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Anti-Müllerian hormone concentrations and parity in fertile women: the model of oocyte donors

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KEY MESSAGE

Serum anti-Müllerian hormone (AMH) concentration measured in a fertile female cohort showed too much variability to be a good fertility index. Assessment of serum AMH should only be discussed for patients at risk of ovarian failure because of personal or family history.

A B S T R A C T

In France until the end of 2015, oocyte donors must have had at least one child and be aged 18–37 years. This population of fertile women was selected to examine whether serum anti-Müllerian hormone (AMH) concentration could be a reliable correlate of spontaneous pregnancy in women who had proven their fertility before. A cohort of 217 women followed between 2009 and 2015 for oocyte donation at the University Hospital of Lille comprised this retrospective study. In these egg donors, aged 20–37 (median: 32 years), the median serum AMH level was 22 pmol/l (5–95th percentiles: 4.9–61.8). No significant correlation was found between serum AMH level and the number of children or the youngest child's age. Among the 32 women with AMH <10 pmol/l, 9 and 3 were less than 30 and 25 years old, respectively. Six women (2.8%) had undetectable serum AMH, i.e. <3 pmol/l. In conclusion, serum AMH level measured in this fertile female cohort showed too much variability to be a good fertility index. Assessment of serum AMH should only be discussed for patients at risk of ovarian failure.

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Introduction

Although it is well established that female fertility declines with age, the rate and timing of this decline varies significantly among women (Broer et al., 2014). This is mainly due to inter-individual differences in ovarian reserve. The ovarian reserve refers to the number of primordial follicles defined at birth, which gradually decreases throughout reproductive life, with the continuous initiation of growth of some follicles, and then mostly their apoptosis. The ovarian reserve cannot directly be measured, but it can be estimated through the number of growing follicles, and more specifically the antral follicles. Anti-Müllerian hormone (AMH) is the follicle marker known to best reflect the ovarian reserve (Broer et al., 2014). AMH is a homodimeric glycoprotein from the transforming growth factor b (TGFβ) family and is produced in women by granulosa cells in the ovarian follicles. AMH is expressed at all stages of folliculogenesis, but mostly in pre-antral and small antral follicles (Weenen et al., 2004). Serum AMH is then a good assessment of the number of growing follicles, and therefore of ovarian reserve. One of the roles of AMH is to inhibit early follicular growth, preventing the entry of primordial follicles into the growing pool and thus premature exhaustion of follicles/oocytes (Durlinger et al., 2002). Serum AMH is the first marker to decrease when the ovarian reserve declines (Broer et al., 2014). Its serum concentration peaks around 25 years of age, and then progressively decreases until menopause (Lie Fong et al., 2012).

Women frequently seek assessment of fertility and their ability to become pregnant (Birch Petersen et al., 2015). In many countries, with women's education and access to secondary schools, the average age of the first pregnancy is almost 30. However, delaying childbearing after 30 years of age is associated with a reduced probability of spontaneous pregnancy and a longer time before conception (Broer et al., 2014). Accurate ovarian reserve assessment may modify the childbearing plan of some women. Similarly, predicting the approximate age of menopause could allow women to think differently about their fertility and pregnancy plans (Dolleman et al., 2014). It could perhaps influence some women to consider pregnancy sooner, if they knew that their fertility was reduced. By contrast, it could comfort some other women in delaying the time for pregnancy. Some authors proposed assessing the ovarian reserve before starting hormonal contraception, in order to screen patients for premature ovarian failure.

So, it is tempting to use serum AMH assay in the general population, in order to facilitate short- and long-term pregnancy planning. In assisted reproductive technology, many studies demonstrate that serum AMH is a good predictive marker for ovarian response in ovarian stimulation (Broer et al., 2014), but not for pregnancy (Broer et al., 2014). Yet, no study has demonstrated a correlation between serum AMH levels and probability of spontaneous pregnancy, in women of childbearing age without a fertility issue. Thus, it is not recommended for use in the general population as an assessment of spontaneous fertility (La Marca et al., 2009; Zarek et al., 2015).

At the University Hospital of Lille, there is a specific clinic for women wishing to be egg donors. Until the end of 2015, these potential donors were required to be biological mothers (with at least one child) and between 18 and 37 years of age. This population has demonstrated its fertility and represents a good model to assess serum AMH concentration as a fertility index. The aim of the present study was to determine whether serum AMH concentration could be a reliable correlate of spontaneous pregnancy in women with previously proven fertility, parity being the main outcome. AMH concentrations were assayed a few years after the egg donor's spontaneous pregnancies, but numerous studies confirmed that in young women AMH serum concentrations decline slowly with age. In women aged 21–41, Bentzen et al. (2013) calculated that serum AMH concentration declines by 5.6% per year.

Materials and methods

This was a retrospective study from 2009 to 2015 in Lille University Hospital. Data were collected from 217 fertile women who wished to be egg donors. These women were biological parents (with at least one child) and aged between 18 and 37. This study was approved by the Institutional Review Board of the University Hospital on 19 July, 2016 (reference DEC16–25).

Data collected during the first appointment were: age, parity, body mass index (BMI), smoking, contraception and the age of the youngest child. A blood test for serum AMH was carried out on the same day, regardless of the day of the cycle and the type of contraception. Throughout the duration of data collection, the immunoassay used was the ultrasensitive manual enzyme-linked immunosorbent assay (ELISA) EIA AMH/MIS kit (A11893 Immunotech, Beckman Coulter, France). The intra-assay coefficient of variation varies from 3.7% to 9.5% for a 5.8 to 151.4 pmol/l concentration range. The inter-assay coefficient of variation varies from 7.8% to 21.1% for a 2.2 to 140 pmol/l concentration range. The samples were immediately assayed for AMH. Serum AMH concentration was considered 'low' if <10 pmol/l (5th percentile of 66 control women), and 'high' if >35 pmol/l, which is the threshold used in this centre as a surrogate for polycystic ovarian morphology (PCOM) (Dewailly et al., 2011).

The antral follicle count (AFC) was evaluated later during a second consultation, between day 2 and day 5 of a spontaneous cycle (off any hormonal contraception). The ultrasound device used was a General Electric Voluson E8 (vaginal probe frequency 5–9 MHz). All follicles between 2 and 9 mm, on both ovaries, were included in the assessment of the AFC.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 22.0 for Windows, IBM Corp., USA). Quantitative variables were compared using the nonparametric Mann–Whitney *U*-test or the Kruskal–Wallis test if more than two groups. Qualitative variables were compared using a chi-squared test. The Spearman test was used to look for significant correlations. A covariance analysis was performed to adjust for potential confounding factors. Results were considered significant when P was <0.05.

Results

Two hundred and seventeen women were included in the study (**Table 1**). The youngest woman was 20 years old and the oldest was 37 years old. All these women had at least one child.

Women were divided into three groups, according to their serum AMH concentration (**Table 1**): low serum AMH <10 pmol/l (group 1), normal serum AMH 10–35 pmol/l (group 2) and high serum AMH >35 pmol/l (group 3). Six women (2.8%) had undetectable serum AMH concentration (<3 pmol/l). Clinical data, AMH and AFC were compared between these three groups (**Table 1**). There was no significant difference with age in the relatively young donor population, al-

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