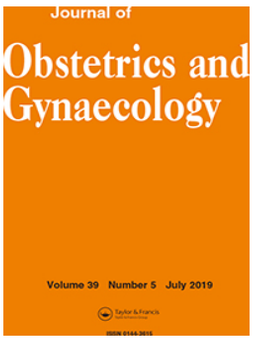

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ORIGINAL ARTICLE

Anti-Müllerian hormone levels in recurrent embryonic miscarriage patients are frequently abnormal, and may affect pregnancy outcomes

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ABSTRACT

This prospective cohort study measured anti-Müllerian hormone (AMH) levels in recurrent miscarriage (RM) patients, compared them to a normal population, and assessed the pregnancy outcomes. The RM patients demonstrated AMH levels that were significantly lower than the normal population, both in women aged ≤35 years, and those aged >35 years. AMH percentiles were found to be significantly lower in the study group of RM patients ≤35 years ($p < .004$) in the 5th and 50th percentiles, and in all percentiles in women >35 years ($p < .03$), were compared to women from a normal population. Serum AMH levels may reflect quality, and quantity of the remaining oocytes in these patients, and RM patients may have a low ovarian reserve, and a potentially poor oocyte quality, as shown by low circulating AMH. The evaluation of AMH levels in a RM work up may allow realistic counselling and possible ART referral in RM patients.

KEYWORDS

Anti-Müllerian hormone; recurrent miscarriages; ovarian reserve; subfertility; embryonic losses; foetal losses

IMPACT STATEMENT

- **What is already known on this subject**? There is some evidence to show that low AMH levels are associated with recurrent miscarriages and this is thought to be due to a decreased oocyte quality. The AMH levels are lower in the patients with endometriosis, and are often significantly higher in the patients with polycystic ovarian syndrome. Both conditions are independently associated with miscarriages.
- **What the results of this study add?** Anti-Müllerian hormone (AMH) levels were found to be significantly lower in recurrent miscarriage patients, compared to a normal population. This may be another factor contributing to miscarriages. The spontaneous pregnancy rates in the miscarriage group significantly improved with increasing AMH levels. This may confirm that patients with low AMH levels have poorer quality oocytes, and thus may be considered 'sub-fertile'. It was also found that the utilisation of assisted reproductive technologies (ART) to achieve a pregnancy was significantly reduced in the groups with a higher serum AMH.
- **What the implications are of these findings for clinical practice and/or further research?** Serum AMH levels should be offered to all patients as part of a recurrent miscarriage work up. Detecting the low AMH levels and counselling the patients on these findings may allow them the option of accessing ART. ART may have the ability to expedite conception rates, and with pre-implantation genetic analyses, could possibly select the embryos with the greatest chance of survival. Further research is needed to establish how the decreased AMH levels contribute to recurrent miscarriages.

Introduction

Ovarian reserve is the terminology used to describe the existing number of follicles within the ovaries. Although serum AMH levels are an indirect reflection of ovarian reserve, they have already been shown to be highly correlated with the remaining number of antral follicles, another indirect measure of ovarian reserve (Gruijters et al. 2003; Visser et al. 2006; Barad et al. 2009; Hansen et al. 2011; Kelsey et al. 2012). Early pregnancy losses are the most common complication of human gestation, occurring in 50–75% of all women trying to conceive (Petrozza 2006). Many of these losses occur before or with the next expected menses. With the advent of sensitive pregnancy detection kits available to the general public, previously unrecognised losses are frequently detected. With the losses that occur after the first missed menstrual cycle, approximately 15–20% are spontaneous miscarriages or ectopic pregnancies (Petrozza 2006). Approximately, 5% of couples trying to conceive will have two consecutive losses, and approximately 1% of couples will suffer three consecutive losses during their reproductive lives which is unlikely to be due merely to chance since it has been estimated that the probability of three consecutive losses is 0.34% (Bopp and Seifer 1998; RCOG 2011; Petrozza 2012). Christiansen stated that a risk factor could be detected in approximately 50% of couples experiencing pregnancy loss, there was very seldom a single factor, and that the majority of losses have a multifactorial background involving

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the interaction of multiple genetic and environmental risk factors (Christiansen 2016). It is possible that some of these patients may have low ovarian reserves, and poorer quality oocytes. The purpose of this study was to assess the AMH levels in patients attending a recurrent miscarriage (RM) clinic, compare the results with those of a normal population, and to document the subsequent pregnancies.

Materials and methods

Recurrent embryonic miscarriage patients attending a RM clinic between June 2008 and May 2014 were included. They were offered serum anti-Müllerian hormone (AMH) testing, as well as the routine investigations that are typically offered in a RM clinic, which includes a 3D ultrasound, blood tests for endocrine (thyroid, prolactin levels) metabolic (GTT and insulin studies, homocysteine levels) autoimmune (thyroid antibodies, antinuclear antibodies), obstetric antiphospholipid syndrome, nutritional vitamins D and B, and folate, and a karyotype of both partners. Women with at least two consecutive embryonic losses (less than 10 weeks from the last menstrual period) were included (Kolte et al. 2015). An informed consent was obtained from all of the patients.

The women were divided into two groups, those aged 35 years or younger, and those aged over 35, because of the well-known effects of advanced maternal age (Nybo Andersen et al. 2000).

AMH assay

The serum AMH was quantified by immunoassay at Clinpath Laboratories using a DSL AMH generation II method (Beckman-Coulter Anti-Müllerian immunoassay).

The AMH levels were recorded and all of the pregnancy outcomes documented, including those in each group who did not achieve a pregnancy over a period of two years after the test was done, and those who only had further pregnancy losses. These outcomes were documented for all AMH levels (low, normal and high) in the two age groups. The women were followed up in the clinic for two years to ascertain whether they had achieved their pregnancy spontaneously or by ART and whether they had a live birth (LB).

Ethics approval

This study formed part of a Clinical Trial named the PAPO (Prediction of Adverse Pregnancy Outcomes) study (Clinical Trial Number ACTRN12609000254291). The study was approved by the Human Research Ethics Committee REC1481/6/09.

Statistics

The serum AMH concentrations in these women were compared with those from a healthy cohort using data obtained with permission from Shebl et al. (2011). The 5th, 50th and 90th percentiles in the age groups ≤35 and >35 years were compared, and data were analysed using the Chi-square test. The pregnancy outcomes in the women from the RM clinic who achieved an ongoing pregnancy, spontaneously or via ART, with low (<10 pmol/L), medium (10.1–30 pmol/L) or high (>30 pmol/L) serum AMH were compared by ANOVA (SPSS Version 19, SPSS Inc., Chicago, IL).

Results

During the study period, 202 patients were offered AMH testing, 182 women accepted, and 20 declined testing. Serum AMH results in the miscarriage group were compared with 1105 women in a presumably healthy sub group. The 5th, 50th and 90th percentiles were compared in the two groups – women aged ≤35 years, and women aged >35 years. The ethnicities of the patients were: Caucasian 88%, African 3.4%, Vietnamese/Chinese 3.4%, Middle Eastern 3.4% and Indian 1.7%. The numbers of losses ranged from 2 to 11. AMH centiles were found to be significantly lower in the study group of RM patients ≤35 years ($p < .004$) and in those aged greater than 35 years ($p < .03$), compared to women from a healthy population (Figures 1 and 2).

The percentages of women with low, normal and high serum AMH concentrations were assessed. Overall, 53.3% of all patients tested had low serum AMH, 34.6% were in the normal range and 12.1% were in the high range. In the group of women aged ≤35 years, 41.2% had serum levels of AMH considered to be low, 36.8% had normal levels and

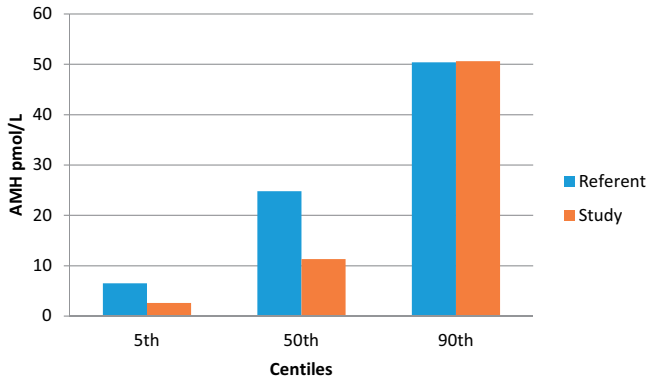

Figure 1. Anti-Müllerian hormone (AMH) levels in women aged ≤35 years, compared to a normal (referent) population (data derived from Shebl et al. 2011, with permission). The 5th, 50th and 90th percentiles were considered. The normal population showed significantly higher AMH levels in the 5th and 50th centiles ($p < 0.004$).

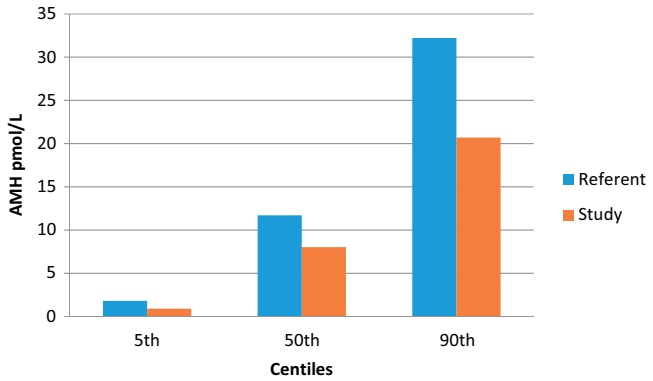

Figure 2. AMH levels in women aged >35 years compared to a normal (referent) population. The 5th, 50th and 90th centiles were compared. The normal population showed significantly higher levels in all centiles ($p < 0.03$).

Table 1. Outcomes regarding infertility, pregnancies, pregnancy losses and deliveries in women aged ≤35 years, in each of the AMH groups.

≤35 years; 37.4%; 68	≤10 pmol/L	10.1–30 pmol/L	>30 pmol/L
Total % patients	41.2% (28)	38.8% (25)	22% (15)
No pregnancies achieved	21.4% (6)	8% (2)	13% (2)
Pregnancies	78.57% (22)	92% (23)	87% (12)
Spontaneous	50% (11)	78.3% (18)	100% (12)
ART	50% (11)	21.7% (5)	0% (0)
Miscarriages	27.3% (6)	26.1% (6)	25% (3)
Spontaneous	66.7% (4)	66.7% (4)	100% (3)
ART	33.3% (2)	33.3% (2)	60% (0)
Deliveries	57.1% (16)	68% (17)	75% (9)
Spontaneous	43.7% (7)	82.35% (14)	100% (9)
ART	56.3% (9)	17.65% (3)	0% (0)

Low, <10 pmol/L; normal, 10.0–30 pmol/L; high, >30 pmol/L.

22% had high levels. PCOS had been diagnosed in 84% of those with an AMH > 30 pmol/L.

The women aged >35 years had lower AMH levels compared to women 35 years or less ($p<$ .000) as would be expected with 60.5% with low AMH, 33.3% with normal levels, and 6% had high levels. PCOS had been diagnosed in 50% of those with AMH levels >30 pmol/L.

Pregnancy outcomes

Patient follow up showed that among women aged ≤35 years with low AMH levels, 21.4% were designated infertile; in that they did not achieve a desired pregnancy over a two-year period. Precisely, 27.3% only had miscarriages, resulting in an overall LB in women with low AMH levels of 57.1%. Of the latter, 43.7% were spontaneously conceived pregnancies, and 56.3% utilised assisted reproductive technologies (ART). In the women ≤35 years with normal AMH levels, 8% were infertile, 26.1% had only miscarriages, and the overall LB rate was 68%; 82.4% of which were spontaneous pregnancies, and 17.6% were the result of ART (Table 1).

The higher rate of ART between the women with low and those with normal AMH levels was statistically significant ($p<$ .002). The women with high AMH levels had a 13% infertility rate, 25% pregnancy loss rate and an LB rate of 60%, all following spontaneous conceptions (Figure 3).

In the women aged >35 years, with low AMH levels, 36.2% were infertile, and 52.3% of them experienced only miscarriages. There was an LB rate of 30.45%, of which 47.6% were spontaneous conceptions, and 52.4% were the result of ART. Those women with normal AMH levels had infertility rates of 28.9%, and 'losses only' of 55.6%. The overall LB rate was 44.4%, of which 91.7% were conceived spontaneously and 8.3% were the result of ART. The higher rate of ART in women with low versus normal AMH levels was statistically significant ($p<$ .007) (Figure 4).

In the women with high AMH levels, there were no infertile patients, 'losses only' 57.1%, and the LB rate was 42.85%, and all were conceived spontaneously (Table 2). The LB rate was reduced in all three AMH groups in women aged >35 years, as would be expected, with the greatest losses occurring in the women >35 with high AMH levels.

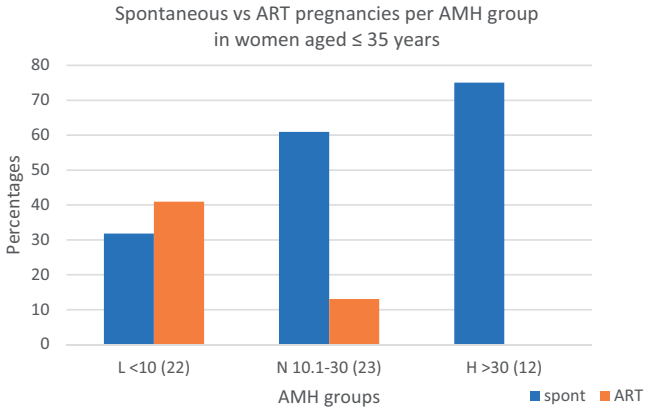

Figure 3. Spontaneous pregnancies versus assisted reproductive technology (ART) pregnancies in low, normal and high AMH groups, in women aged ≤35 years, in each of the AMH groups. The need for ART decreased in women in normal and high serum AMH levels ($p < 0.002$). Spont: spontaneous pregnancies; ART: assisted reproductive technology; L: low; N: normal; H: high AMH levels.

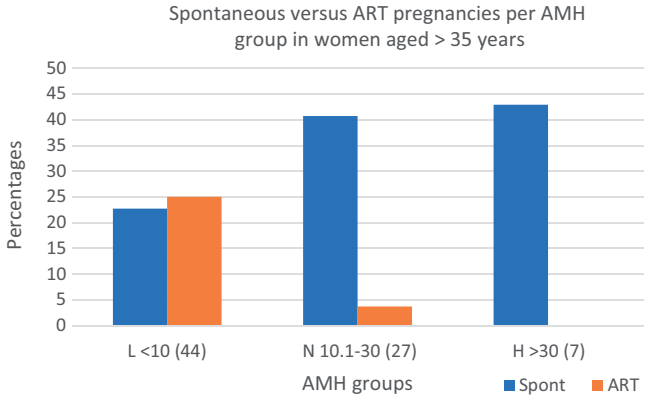

Figure 4. Spontaneous pregnancies versus ART pregnancies in low, normal and high AMH groups in women aged >35 years. The need for ART decreased in the normal and high AMH groups ($p < 0.007$). Spont: spontaneous pregnancies; ART: assisted reproductive technology; L: low; N: normal; H: high AMH levels.

Discussion

Fertility trends in the twenty-first century are different from previous centuries, with many women choosing to delay the birth of their first child until their mid-thirties, due to career choices, divorces and re-marriages. Traditionally the 'perimenopause' is described as the time when ovarian function declines, resulting in clinical symptoms such as menstrual irregularities. It is

Table 2. Outcomes regarding infertility, pregnancies, pregnancy losses and deliveries in women aged >35 years, in each of the AMH groups.

>35; 62.5% (114)	≤10 pmol/L	10.1–30 pmol/L	>30 pmol/L
Total patients	60.5% (69)	33.3% (38)	6.2% (7)
Infertility	36.23% (25)	28.95% (11)	0
Pregnancies	63.77% (44)	71.05% (27)	100% (7)
Spontaneous	50% (22)	70.37% (19)	85.71% (6)
ART	50% (22)	29.63% (8)	14.29% (1)
Miscarriages	52.27% (23)	55.56% (15)	57.14% (4)
Deliveries	30.44% (21)	31.58% (12)	42.85% (3)
Spontaneous	47.62% (10)	91.67% (11)	100% (3)
ART	52.38% (11)	8.33% (1)	0

Low, ≤10 pmol/L; normal, 10.1–30 pmol/L; high, >30 pmol/L.

thought to be due to the continuous loss of oocytes with ageing; however, in recent years, ART have identified the events that precede menopause (Seifer and Naftolin 1998; Dólleman et al. 2014). An accelerated deterioration of ovarian function begins much earlier than previously thought, probably in the mid-thirties (Bopp and Seifer 1998), and possibly earlier in some women, often without obvious symptoms. While it is well established that ovarian reserve declines with age (Nikolaou et al. 2002; Baird et al. 2005), the rate of this decline seems to vary among individuals and depends on the family history, medical history, as well as on various environmental and genetic factors. Severe endometriosis, pelvic inflammatory disease, ovarian surgery, various systemic illnesses, chemotherapy and possibly smoking are all known factors affecting ovarian reserve (Faddy et al. 1992; Sharara et al. 1998). It is possible that such 'sub fertility' could play a role in miscarriages, and AMH levels could predict the LB chances of patients attending the clinic (Lukaszuk et al. 2014). It is not ethically possible to directly measure ovarian reserve as this would involve an invasive and potentially ovarian damaging biopsy. Studies have shown highly significant positive correlations between AMH levels and the ovarian reserve assessed by manual stereological counts of non-growing follicles in ovarian tissue samples (Hansen et al. 2011). Whether low AMH levels reflect the quantity and quality of the remaining oocyte pool or not, has been widely discussed. Lehmann et al. (2014) described AMH as a 'valuable biomarker of oocyte quality in IVF'. Irez et al. (2011) also showed that AMH levels may predict the oocyte quality. Conversely, high levels reflect the polycystic ovarian syndrome, and thus the metabolic factors associated, such as hyperinsulinism, dyslipidaemia and hypertension, may be independent risk factors for pregnancy losses (Cocksedge et al. 2009).

Pils et al. (2016) and Atasever et al. (2016) both demonstrated that AMH levels were significantly lower in the RM groups compared to controls. Our findings suggest that a low ovarian reserve may be a factor in RM patients, and as such, should possibly be considered when offering assessments of such couples, as the detection of low levels, particularly in a younger patient, may be significant for their pregnancy planning. Kedem et al. 2013, showed that it is unnecessary to distinguish between low and extremely low AMH levels, when counselling patients or referring them for ART. They showed that both the low and extremely low AMH group had similar pregnancy rates in IVF cycles (Kedem et al. 2013).

The spontaneous pregnancy rates improved with increasing AMH levels, this may suggest that patients with low AMH levels have poorer quality oocytes and may thus be considered as 'sub-fertile' (Gnoth et al. 2005; Ebner et al. 2006). Greenwood et al. 2017 found that patients with rigorously defined infertility had AMH levels and antral follicle counts (AFC) no different to community-based controls. Their findings challenge the assumption that ovarian reserve is an indicator of fertility. AMH correlates well with AFC in normo-ovulatory IVF populations and is also strongly associated with a poor ovulatory response to stimulation when low, and has the ability to predict an excessive response to ovarian stimulation when high (Greenwood et al. 2017). However, RM patients may be an entirely different cohort with additional factors contributing to decreased AMH levels, as well as adverse pregnancy outcomes. Detecting the low AMH levels and counselling the patients about these findings may have increased the use of ART in this group. ART may have the ability to expedite conception rates, and with pre-implantation genetic analyses, ART could possibly select embryos with the greatest chance of survival (Brezina et al. 2013). In support of this concept, the need for ART was significantly reduced in the groups with higher serum AMH. Detecting high levels could alert the clinician to the possibility of PCOS and its consequences.

The LB rate was reduced in all three AMH groups in the women aged greater than 35 years, as would be expected; with the greatest losses occurring in the women aged over 35 with high AMH levels. High levels at this age are more likely to reflect the contribution of PCOS, and the consequent metabolic disturbances that may be embryotoxic (Kdous et al. 2009).

Strengths and limitations

This is a small study; larger studies are needed to confirm these findings. AMH levels are not thought to be influenced by the stage of the menstrual cycle, and as such AMH is an excellent marker of ovarian reserve, allowing the clinician to assess where the patient is in her reproductive lifespan. This may be critical in patients experiencing miscarriages.

Conclusions

The patients attending a RM clinic may have a low ovarian reserve, and potentially a poor oocyte quality, as shown by low circulating AMH. Establishing the ovarian reserve early in the work up allows the clinician to concentrate on possible interventions that may expedite the patient's journey towards the goal of achieving a successful pregnancy. Women should still undergo a full miscarriage work up, and any potential contributing factors should be treated as expeditiously as possible. Early detection allows a realistic counselling, reassurance and relevant interventions in this traumatised group of patients.

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Disclosure statement

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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