC category. It was, therefore, not possible to perform a meta-analysis for identifying differences between subject ages across the various ORTs groups. To accommodate this limitation, we independently calculated the risk estimate in women aged < 35 years old and in those ≥ 35 years old and drew conclusions about the impact of ORTs level on miscarriage rate that were independent of age. However, we note that this was an arbitrary choice being used by many of the included studies. Without a robust biological rationale, we urge caution in interpreting these results.

A fifth limitation is that indication to IVF cycles may possibly impact miscarriage rate. As such, endometriosis and tubal factor infertility emerged as possible risk factors for miscarriage (Kawwass *et al.*, 2013; Zullo *et al.*, 2017). Unfortunately, we could not control for these possible confounders in our results.

A sixth limitation is the quality of available evidence, which was between low and very low when evaluated according to the GRADE system.

Lastly, our meta-analyses were performed on studies using an ART population. Therefore, our pooled results may not be applicable to

women who achieve pregnancy through natural conception: prospective studies focused on this latter population are required to provide data that can be combined with existing studies (Lyttle Schumacher *et al.*, 2018; Kostrzewa *et al.*, 2020).

Wider implications

Given the effect estimates and our described limitations, we are not able to make inferences regarding a causal relation between DOR and increased miscarriage risk. There is modest clinical relevance for our findings. An OR of 1.35, means there is 35% relative increase in miscarriage rate. Therefore, if a woman of a specific age has a 20% risk of miscarriage, a low AMH would expose her to an additional 7% absolute risk, increasing her absolute risk from 20% to 27%. The magnitude of this increase is of debatable clinical interest and thus there may be little benefit in providing this information to a patient. However, we believe that even given the modest effect, the association between DOR and an increased risk of miscarriage may guide future research. Overall, we suggest that future research focuses on two main areas. First, we encourage efforts towards elucidating the pathophysiological basis for the association between DOR and miscarriage risk. Clarifying the aetiology of this association may provide new therapeutic opportunities. Second, we encourage the development of study designs capable of controlling for confounding factors and effect modifiers in their results. If our meta-analysis findings were confirmed by such well-designed studies, this information would be of considerable interest in preconception counselling.

Conclusion

In conclusion, the data synthesis provided by our present systematic review and meta-analysis suggests an association between low values of the most reliable ORTs (i.e. serum AMH concentration and AFC) and increased miscarriage risk. Our findings allow us to speculate that, at least in a subgroup of patients with DOR, the levels of these biomarkers could correlate not only with the quantitative but also the qualitative aspects of ovarian reserve. Unfortunately, several methodological weaknesses and discrepancies between studies (primarily owing to the lack of an international standard for AMH values and of information about embryonic chromosomal status) significantly impaired the strength of evidence and conclusions. Therefore, currently published data are insufficient to provide clinical recommendations. However, if our findings are confirmed by future well-designed studies, they may serve as the basis for preconception counselling and guide future research opportunities.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Data availability

The data underlying this article have been extracted from already published articles. All the new generated data are reported in the present version of the manuscript.

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None.

Authors' roles

A.B. conceived the study. A.B., E.S. and P.E.L.S. designed the study protocol. All authors participated in study selection. A.B. and E.S. were involved in quality assessment. A.B. and F.C. extrapolated data. All authors analyzed and interpreted data. A.B. drafted the first version of the manuscript. E.S., F.C. and P.E.L.S. revised the first version of the manuscript. All authors approved the final manuscript version to be published.

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Conflict of interest

E.S. received honoraria from Theramex, MerckSerono and HRA. He also handles grants of research from Theramex, Merck-Serono and Ferring. All the other authors do not have any financial and non-financial competing interest to declare.

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