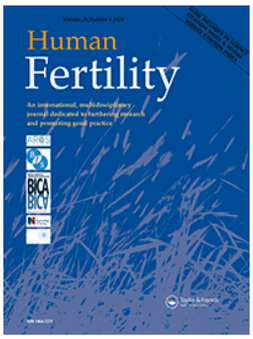

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ORIGINAL ARTICLE

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Is low anti-Mullerian hormone (AMH) level a risk factor of miscarriage in women <37 years old undergoing *in vitro* fertilization (IVF)?

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ABSTRACT

Anti-Mullerian Hormone (AMH) is considered to be one of the most relevant markers of ovarian reserve. However, its association with oocyte quality, pregnancy occurrence and evolution remain to be further investigated. The objective of this study was to compare miscarriage rate after fresh blastocyst(s) transfer in young women (<37 years old) with or without diminished ovarian reserve (DOR), as reflected by low serum AMH levels. This monocentric retrospective study was conducted in 669 women undergoing 1,891 blastocyst transfers. Patients were divided into 2 groups: (1) 190 transfers performed in 106 women with a 'low' serum AMH (< 10th percentile) (i.e. AMH < 0.85 ng/mL); and (2) 961 transfers performed in 563 patients with a 'normal' serum AMH (25th–75th percentile) (i.e. AMH 1.4–4 ng/mL). Miscarriage rate was comparable in both groups (9.5 and 6.8% respectively; $p = 0.2$) as well as implantation rate, pregnancy rate, live birth rate per transfer ($p = 0.4$, $p = 0.07$ and $p = 0.6$, respectively). After multivariate analysis, no significant association was found between serum AMH level and miscarriage rate ($p = 0.22$). In women <37 years, low serum AMH level is not associated with an increase in miscarriage rate after fresh blastocyst transfer.

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Anti-mullerian Hormone; miscarriage; pregnancy loss; spontaneous abortion; diminished ovarian reserve; *In Vitro* Fertilization

Introduction

Anti-Mullerian hormone (AMH) and antral follicle count (AFC) are currently considered the two best ovarian reserve markers (Dewailly et al., 2014). Ovarian reserve decreases physiologically with age. The decline in serum AMH levels accelerates beyond 35–37 years and becomes undetectable 3–5 years before the onset of menopause (Kelsey et al., 2011). However, in some women this is accelerated, with a lower ovarian reserve than expected at their age. Except for some specific cases such as women with Turner syndrome or a history of gonadotoxic treatment, the aetiologies of this phenomenon called 'diminished ovarian reserve' (DOR) are poorly understood (Greene et al., 2014). Although this concept is commonly accepted, and schemes such as the Bologna criteria and the Poseidon criteria to define women with lower prognosis are proposed (Abu-Musa et al., 2020), there is no consensus definition in the literature (Cohen et al., 2015). This entity differs from premature ovarian failure (POF), which has been well defined by the European Society of Human Reproduction and Embryology (European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI et al., 2016). Patients with DOR are generally identified by low AMH and/or low AFC by infertility specialists. Low serum AMH level and/or low AFC are associated with a poor quantitative ovarian response to controlled ovarian hyperstimulation (COH), a greater risk of cycle cancellation, a lower number of collected oocytes, and a reduced number of embryos available for transfer and freezing (Tal et al., 2015).

While the quantitative evaluation of ovarian reserve by AMH level has been largely demonstrated, its association with oocyte quality, and further embryo implantation potential and establishment of an ongoing pregnancy remains debated (Zamah & Stephenson, 2018). The assessment of oocyte quality still remains an unmet challenge. It can only be estimated indirectly through morphological assessment, fertilization rate, embryo morphology and/or aneuploidy, and subsequently implantation rate, miscarriage rate and live birth rate (Chang et al., 2018).

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Early pregnancy loss (spontaneous expulsion of an intra uterine pregnancy of less than 12 weeks), complicate 10–25% of clinical pregnancies (Neilson et al., 2010), both spontaneous and after assisted reproductive technology (ART). The association of maternal age with increased risk of miscarriage (Nybo Andersen et al., 2000), has been largely demonstrated to be caused by embryonic aneuploidy, mainly originating from an increased prevalence of meiotic errors during oogenesis and reflecting an alteration of oocyte quality with age (Spandorfer et al., 2004). However, in young women with DOR, it remains controversial whether the quantitative alteration of ovarian reserve is associated with a qualitative alteration of oocyte quality, which could ultimately lead to increased risk of miscarriage.

Several studies evaluated the link between DOR and occurrence of miscarriage with conflicting results. Levi et al. (2001) reported extremely high pregnancy loss rate with elevated serum FSH regardless of age. On the contrary, some authors found no correlation between FSH levels and miscarriage rate (Bishop et al., 2017), or embryonic aneuploidy (Thum et al., 2008; Weghofer et al., 2007). However, serum FSH is a less relevant ovarian reserve (OR) marker than AMH (Broer et al., 2014). Only 3 studies have evaluated the association between AMH and miscarriage rate, leading to contradictory results (Lyttle Schumacher et al., 2018; Peuranpää et al., 2020; Tarasconi et al., 2017). However, the heterogeneity between these 3 studies in terms of age, AMH threshold and mode of conception (i.e. spontaneous or IVF) means no conclusion can be reached and further studies are needed.

Therefore, the objective of this study was to compare miscarriage rate in women $<$37 years old with DOR and in women with normal ovarian reserve undergoing IVF.

Materials and methods

Population

This longitudinal observational monocentric study was conducted between November 2015 and June 2019. Patients gave their consent for the anonymous use of their clinical data collected from computerized files on the local database, declared to the CNIL (National Commission for Information Technology and Liberties). The study included all women aged 18–37, who had completed an IVF or ICSI (Intra Cytoplasmic Sperm Injection) cycle with fresh embryo transfer.

Exclusion criteria were: (i) patients without serum AMH measurement; (ii) patients at risk for recurrent pregnancy loss (genetic pathology, antiphospholipid syndrome, uterine malformation, cure of synechiae); and (iii) patients with a history of gonadotoxic treatment (chemotherapy, whole body radiotherapy, ovariectomy). Oocyte donation or fertility preservation cycles were also excluded.

The patients were divided into two groups according to serum AMH level: group 1 'low' AMH (AMH $<$ 10th percentile of our population) and group 2 'normal' AMH (25–75th percentile).

Protocol

Ovarian reserve was evaluated by serum AMH and AFC between the 2nd and 5th day of the cycle in the 6 months preceding the IVF attempt. AMH measurement method was electrochemiluminescence (Elecsys©, Roche). AFC was performed by transvaginal ultrasound (Voluson S6 device©, endovaginal probe of 4–9 MHz) according to a standardized protocol.

An antagonist protocol was used for Controlled Ovarian Hyperstimulation (COH). The starting dose of gonadotropins was individually adjusted according to: Body Mass Index (BMI), AMH level, AFC or the ovarian response to previous COH. Hormonal and ultrasound monitoring was performed during treatment. When conditions were favourable (at least 3 follicles $>$ 17mm), ovulation was triggered by recombinant hCG (Ovitrelle© 1 injection of 250 µg). Ovum pickup was performed 36 hours later. Embryos were cultured for 5–6 days up to blastocyst stage for all patients. One or 2 blastocysts were transferred, and supernumerary embryos were vitrified. Luteal phase supplementation with vaginal progesterone (400 mg/day) was performed from ovum pickup to pregnancy test 11 days after embryo transfer.

The pregnancy test was considered positive if the HCG level was $>$100 IU/L. A transvaginal ultrasound was performed between 6 and 8 weeks of amenorrhoea to confirm the course of the pregnancy. Clinical pregnancy was defined as the presence of one or more gestational intrauterine sac with visualized embryonic cardiac activity. Miscarriage was defined as pregnancy loss before 12 weeks of amenorrhoea.

Statistical analysis

The statistical analysis was performed with GraphPad Prism 5 software. The quantitative variables were expressed as a mean ± standard deviation and compared using Student's t-test. Qualitative variables were expressed in terms of numbers (percent) and compared using either the Chi square test or the Fisher

Exact Test by numbers. A value of $p < 0.05$ was considered statistically significant.

The primary outcome of the study was the occurrence of miscarriage. The same analyses were performed including biochemical pregnancies (i.e. very early miscarriages with a bHCG $>$ 100 IU/L).

To rule out possible confounding factors effects, a multivariate logistic model adapted to repeated measures (GEE) was constructed accounting for the repetition of cycles within each patient. An exchangeable correlation structure and robust standard error estimation procedure were used. Multivariable analysis was performed with the R software, v 3.6. Regarding variable selection, a pragmatic approach was used. All variables declared by clinicians likely to interfere with the relationship between AMH level and miscarriage rate were included directly in the model in order to avoid construction of multiple models and the associated alpha risk inflation.

Results

A total of 1,891 fresh blastocysts transfers performed in 669 patients $<$37 years old between November 2015 and June 2019 were included (Figure 1). Two groups were defined: (1) 190 blastocyst transfers performed in 106 women with a 'low' serum AMH $<$ 10th percentile (i.e. AMH $<$ 0.85 ng/mL); and (2) 961 blastocyst transfers performed in 563 patients with a 'normal' serum AMH between the 25th and 75th percentile (i.e. AMH between 1.4 and 4 ng/mL).

Characteristics of the population

The general characteristics of our population are presented in Table 1. The two groups were significantly different in terms of age, BMI, gestity, parity, AFC, basal FSH and AMH. The proportion of women with idiopathic recurrent spontaneous abortion (i.e. $\geq$2 spontaneous abortions including biochemical pregnancies with negative aetiologic assessment, as defined in the ESHRE guideline) (ESHRE Guideline Group on RPL et al., 2018) were comparable (11.1% in group 1 vs. 8.5% in group 2; $p = 0.27$).

Characteristics of IVF cycles

The results of IVF cycles are presented in Table 2. In agreement with lower AMH levels, the total

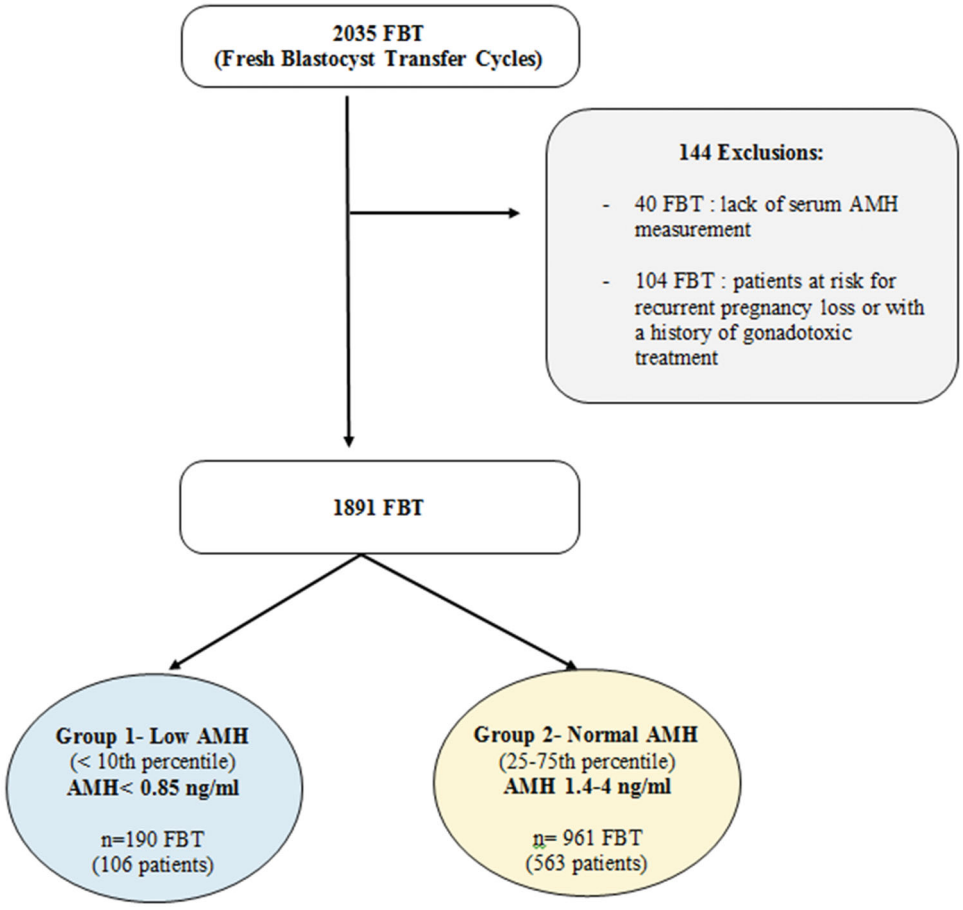

Figure 1. Flow chart diagram showing the recruitment and allocation of study subjects to the two groups.

Table 1. Comparison of general patient characteristics according to AMH concentrations.

	Total population	Group 1 AMH< 0.85 ng/mL $n = 190$ cycles (106 patients)	Group 2 AMH 1.4–4 ng/mL $n = 961$ cycles (563 patients)	p
Age (years)	32.2 ± 3.6	33.7 ± 2.9	32.2 ± 3.6	<0.001*
BMI (kg/m^2)	24.1 ± 5.1	22.8 ± 4.4	24.2 ± 5.2	0.004*
Gravidity	0.9 ± 1.2	1.2 ± 1.5	0.9 ± 1.2	<0.001*
Parity	0.4 ± 0.7	0.6 ± 0.9	0.4 ± 0.7	<0.001*
Smoking status (% active smoker)	223 (19.5%)	29 (15.3%)	194 (20.3%)	0.10
AFC	17.6 ± 9.5	9.2 ± 4.0	19.3 ± 9.4	<0.001*
FSH (mUI/mL)	7.1 ± 2.5	9.1 ± 4.1	6.7 ± 1.8	<0.001*
AMH (ng/mL)	2.2 ± 1.0	0.6 ± 0.2	2.5 ± 0.7	<0.001*

Results are expressed as mean ± standard deviation and numbers (percentage); *Key:* AMH: Anti-Mullerian hormone; BMI: Body Mass Index; AFC: Antral Follicle Count; FSH: Follicle Stimulation Hormone; FET: Fresh Embryo Transfer; *$p < 0.05$.

Table 2. Comparison of IVF cycles' characteristics and pregnancy outcomes according to AMH concentrations.

	Group 1 AMH< 0.85 ng/mL $n = 190$ cycles (106 patients)	Group 2 AMH 1.4–4 ng/mL $n = 961$ cycles (563 patients)	p
Ovarian stimulation Protocol			0.6
Antagonist	183 (96.3%)	933 (97.1%)	
Agonist	7 (3.7%)	28 (2.9%)	
Ovarian stimulation duration (days)	10.6 ± 1.4	9.9 ± 1.4	0.9
Initial dose of gonadotropins (IU)	307.2 ± 69.5	256.6 ± 72.8	0.4
Total gonadotropin dose (IU)	2598 ± 1165	2406 ± 869	<0.001*
Number of mature oocytes retrieved	5.2 ± 3.1	8.5 ± 3.8	<0.001*
Fertilization rate	72.6 ± 24.4	69 ± 22.0	0.06
Number of usable blastocysts	2.1 ± 1.2	2.7 ± 1.9	<0.001*
Number of blastocysts transferred	1.3 ± 0.5	1.3 ± 0.4	0.20
Number of vitrified blastocysts	0.7 ± 1.1	1.2 ± 0.4	<0.001*
Spontaneous abortion rate per transfer	18 (9.5%)	65 (6.8%)	0.2
Implantation rate	22.3 %	25.6%	0.4
Pregnancy per transfer	54 (28.4%)	338 (35.2%)	0.07
Ectopic pregnancy per transfer	2 (1.1%)	15 (1.6%)	0.99
Late miscarriage/MTP/FDIU per transfer	0 (0%)	10 (1%)	0.4
Live birth rate per transfer	34 (17.9%)	248 (25.8%)	0.6

Results are expressed as mean ± standard deviation and numbers (percentage). MTP: medical termination of pregnancy; FDIU: foetal death in utero; IU: international unit; *Statistically significant.

gonadotropin dose was significantly higher in group 1 than in group 2, while the number of oocytes retrieved, the number of usable blastocysts obtained and the number of blastocysts frozen were significantly lower in group 1 than in group 2. The proportion of women with single blastocyst transfer (SBT) was comparable between the 2 groups (127 SBT or 66.8% in group 1 versus 711 or 74% in group 2; $p = 0.4$). The number of cycles per woman was comparable between the two groups ($p = 0.4$).

Pregnancy outcomes

Pregnancy outcomes are summarized in Table 2. In bivariate analysis, spontaneous abortion rate was comparable in the two groups. Among live births, 6 (17.6% of births) were twin pregnancies in group 1 versus 28 (11.3%) ($p = 0.27$). No higher-ranked pregnancies were reported. The same analyses were performed including biochemical pregnancies. Spontaneous abortion rate was comparable in the two groups (18.9 versus 13.4%, $p = 0.08$).

The final logistic regression model included the following predictors: age, BMI, smoking status, the number of embryos transferred and AMH level. Results are presented in Table 3. After adjustment, no significant association was found between serum AMH level and spontaneous abortion rate.

Discussion

In this study we found that miscarriage rate after fresh embryo transfer was not significantly different in women <37 years with either low or normal AMH level after adjustment for age, BMI, and smoking status.

In the literature, the use of serum AMH level as a predictive marker for the occurrence of miscarriage is controversial. Several studies have analysed

Table 3. Multivariate logistic regression analysis: independent explanatory variables associated with miscarriage's occurrence.

	Adjusted OR (CI 95 %)	*p*
Age	1.03 (0.96–1.12)	0.391
BMI	1.06 (0.999–1.11)	0.040
Smoking status	1.20 (0.58–2.48)	0.632
Number of blastocysts	1.55 (0.75–3.23)	0.239
AMH	1.46 (0.73–3.23)	0.239

95% CI: 95% confidence interval; BMI: Body Mass Index; AMH: Anti-Mullerian hormone.

miscarriage rate after IVF ± ICSI according to the serum AMH level (Chang et al., 2018; Lekamge et al., 2007; Morin et al., 2018; Pereira et al., 2016). However, these studies took AMH as a secondary endpoint. In addition, the definition of miscarriage was sometimes unclear, as the inclusion of biochemical pregnancies as miscarriages was not mentioned. Finally, confounding factors such as age, smoking status or BMI were sometimes not taken into account (Chang et al., 2018). Only two studies were specifically designed to evaluate the association between low serum AMH level and post-IVF miscarriages (Peuranpää et al., 2020; Tarasconi et al., 2017). Tarasconi et al. (2017) found a significant increase in miscarriage rate in women with serum AMH < 1.60 ng/mL versus those with AMH > 5.60 ng/mL, regardless of female age and number of oocytes retrieved. However, this study included women with Polycystic Ovarian Syndrome (PCOS) and women over 37 years of age, both at increased risk of miscarriage. Of note, miscarriage rate was comparable between the two groups in women under 34 years of age, in line with our results. Our results are also consistent with those presented in a very recent study reporting the absence of over-risk of miscarriage in 235 women with DOR compared to 870 women with normal AMH level, and to 278 women with intermediate AMH level (Peuranpää et al., 2020). In contrast to this study, we excluded women >37 years of age, and with a history of ovarian surgery in order to analyse only patients with DOR of idiopathic (or unknown) aetiology. It should be noted that AMH thresholds used to classify patients among the 3 groups were chosen arbitrarily in this study (Peuranpää et al., 2020), while we decided to use centiles, which seems to be a more relevant approach in a local database.

The association between low serum AMH and miscarriage rate has also been evaluated in women with spontaneous pregnancy. A first study reported an increased miscarriage risk in women <35 years with serum AMH level < 0.4 ng/mL as compared to those with AMH > 1 ng/mL (OR = 2.3 95% CI 1.3–4.1) after adjustment for age, race, obesity and history of miscarriage (Lyttle Schumacher et al., 2018). Another cohort study found a higher prevalence of low ovarian reserve (AMH < 1 ng/mL) in women with a history of recurrent spontaneous abortion (RSA) than in control women of the same age without history of RSA (19.7 vs 5.7%, $p = 0.013$) (McCormack et al., 2019). Finally, a significantly lower AMH level was reported in women with a history of idiopathic RSA compared with women with RSA of known aetiology (1.2 vs 2 ng/mL; $p < 0.05$) (Pils et al., 2016). Altogether, these results suggest that women with DOR conceiving spontaneously have a higher risk of miscarriage than those with normal ovarian reserve. Further studies including IVF conducted in natural cycles might bring new insights into the complex relationship between ovarian reserve, ovarian stimulation and miscarriage.

We acknowledge that this study has a few limitations. First, its retrospective design exposes to a risk of bias, even if data collection was prospective and exhaustive. Second, there is no consensus AMH threshold for the definition of diminished ovarian reserve. However, and as stated above, we used percentiles distribution which might be the least arbitrary and the most relevant approach in a local database. Third, we arbitrarily decided to include only women <37 years in order to limit the impact of age on miscarriage and to have widely distributed AMH values, so that both groups were clearly defined and separated from each other. Indeed, serum AMH levels fall down to very low levels in women >40 years, and the literature suggests that the physiological decline of the follicular pool (as reflected by AMH level) worsens from the age of 37 years onwards (Kelsey et al., 2011). Finally, aneuploidy screening (PGT-A) could not be performed for legal reasons. Some authors have reported an association between low AMH level and embryonic aneuploidy rate (Katz-Jaffe et al., 2013; Shim et al., 2015), while a more recent study found no increase in aneuploidy rate in women <38 years of age with DOR (Morin et al., 2018). Interestingly, it has been shown in a recent study that implantation rate after euploid embryo transfer was stable, regardless of serum AMH level, while miscarriage rate was surprisingly lower in women with DOR than in reference group with normal AMH level (Wang et al., 2019).

Our study was not designed to provide a pathophysiological explanation for the putative association between AMH and oocyte quality. Nevertheless, it can be noted that several studies reported the absence of oocyte morphological quality impairment with a decrease in AMH (Aydin et al., 2015) as well as the existence of normal embryonic cleavage profiles and

morphokinetic characteristics in women with DOR (Alexopoulou et al., 2019). However, it has been hypothesized that low serum AMH level may be related to deficient AMH production by 'unhealthy' ovarian follicles containing an incompetent oocyte (Tarasconi et al., 2017). Indeed, higher intrafollicular AMH concentrations have been reported in patients with fertilized oocytes compared to those with unfertilized oocytes (Takahashi et al., 2008) but also significantly higher clinical pregnancy rate (Fanchin et al., 2007). Furthermore, recent studies reported a good prediction by follicular fluid AMH levels on embryo development and live birth (Ciepiela et al., 2019; O'Brien et al., 2019). Altogether, this might suggest a relationship between intra follicular AMH level and oocyte competence. However, the local action of intra follicular AMH might not be extrapolated to general effects of circulating AMH levels.

In conclusion, AMH has proven its relevance in the management of IVF patients, particularly in predicting ovarian response to stimulation. Besides this quantitative aspect, the relatively high prevalence of young women with diminished ovarian reserve seeking for IVF also raises the issue of oocyte quality. The question whether AMH level is also a relevant predictor of oocyte quality remains to be addressed. In this study conducted in women $<$37 years, low serum AMH level was not associated with an increase in miscarriage rate after fresh blastocyst transfer, therefore not supporting the concept of impaired oocyte quality in young women with diminished ovarian reserve. This aspect might be important for the counselling of patients.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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