Fu *et al. Journal of Ovarian Research* (2025) 18:57
https://doi.org/10.1186/s13048-025-01640-3

Journal of Ovarian Research

CASE REPORT Open Access

Negligible serum anti-Müllerian hormone levels and successfully spontaneous pregnancy three times: a case report

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Abstract

Background Anti-Müllerian hormone (AMH) is a useful marker of ovarian reserve in reproductive-aged women. However, the predictive value of AMH for the occurrence of a spontaneous ongoing pregnancy has limits. We reported a patient with extreme low AMH achieved spontaneous conception three times.

Case presentation A 35-year-old woman, gravida 1, para 0, with a history of one miscarriage, presented with a one-year history of secondary infertility seeking reproductive assistance. Laboratory evaluation showed negligible (0.072 ng/mL or 0.514 pmol/L) AMH levels and ultrasound revealed reduced bilateral antral follicle count (AFC). She was diagnosed with diminished ovarian reserve (DOR) and counseled about her limited fertility prognosis. Despite recommendations for assisted reproductive techniques (ART), the patient pursued spontaneous conception. Two natural cycles and two ovulation induction cycles were conducted, utilizing recombinant follicle-stimulating hormone (FSH) with ovulation triggered by 8,000 IU of human chorionic gonadotropin (HCG). Remarkably, the patient successfully conceived three pregnancies and delivered four healthy children. In April 2022, she gave birth to a healthy boy weighing 3.17 kg via spontaneous vaginal delivery. In August 2023, she delivered another healthy boy weighing 3.80 kg via spontaneous vaginal delivery. Subsequently, in November 2024, she delivered healthy twins—one boy and one girl—via spontaneous vaginal delivery.

Conclusions This case underscores the clinical significance of specialized reproductive medicine intervention in achieving successful pregnancy outcomes in patients with rapidly declining and persistently low AMH levels. It highlights that even in cases of severely diminished ovarian reserve, natural conception is possible with expert guidance. Clinicians should exercise prudence when providing prognostic guidance regarding fertility among patients presenting with markedly diminished or undetectable AMH concentrations. The application of AMH measurement for fertility assessment in the general population still need to be clarified in well-designed prospective studies.

Clinical trial number Not applicable.

Keywords Anti-Müllerian hormone, Infertility, Pregnancy

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Background

Serum anti-Müllerian hormone (AMH), a member of the transforming growth factor (TGF-β) superfamily [1, 2], is produced exclusively by granulosa cells in adult females, declining with advancing age. It correlates with the number of ovarian early antral follicles and is widely considered a highly sensitive marker of ovarian reserve [1]. The predictive value of AMH levels in prediction of embryological and clinical outcomes has been extensively investigated [3–6]. In assisted reproduction techniques (ART), the AMH levels has been used to predict ovarian response, the outcomes of fertilization rate, number and quality of embryos [7, 8], nonpregnancy [9, 10], chemical or clinical pregnancy [11–13], incidence of miscarriage [7, 14], or live birth [6]. Increasingly, AMH has been used as a "fertility test". Several studies have investigated potential threshold values of AMH capable of differentiating between successful and unsuccessful pregnancy outcomes. One study [15] demonstrated a significant positive correlation between basal AMH levels and live birth rates. AMH levels < 1.1 ng/mL [16] or < 1.4 ng/mL [17] have been associated with nonpregnancy. Nevertheless, the predictive value of AMH measurement for pregnancy rate remains a critical research question.

We described a patient with an AMH level of 0.072 ng/mL (0.514 pmol/L) successfully conceived naturally three times following two course of natural cycles (NC) and two ovulation induction (OI) cycles in our department. The case presented highlights that even with extremely low AMH levels, natural conception can still be achievable. The clinical implications of AMH to predict fertility still need to be unraveled.

Case presentation

First spontaneous pregnancy

In June 2021, a 35-year-old woman, gravida 1, para 0, with a history of one miscarriage, presented with a one-year history of secondary infertility. She reported a history of undergoing multiple ovulation monitoring at other hospitals without successful conception. Her obstetric history revealed a medical abortion with uterine curettage at 12 weeks of pregnancy, and she denied other significant past medical or gynecologic history. She had regular 30-day menstrual cycles, and her body mass index (BMI) was 23.43 kg/m^2. At that time, her AMH levels were 1.130 ng/mL (8.136 pmol/L), which corresponds to approximately the 25th-50th percentile for her age group based on the reference population [15]. Her serum follicle-stimulating hormone (FSH) was 9.470 mIU/ml, and antral follicle count (AFC) was < 5 per ovary. She also reported extended menstrual cycles and a two-month delay in menstruation. The patient was diagnosed with diminished ovarian reserve (DOR) [18] based on her reduced AFC and increased serum FSH level. She was informed that she had a small chance of spontaneous pregnancy. We advised her to consider assisted reproductive techniques (ART). Due to her irregular cycles, hormone therapy was initiated with micronized estradiol (Estradiol Valerate) and dydrogesterone as a continuous regimen. The patient was instructed to return for follow-up on days 2 to 3 of her next menstrual cycle. On day 3 of her cycle in July 2021, her FSH and luteinizing hormone (LH) levels were 8.740 mIU/ml and 5.610 mIU/ml, respectively, whereas serum AMH levels were 0.072 ng/ml (0.514 pmol/L). Additional laboratory evaluation, including immune-related markers (lupus-like anticoagulant, antiphospholipid antibodies IgG, antinuclear antibodies, etc.), thyroid antibodies (antithyroglobulin and thyroid antimicrosomal antibodies), thyroid-stimulating hormone (TSH), free thyroxine (T4), and complete blood count were within normal ranges. Hysterosalpingography (HSG) demonstrated that both fallopian tubes are patent. Ultrasound revealed abnormal intrauterine echoes and a total of 4 antral follicles distributed across both ovaries. Her partner's semen analysis showed no abnormalities. The patient was recommended to consider ART. However, she declined this treatment option and opted for regular follicular monitoring via ultrasound in our department. On day 9 of the menstrual cycle, July 16, a mature follicle (19 mm × 17 mm) in the right ovary was detected, and ovulation was triggered using 8,000 IU of human chorionic gonadotropin (HCG). On July 18, an ultrasound revealed the presence of a corpus luteum in the right ovary, confirming ovulation. We administered dydrogesterone (Duphaston) 10 mg twice daily to support luteal phase function. On July 30, pregnancy was confirmed via a positive test, and in April 2022, she delivered a healthy boy weighing 3.17 kg via spontaneous vaginal delivery. During delivery, manual removal of the placenta was required due to retained placenta.

Second spontaneous pregnancy

In October 2022, the patient presented for fertility consultation regarding second conception. At that time, a 55 mm × 42 mm ovarian cyst was observed in the right ovary, and 4 antral follicles were noted in the left ovary. We emphasized that the likelihood of pregnancy was extremely low. The patient insisted on pursuing natural conception and underwent natural cycle (NC) monitoring but did not conceive. On November 13, she proceeded with ovulation induction (OI) cycle. Subsequent ultrasonography revealed the right ovarian cyst had reduced to 14 mm × 10 mm, with 2 antral follicles in the right ovary. A dominant follicle (13 mm × 9 mm) was observed in the left ovary on day 4 of her menstrual cycle, and 75 IU of Follitropin Alfa (Gonal-F, r-FSH, Recombinant human follicle stimulating hormone) was administered. Serial monitoring was conducted based on

follicular development, and Follitropin Alfa was administered for a total of 2 days. On November 24, a mature follicle (18 mm × 16 mm) was observed on the 15th day of her menstrual cycle. On day 16 of her cycle, 8,000 IU HCG was administered. Pregnancy was confirmed on December 13, and in August 2023, she delivered a healthy boy weighing 3.80 kg via spontaneous vaginal delivery.

Third spontaneous pregnancy

In December 2023, the patient presented seeking consultation for third conception. Comprehensive counseling was provided regarding the low probability for spontaneous conception. After acknowledging the prognosis, the patient still requested to proceed with follicular monitoring in our department. Baseline hormonal and ultrasonographic evaluations were conducted, followed by menstrual regulation treatment. In February 2024, serum hormone profile showed: FSH 7.56 mIU/ml, LH 6.00 mIU/ml, Estradiol (E_2) 127.40 pg/ml, Prolactin (PRL) 2.64 ng/ml, and testosterone (T) 0.216 ng/ml. Transvaginal ultrasonography revealed an inhomogeneous local echogenicity of endometrium. Her AFC was 2 in the left ovary and 1 in the right ovary. We informed the patient about the impact of low PRL levels on pregnancy, and she elected to proceed with OI. Subsequently, 75 IU of Follitropin Alfa was initiated on day 8 of her menstrual cycle, following the observation of a dominant follicle (11 mm × 9 mm) in the right ovary. Serial monitoring was conducted to assess follicular development, and Follitropin Alfa was administered for a total of 6 days. On February 27, 14th of the menstrual cycle, two dominant follicles (18 mm × 16 mm, 15 mm × 15 mm) were identified in the right ovary, warranting administration of 8,000 IU HCG. On February 29, a follow-up ultrasound revealed the presence of two corpora lutea in the right ovary. Pregnancy was confirmed on March 13, and in November 2024, the patient delivered healthy twins, one boy and one girl via spontaneous vaginal delivery (Fig. 1).

All health information regarding the patient have been rendered anonymous and she consented to this publication.

Discussion

In the present study, serum AMH levels were found to be markedly reduced (0.072 ng/mL or 0.514 pmol/L) in a 35-year-old multiparous woman with an unremarkable obstetric history, who had achieved three spontaneous conceptions resulting in four live births. The patient exhibited a rapid decline in AMH levels, which posed significant challenges to achieving successful conception and delivery. Through specialized reproductive medicine consultation and tailored clinical management, we were able to guide the patient to a successful pregnancy outcome. Without such medical intervention, the patient would likely have faced increased risks of infertility, pregnancy loss, or a missed reproductive window. This case aligns with current clinical evidence indicating that while AMH is a reliable biomarker for ovarian reserve and response to stimulation, its predictive value for natural conception potential and pregnancy outcomes remains limited. Our findings underscore the importance of timely and expert reproductive medicine intervention, particularly for patients who decline in vitro fertilization (IVF), to optimize fertility preservation and achieve successful pregnancy outcomes.

Nowadays, infertility is a major issue in human reproductive health that challenges the wellbeing of the couple. It has been widely accepted that couples should undergo fertility evaluation after one year of unprotected sexual intercourse without conception [19]. Women with irregular menstrual cycles and prolonged amenorrhea should seek early fertility assessment, as these characteristics may indicate anovulation. Individuals over 35 years of age should undergo infertility evaluation after six months of unsuccessful conception attempts [20]. Our patient has reached the criteria of infertility for one-year, irregular menstruation, and the age threshold of 35. Therefore, we conducted a comprehensive evaluation, which revealed a low antral follicle count, and an extremely low AMH levels.

AMH demonstrates superior ovarian reserve assessment compared to FSH and E_2, due to its consistent levels across and between menstrual cycles, and was initially believed to be unaffected by contraceptive use or anovulatory states [21]. Previous studies have established that AMH levels predict ovarian responsiveness in women undergoing controlled ovarian hyperstimulation (COH), correlating with the number of follicles that can be stimulated. Additionally, in IVF, AMH levels have been linked to treatment outcomes [3–6]. However, recent research has challenged this presumed stability. Several studies have demonstrated significant predictive value [6, 16, 22, 23], whereas others did not [12, 24], necessitating careful consideration of other factors when interpreting results. A comprehensive meta-analysis [9] identified 13 studies examining AMH and 17 studies investigating AFC to compare the predictive potential of serum AMH levels with AFC as diagnostic markers for ovarian reserve and reproductive outcomes after IVF. Receiver Operating Characteristic (ROC) curves for predicting poor ovarian response demonstrated no statistically significant difference between the predictive capabilities of AMH and AFC. Regarding non-pregnancy prediction, both serum AMH levels and AFC exhibited comparably limited prognostic performance.

The clinical significance of low AMH levels remains to be established [10]. Preliminary studies initially proposed a correlation with natural fecundity, subsequent

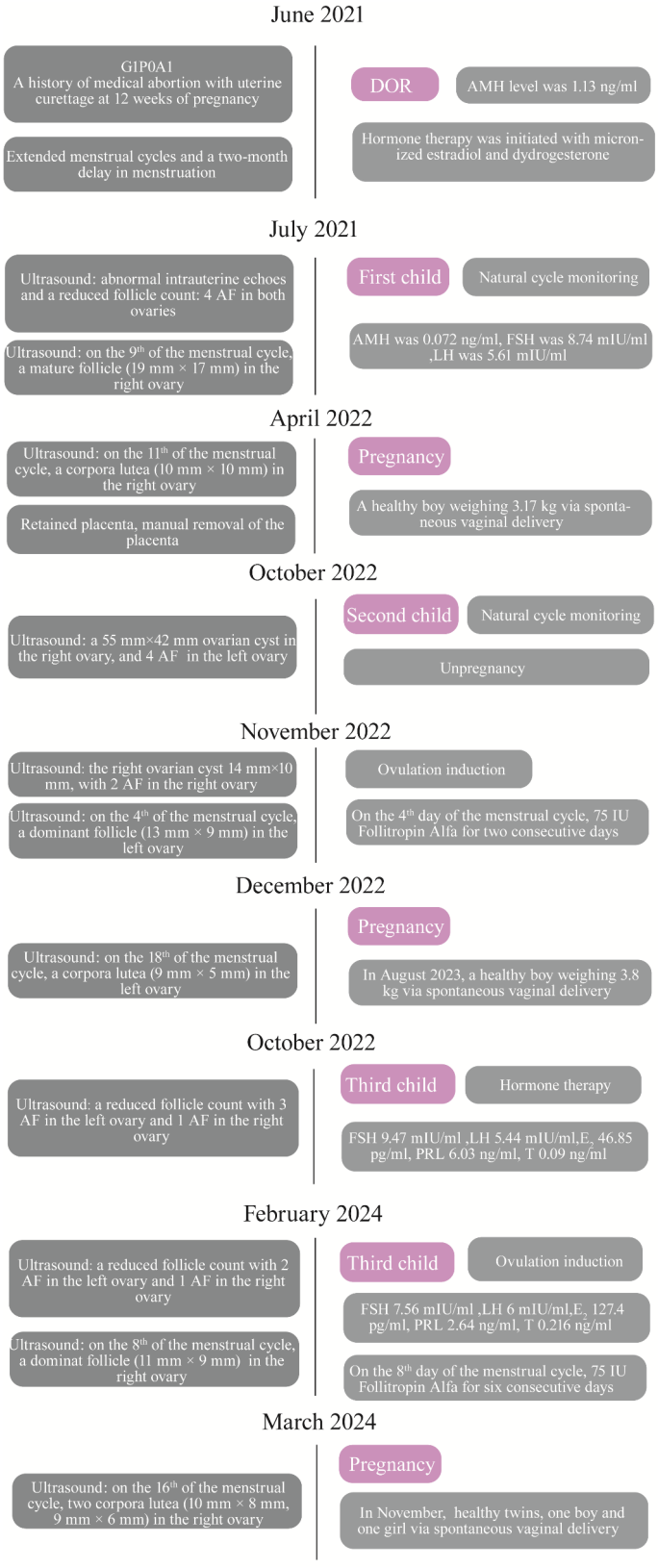

Fig. 1 Patient consultation flowchart. Abbreviations: DOR diminished ovarian reserve; AMH anti-Müllerian hormone; AF antral follicle; FSH follicle-stimulating hormone; LH luteinizing hormone; E_2 estradiol; PRL prolactin; T testosterone

investigations [25–27] have failed to demonstrate a significant association between AMH and fecundity. Cases of spontaneous pregnancy have been reported in patients with secondary infertility or premature ovarian failure (POF) despite undetectable AMH levels (< 0.4 ng/mL or < 3.0 pmol/L) [28]. In another case report, a woman with negligible serum AMH levels (< 0.5 ng/mL or < 3.6 pmol/L) who underwent intracytoplasmic sperm injection (ICSI) had a singleton pregnancy and delivered a healthy boy [29]. In our case, this woman had a lower AMH levels (0.072 ng/mL or 0.514 pmol/L) and successfully achieved natural conception three times. Our findings revealed significantly lower AMH values compared to previous literature, suggesting the potential for spontaneous conception and challenging the utility of AMH as a definitive fertility predictor. Consequently, AMH cannot be considered a direct 'fertility marker' and its clinical interpretation must be contextualized to individual patient characteristics.

Currently, the biggest issue lies in the lack of international standardization of AMH and its variability in assays [30]. AMH levels have been measured using various immunoassay methods in studies investigating threshold values for pregnancy prediction. In one study comparing two AMH immunoassays, indicating that pregnancy occurred only with AMH values > 1.40 ng/mL (10.08 pmol/L) with Beckman Coulter ELISA, while with DSL ELISA, no threshold level could be established for predicting non-pregnancy [17]. In contrast, a recent study using DSL ELISA demonstrated that AMH values below 0.13 ng/mL (1.0 pmol/L) accurately predicted non-pregnancy [15]. A larger retrospective analysis using Beckman Coulter ELISA found that AMH levels < 1.1 ng/mL (7.92 pmol/L) were usually associated with non-pregnancy [16]. These studies suggested that ongoing pregnancy was improbable in cases with undetectable AMH levels. However, our case demonstrated that successful ovulation leading to a naturally ongoing pregnancy remains possible in patients with negligible AMH values. Consequently, AMH's predictive value for fertility assessment in the general population remains limited.

Although AMH is increasingly employed as a purported diagnostic tool for assessing fertility potential, current evidence does not support its efficacy in predicting fertility outcomes. Therefore, clinicians should exercise caution when counseling about future fertility in infertile women with extremely low or undetectable AMH levels and refuse ART. Owing to the association of AMH with time to menopause [31–33], a low AMH value may indicate a potentially shortened reproductive window, but remains an unreliable predictor of current fertility status.

While this case demonstrated the successful achievement of three pregnancies in a 35-year-old woman with significantly low AMH levels through follicular monitoring and ovulation induction in our department, its limitation should be noted. This report is based on a single case, which limits the generalizability of the findings. The outcomes observed in this patient may not be representative of all women with low AMH levels, as individual responses to ovarian stimulation and fertility treatments can vary widely.

In summary, this case provides valuable insights into the potential for successful pregnancy outcomes in women with low AMH levels when managed with tailored reproductive interventions. However, further research involving larger, diverse cohorts and controlled studies is needed to validate these findings and establish evidence-based guidelines for similar cases.

Author contributions

YF conducted the data acquisition, data analysis, and drafted the original manuscript. BH, LM were responsible for clinical diagnosis and treatment, conceptualized and designed the study. LM critically reviewed and edited the paper. LM provided supervision throughout the project. All authors have thoroughly reviewed and approved the final version of the manuscript for publication.

Funding

This work was supported by Basic Research Fund in Shenzhen Natural Science Foundation (Grant No. JCYJ20230807110317036 to LM), and the Seventh Affiliated Hospital of Sun Yat-sen University (Grant No. ZSQY202473524 to LM).

Data availability

The data underlying this article cannot be shared publicly due to the privacy of the participating patient. Some de-identified parts of the data can be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

Competing interests

The authors declare no competing interests.

Received: 11 December 2024 / Accepted: 28 February 2025
Published online: 18 March 2025

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