

Induced multiple follicular growth and ongoing twin pregnancy by IVF in a woman with premature menopause

Abstract

Menopause, natural or premature, was long been considered to be incompatible with conception with the own eggs of the women affected. Here we describe a case of a 32-year-old woman with premature menopause, characterized by amenorrhea, the absence of antral follicles in the ovaries, high basal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels and extremely low antimüllerian hormone (AMH) levels. After preliminary treatment with contraceptive pill for two months, and an injection of recombinant human chorionic gonadotropin (HCG) to boost intrinsic androgen production, ovarian stimulation, using a customized protocol with a patient-tailored combination of recombinant FSH and LH, in addition to daily injections of growth hormone, resulted in the recovery of 3 metaphase II eggs after double triggering with recombinant HCG. After transfer of two embryos, obtained by intracytoplasmic sperm injection, an ongoing twin clinical pregnancy was achieved. These data show that oocyte recovery, fertilization, embryo development and pregnancy can be achieved, with the use of a customized ovarian stimulation protocol, even in young women with clear signs of advanced premature menopause.

Keywords: premature menopause, ovarian stimulation, customized protocol, in vitro fertilization, pregnancy

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Abbreviations: IVF, in-vitro fertilization; FSH, follicle-stimulating hormone; LH, Luteinizing hormone, AMH, anti-müllerian hormone, HCG, human chorionic gonadotropin

Introduction

Menopause is defined as a condition where a woman has not had any vaginal bleeding for a year.¹ It typically occurs in women between 49 and 52 years of age.¹ If symptoms of menopause occur before the age of 40, the condition is called premature menopause or premature ovarian failure.² Both the typical and the premature menopause are characterized by specific changes in serum hormone levels, namely high concentration of follicle-stimulating hormone (FSH) and low concentrations of antimüllerian hormone (AMH). It has been traditionally supposed that women showing these characteristics are not able to procreate, independently of their age. Accordingly, many women in this condition are excluded from treatment without any convincing scientific basis.

Here we report a case of a 32-year-old woman showing all signs of premature menopause in whom ovarian stimulation resulted in the recovery of 3 mature oocytes, transfer of two embryos and the establishment of an ongoing twin pregnancy.

Material and methods

Ovarian stimulation

Serum concentrations of FSH and AMH, along with basal antral follicle count (AFC) were used to evaluate the ovarian function. Ovarian stimulation was carried out according to the customized assisted reproduction enhancement (CARE) protocol, described

previously.³ Briefly, on the 19th day of a cycle induced with a contraceptive pill (Yasmin, Bayer Leverkusen, Germany) treatment, a single injection of 250µg recombinant human chorionic gonadotropin (rHCG, Ovitrelle, Merck, Amsterdam, The Netherlands) was administered. Five to nine days after the last contraceptive pill (3-6 days after the onset of the vaginal bleeding), ovarian stimulation was started. Ovarian stimulation was carried out using a personally adapted combination of drugs containing FSH and LH activities, Puregon (Merck Sharp & Dohme, Haarlem, The Netherlands) and human menopausal gonadotropin (HMG), Menopur (Ferring Pharmaceuticals, Parsippany, NJ, USA), respectively. The stimulation protocol was started with 450-525U Puregon and 75-150U Menopur, according to the value of serum LH measured 1-3 days before the beginning of the stimulation. Afterwards, the FSH-to-LH ratio was adapted, in a customized manner, according to the patient's serum concentrations of LH.³ Briefly, Menopur (source of LH activity) was maintained if serum LH levels were below 1IU/l. These adaptations were applied from the 5th day of the stimulation and then every other day. One mg of growth hormone (GH) was administered from the first day till the 10th day of stimulation. Gonadotropin releasing hormone antagonist (Orgalutran) was added when at least one follicle reached 12mm in diameter. When at least one follicle reached 18 mm in diameter, 250µg rHCG (Ovitrelle) was injected 36.5 h before the planned follicular aspiration for oocyte recovery.

Oocyte recovery, in vitro fertilization, and embryo culture and transfer

Ovarian puncture was carried out under deep sedation, 36.5 h after rHCG injection. Antral follicles were aspirated and oocyte-cumulus complexes were identified in the aspirated fluid. The complexes

were incubated in vitro for 3-4 h before the removal of the cumulus and corona radiata cells with a hyaluronidase solution and repeated pipetting, respectively. Metaphase II oocytes were inseminated by intracytoplasmic sperm injection (ICSI), and the resulting embryos were transferred under transabdominal ultrasound control 3 days later. Luteal phase was supported with a single subcutaneous injection of 250µg rHCG on the day of embryo transfer, intravaginal progesterone (Utrogestan, Besins Manufacturing, Drogenbos, Belgium) and a subcutaneous injection of 0.1 mg recombinant gonadotropin-releasing hormone agonist (Triptorelin, Decapeptyl, Ipsen, Slough, Berkshire, UK). The dose and duration of intravaginal progesterone treatment was adapted individually, according to serum progesterone concentrations. Details of these procedures were described previously.^{3,4}

Results

A 32-year-old woman had been suffering from premature menopause for more than one year. Her situation was characterized by the absence of menstrual bleeding for the last one year, and serum FSH and AMH concentrations of >20IU/L and 0.05ng/mL, respectively. The patient's husband had normal sperm (Table 1).

Table 1 Basic characteristics of the couple

Male age	33 years
Female age	32 years
Sperm count	81 million
Sperm DNA fragmentation index	11%
Female AMH	0.05ng/ml
Female FSH	25IU/L
Number of oocytes recovered	3
Number of embryos transferred	2
Number of embryos with heartbeat	2

Ovarian stimulation was carried out with a personally adapted combination of recombinant FSH and HMG. The total dose of recombinant FSH, HMG and recombinant GH used was 4500IU, 675IU and 10mg, respectively. On the 10th day of ovarian stimulation, three large antral follicles had developed, and a cumulus oophorus was detected in each of them with the use of virtual sonographic folliculocopy.⁵ Ovarian puncture was thus performed. On the day of ovarian puncture, three oocytes were recovered. All of them were mature (metaphase II) and were processed by ICSI. Two embryos were obtained and were transferred to the patient's uterus 3 days after ICSI. Luteal phase was supported with 250µg recombinant HCG on the day of embryo transfer, 600mg vaginal progesterone for the first 3 weeks after embryo transfer and with a single injection of GnRH agonist three days after embryo transfer.

Two weeks after embryo transfer, the patient showed a plasma βHCG concentration of 1244IU/L, and this level rose steadily over the following days. A twin pregnancy with embryos showing active heartbeat was detected by vaginal ultrasound two weeks later. Five months after embryo transfer, the twin pregnancy is still ongoing.

Discussion

Traditionally, menopausal women with more than one year of amenorrhea have been thought to be incapable of conceiving spontaneously, and the only method considered for them to bear a child was oocyte donation.^{1,2} However, this may not be true for premature menopause, since a recent study reported encouraging outcomes with a customized assisted reproduction enhancement (CARE) protocol in this group of women.³ However, these results were achieved in women who were rather premenopausal than menopausal, their AMH levels ranged between 0.1 and 0.2ng/mL, showed scarce antral follicle on vaginal ultrasound and had a menstrual bleeding every 3-4 months. In this study we report a case of a relatively young woman (32 years) with no menstrual bleeding over the last one year, no antral ovarian follicle detected by ultrasound and virtually unmeasurable serum AMH levels. According to the current practice recommendation, women in this condition should not be treated by ovarian stimulation and should be recommended oocyte donation. In fact, this was done, but the patient insisted in trying at least one IVF attempt with her own oocytes. Given her young age and a good overall health status, our clinic has accepted to try an ovarian stimulation and IVF attempt, although the patient was informed about the extremely low chance of success. Surprisingly, both of the embryos transferred implanted successfully, and a twin pregnancy was established and is still ongoing. These findings are in accordance with those of another recent study suggesting that young women can procreate even with very low AMH levels. However, to the best of our knowledge, this is the first demonstration showing that women can conceive even if they have the absence of menstrual bleeding for more than one year.⁶

These data show that assisted reproduction should not be automatically refused to any woman with complete menopause, without any antral follicle seen on ultrasound and with virtually unmeasurable serum AMH concentrations, especially if they are relatively young.

Conclusion

Assisted reproduction should not be automatically refused to any woman with complete menopause, without any antral follicle seen on ultrasound and with virtually unmeasurable serum AMH concentrations, especially if they are relatively young.

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Conflicts of interest

The authors declare there are no conflicts of interest.

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