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The value of Anti-Müllerian hormone in low and extremely low ovarian reserve in relation to live birth after in vitro fertilization

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ABSTRACT

Objective: To determine the relation of Anti-Müllerian hormone (AMH) with live birth after in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) in women with (extremely) low ovarian reserve.

Study design: This study was a retrospective cohort study in a Dutch tertiary fertility clinic. Between January 2009 and March 2012, AMH levels were measured in infertile women when ≥36 years of age or when showing clinical signs of diminished ovarian reserve, before they underwent IVF or ICSI treatment. Ultimately, 156 women with (extremely) low ovarian reserve were included and evaluated for cumulative live birth rates. Of each woman, only one treatment cycle was analyzed, either the one in which she became pregnant or her first treatment cycle if she did not reach pregnancy. The relation between AMH and live birth was evaluated with multivariable logistic regression analysis. A ROC curve was composed to evaluate the discriminative value of AMH in relation to live birth after IVF/ICSI.

Results: Thirty-three out of 156 women (21.2%) gave live birth. Live birth was significantly lower in women with AMH ≤0.1 ng/ml (4/37 women; 10.8%) or AMH >0.1–0.4 ng/ml (7/42 women; 16.7%), compared to women with AMH >0.4–1.05 ng/ml (22/77 women; 28.6%), $p < 0.001$. Multivariable logistic regression revealed an association between the severity of low ovarian reserve and live birth (per 0.1 ng/ml increase in AMH value, Odds ratio 1.21; 95% CI 1.07–1.36).

Conclusions: The level of AMH is related to live birth after IVF/ICSI in women with (extremely) low ovarian reserve. The live birth rate in women with AMH >0.4 ng/ml was significantly higher than in women with AMH ≤0.4 ng/ml. AMH could serve as a tool in the pre-treatment counseling for pregnancy and live birth chances in women with (extremely) low ovarian reserve.

Introduction

Recently, the public discussion about offering and reimbursing fertility treatment to infertile couples has flared [1,2]. In today's practice, fertility treatment is offered to couples when their chances of conceiving spontaneously are below 30%. It is questioned whether fertility treatment should be offered to all infertile couples or only to them with reasonable pregnancy chances after treatment. Furthermore, adequate counseling prior to a treatment cycle of in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) is indispensable in order to adjust both practitioners' and patients' expectations regarding pregnancy and live birth. Identification of which women with low ovarian reserve would benefit from fertility treatment, would effectuate health care efficacy and quality, but also improve quality of counseling prior to treatment [3].

So far in literature, pregnancy chances have predominantly been related to female age, pregnancy history and the duration of infertility [4]. Ovarian reserve capacity is another possible related factor, as it diminishes as female age increases [5].

According to the literature and the American Society for Reproductive Medicine (ASRM) Committee Opinion on ovarian reserve tests, Anti-Müllerian hormone (AMH), a glycoprotein produced by the ovarian granulosa cells supporting the initial

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follicular development, can serve as a clinical marker for prediction of poor response in infertile women [6–9]. Considering that AMH is a marker of ovarian reserve [6–9], low AMH might also be related to treatment outcome since this relates to ovarian reserve. So far, it has been reported that AMH could identify low responders to ovarian stimulation in IVF and ICSI [6,7,9–13], but it is still unclear whether AMH levels are related to chances of live birth after IVF/ICSI in women with (extremely) low ovarian reserve.

The aim of this study was to determine whether AMH in women undergoing IVF/ICSI and suffering from an (extremely) low ovarian reserve is related to live birth.

Materials and methods

Study design

This retrospective cohort study was designed to evaluate treatment outcomes of women with (extremely) low ovarian reserve after fertility treatment with either IVF or ICSI. Triggered by a study from Gleicher et al. [14], suggesting a cut off point for AMH at 1.05 ng/ml as being discriminative of better or worse chances of live birth [14], we chose to focus on the values below this level. We composed AMH subgroups of $\leq$0.1 ng/ml, $>$0.1–0.4 ng/ml and $>$0.4–1.05 ng/ml, based on the literature and receiver operating characteristic (ROC) curves previously published by other studies [14–16]. Live birth rates were described and compared those for subgroups. Univariate analysis was performed to identify differences in background characteristics in relation to AMH. The relation between AMH and live birth was evaluated with multivariable logistic regression analysis. A ROC curve was composed to evaluate the discriminative value of AMH in relation to live birth after IVF/ICSI. Finally, we calculated negative predictive values to show the predicted chances of live birth per AMH cut off point.

Setting

This study was taken out in a Dutch tertiary fertility clinic licensed for IVF and ICSI treatment, the Radboud University Medical Center (Nijmegen, The Netherlands). Annually, over 1600 IVF and ICSI cycles are performed in this hospital. In the Netherlands, all Dutch citizens have basic health insurance reimbursing the first three cycles of IVF/ICSI [17].

Prior to treatment, a fertility work-up was conducted in all couples according to the national guideline of the Dutch Society of Obstetrics and Gynecology [18]. Female age was calculated at the start of the IVF or ICSI treatment. Primary infertility was defined as an inability to conceive in couples that never achieved pregnancy before. Secondary infertility was defined as an inability to conceive in couples that had previously conceived, including miscarriage or ectopic pregnancy. Sperm was considered normal if the total motile sperm count (TMSC) in the sperm sample was $\geq 10 \times 10^6$, taking both fast and slow motile sperm together. A TMSC $<10 \times 10^6$ was defined as infertility due to a male factor. A normal menstrual cycle has an average range of 24–35 days. Menstrual cycle disorders were defined as a menstrual cycle that deviated from this definition or as amenorrhea, irregular bleeding or menorrhagia. Infertility caused by tubal factor was concluded in case of bilateral tubal occlusion or obstructed ovum pick-up mechanism due to pelvic adhesions. Endometriosis was diagnosed after laparoscopy on indication and consisted of all of the four stages of the modified ASRM Classification [19]. If fertility work-up was normal, the diagnosis of unexplained infertility was established.

In the Netherlands, IVF/ICSI treatment is only indicated when a woman is $<$43 years of age and when previous treatment has not resulted in pregnancy for infertile couples with a confirmed underlying diagnosis. In all other cases, an expectative policy is designated first [18]. For couples with unexplained infertility or mild male infertility (TMSC $>3 \times 10^6$) a prognostic model was used to calculate chances of spontaneous pregnancy within one year. For chances $>$30%, treatment was delayed for a period of 6–12 months. For chances $<$30%, couples were offered three to six cycles of intrauterine insemination (IUI) with controlled ovarian stimulation before offering IVF or ICSI [18,20,21]. Couples with moderate male infertility (TMSC 1–3 $\times 10^6$; TMSC after washing 0.8–5 $\times 10^6$) were offered three to nine IUI's in natural cycle before IVF treatment. Endometriosis, depending on the ASRM stage, was treated with expectant management and/or surgically, with IUI combined with controlled ovarian stimulation or with IVF [19]. Regular IVF was offered if expectant management or alternative assisted reproduction had failed and primarily in couples with a TMSC $\geq 1 \times 10^6$ if there was no indication or willingness for other treatment options. ICSI was offered primarily if the TMSC was $<1 \times 10^6$ or secondarily in case of total fertilization failure with regular IVF. Ovum pick-up (OPU) was done when three or more follicles $\geq$17 mm had developed. In expected poor responders, OPU was also done when only one follicle $\geq$17 mm had developed. After OPU and embryo development, embryo transfer (ET) was performed at day three. The developed embryos were classified according to an own developed system based on number of blastomeres, fragmentation, presence of multinucleated blastomeres (MNB's) and equality of the cells. A good quality embryo (class A) included embryos with 7–9 cells and $<$10% fragmentation on day 3 without MNB's; average quality embryos (class B) were 4 to 7 cell embryos with 10–25% fragmentation; below average quality embryos (class C) were remaining embryos with $>$25% fragmentation [20]. Maximum two embryos were transferred. The choice for single embryo transfer (SET) or double embryo transfer (DET) was made depending on the number of available embryos, female age and contraindications for DET (i.e. uterine anomalies). Patients were excluded from further treatment when less than four follicles or less than two pronuclear embryos developed.

Study population

Infertile couples that started a cycle of IVF or ICSI between January 2009 and March 2012 were retrospectively included in case of (extremely) low ovarian reserve (i.e. AMH $<$1.05 ng/ml). Follow up for treatment outcomes was completed in January 2013. The kit we used for AMH measurement was AMH Gen II, Beckman Coulter, Woerden, The Netherlands. AMH was determined prior to the treatment cycle and was measured in women $\geq$36 years of age or with clinical signs of diminished ovarian reserve, i.e. irregular menstrual cycle ($<$25 or $>$35 days) or shortening of a regular menstrual cycle and/or a total AFC $<$10. Women were excluded when having cryo embryos transferred as a result of previous treatment. Of each woman, only one treatment cycle was analyzed, either the one in which pregnancy arised or the first treatment cycle if pregnancy never occurred.

Data collection

The main treatment outcome was cumulative live birth. Secondary outcome variables were OPU, ET, biochemical and ongoing pregnancy and implantation rate. It is well known that several background characteristics are possible confounders by influencing successfulness of treatment outcome after IVF/ICSI [15]. In this study we focused on female age, type of infertility (primary/secondary), diagnosis of infertility and treatment type (IVF/ICSI) as possible confounders.