The dilemma of counseling patients about poor prognosis: live birth after IVF with autologous oocytes in a 43-year-old woman with FSH levels above 30 mIU/mL

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Abstract Providing reasonable expectations to patients with diminished ovarian reserve prior to attempting pregnancy through in vitro fertilization (IVF) is one of the most challenging aspects of fertility care. In some instances, advice from the clinician to pursue more effective treatment, such as donor oocytes, may not be acceptable to the patient. In this case report, a patient is presented who represents a poor prognosis candidate for IVF treatment. She was 43 years old with six prior failed IVF cycles and repetitive basal FSH values above 30 mIU/mL. Presented are the challenges in patient counseling and decision making. In her seventh IVF cycle, which she was strongly counseled against pursuing, the patient experienced the desired outcome of live birth. Increasing reports are emerging of live birth using autologous oocytes among women of advanced reproductive age. These instances, as well as the case of our patient, raise issues commonly encountered in patient counseling in poor prognosis patients. This discussion should include an emphasis on patient goals as well as an

acknowledgement that no test for ovarian reserve has a 100% positive predictive value.

Keywords Ovarian reserve · Advanced reproductive age · Infertility

Introduction

Counseling patients regarding prognosis and optimal treatment strategy is a very important part of fertility care. The treatment with the best chance of success is often not the one that is most appealing to couples or individuals. For example, some may not want to undergo IVF even if it has the best chance of success, and most couples as well as single women want to try to succeed with their own oocytes even when donor egg IVF may have a much higher chance of success. Counseling is a balance of support and encouragement while presenting the most objective and accurate estimates for prognosis associated with different treatment options. When the prognosis is prohibitively poor, it is especially important to present this information as objectively as possible, and then still be able to offer support and encouragement if the patient chooses a treatment with a low chance of a positive outcome.

Ovarian reserve testing is commonly used to provide prognostic data on patients planning assisted reproduction. In addition to patient age, the most common measurements (with commonly used cutoff values) include the following: the serum antimüllerian hormone (AMH) level <0.7 ng/mL, the serum follicle stimulating hormone (FSH) level ≥ 20 IU/L obtained on menstrual day 3 in conjunction with serum estradiol level, and the antral follicle count (AFC) <10 follicles [1]. Ovarian reserve testing is useful to predict response to ovarian stimulation, but is not as good for predicting the chance of conception [2]. Testing indicative of low ovarian reserve can also be an

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important tool to assist with patient counseling. When low ovarian reserve is noted, the patient might be advised to expedite treatment. If ovarian reserve is very low and if the prognosis appears very poor, the patient might be advised to forego fertility treatment with her own eggs and proceed directly to oocyte donation. The American Society of Reproductive Medicine, in a statement by the Ethics Committee [3] defines “futility” as treatment with $\leq 1\%$ chance of success and “very poor prognosis” as >1 but $\leq 5\%$ chance of success. The topic of futility in fertility treatments has been the subject of multiple publications [4–7] and presents a challenge for physicians who must balance patient desires and autonomy with their own desire to provide the most effective treatment available to patients.

While reports of patients conceiving late in life with their own oocytes have recently appeared [8–10], elevated FSH levels in women over 40 appear to have a high negative predictive value in estimating subsequent live birth with the patient’s own oocytes [11–14]. In our clinic, women over the age of 40 with menstrual day 3 FSH levels above 20 mIU/mL are advised to repeat the test, but if the results are consistently high, they are offered immediate oocyte donation due to the significant improvement in success rates ($>50\%$) that can be expected compared to using autologous oocytes [15]. This discussion must always include not only a realistic discussion of likely outcomes, including the increased risk of aneuploidy in pregnancy with increasing maternal age, but also a frank discussion of patient preference keeping in mind respect for autonomy. We present here a case of a patient who expressed a consistent strong preference for autologous oocytes, in spite of poor indicators of fertility. She eventually successfully conceived at the age of 43 years and 7 months with baseline FSH levels above 30 mIU/mL.

Case report

The patient presented to our clinic at the age of 42 years and 3 months with the chief complaint of secondary infertility. She had been attempting conception with her partner for 15 months and had achieved a pregnancy 10 months prior. That pregnancy resulted in spontaneous miscarriage in the first trimester. She was subsequently diagnosed with uterine fibroids, and 1 month prior to her presentation she underwent abdominal myomectomy with removal of 24 fibroids. Her medical history was otherwise unremarkable. Menses were regular every 26–28 days. Her partner was 33 years of age at the time of presentation. He reported no significant medical history and had fathered one pregnancy ending in miscarriage 7 years prior with a previous partner as well as the abovementioned miscarriage with our patient. Because of the history of two miscarriages, a karyotype was obtained which confirmed a normal 46XY result. The semen analysis was also normal.

Initial ovarian reserve testing revealed an elevated day 3 FSH of 22.3 mIU/mL with E2 of 35 pg/mL (both measured

with the Immulite 2000 immunoassay system, Siemens Healthcare, USA). Serum AMH also indicated diminished ovarian reserve with a value of 0.67 ng/mL. Ten antral follicles were noted on her pelvic ultrasound. The laboratory tests were repeated in her subsequent follicular phase, and the FSH was found to be 26.8 mIU/mL with E2 of 22 pg/mL. The patient was counseled extensively about her very poor prognosis with IVF using autologous oocytes, and IVF with donor oocytes was recommended. However, she and her partner strongly desired an attempt at conception with her own eggs. At the start of her first IVF cycle, FSH was 24.5 mIU/mL with E2 of 24 pg/mL. The patient was given a regimen of clomiphene citrate 100 mg daily for 5 days and concomitant human menopausal gonadotropin (hMG) 600 IU/day. She responded to the stimulation, and ganirelix acetate was added when the lead follicle reached 14 mm average diameter. On the ninth day of her cycle, she received 10,000 IU of human chorionic gonadotropin (hCG) to trigger ovulation, and 10 oocytes were obtained via transvaginal ultrasound-guided follicle aspiration. Six oocytes were fertilized, and five embryos were transferred on day 3. Morphologic embryo assessment was encouraging and the patient conceived, but the pregnancy resulted in an anembryonic gestation, treated with dilation and curettage.

Approximately 10 months following her initial presentation, the patient initiated her second IVF cycle. She was now 43 years old, and her FSH was 21.9 mIU/mL with E2 of 28 pg/mL. She followed a similar protocol of clomiphene citrate and hMG. When ganirelix was administered, 100 IU of hCG (“hCG boost”) was added to the stimulation. Follicle aspiration resulted in seven oocytes, with four embryos transferred on day 3. She did not become pregnant. The following month, her FSH increased to 31.0 mIU/mL with E2 of 19 pg/mL. She initiated a third IVF cycle, utilizing the same protocol. We obtained 10 oocytes, with six fertilized embryos, five of which were suitable for transfer on day 3. She did not become pregnant. In the fourth IVF cycle, the baseline FSH level was 24.2 mIU/mL. A microdose gonadotropin-releasing hormone (GnRH) agonist protocol was attempted, resulting in six oocytes and two embryos and no embryo implantation. A fifth IVF cycle was undertaken at the insistence of the patient and her partner. The combination of clomiphene citrate and hMG protocol used in her second cycle was again utilized, yielding 13 oocytes but only four embryos. She underwent a day 3 transfer of the four embryos and did not become pregnant. Prior to the sixth IVF cycle, the baseline FSH was 35.9 mIU/mL with E2 level of 42 pg/mL. The same protocol was used, resulting in 13 oocytes and five embryos. Three of these were of adequate quality for transfer, but the patient did not become pregnant.

Throughout the time of her treatment, we made a concerted effort to present a realistic view of the poor prognosis of IVF in a woman over the age of 43 with persistently elevated FSH levels, even while remaining supportive of her decision to

continue to try. After six unsuccessful autologous cycles, approximately 16 months after initiating care, a long discussion was undertaken with the patient and her partner about the apparent futility of continued attempts using her own oocytes. Her very poor prognosis was reiterated, indicating that we believed she had less than a 5% chance of success. Donor IVF was again recommended strongly, a treatment that would confer a greater than 50% chance of conception. She and her partner again insisted upon trying once more, with the understanding that this would be her final autologous cycle in our clinic, even if she did not become pregnant.

For her seventh and final cycle, the patient's starting FSH was 32.8 mIU/mL with estradiol of 26 pg/mL. Her age was now 43 years, 7 months. She followed the same protocol with clomiphene citrate, hMG, ganirelix acetate, and hCG boost. Her follicle aspiration on cycle day 11 resulted in the retrieval of 10 oocytes, of which four were fertilized and were transferred on day 3. Nine days after embryo transfer, her serum HCG level was 17.3 IU/L, which increased to 71.2 IU/L 2 days later. At 5-week gestation, the serum HCG was 2884 IU/L, and her 6-week ultrasound showed a singleton intrauterine gestation with cardiac motion. She went on to deliver a live-born infant at term via spontaneous vaginal delivery.

Comment

Ovarian reserve testing is an essential component of the current practice of fertility treatment. The combination of serum tests, antral follicle counts, and patient age has a very good predictive value for conception in assisted reproduction. Ovarian reserve testing is therefore very helpful in directing treatment strategy and identifying patients who may most benefit from more complex interventions such as donor gametes. However, predictive values are necessarily associated with 95% confidence intervals and outliers do occur. Patient counseling therefore must always include the disclaimer that no test is 100% accurate. Because infertility treatment is so difficult emotionally as well as physically, fertility clinics often face dilemmas in counseling patients whose treatment is thought to have a very poor prognosis, or even be futile. The dilemma of poor prognosis in women over the age of 40 using donor sperm was analogously previously pointed out by DeBrucker et al. [16].

Our patient was over age 43, had failed six prior IVF cycles, and had a baseline FSH as high as 32.8 mIU/mL. We considered these values to be poor prognosis at best and futile at worst. Although the treatment strategy desired by the patient—continued use of autologous oocytes—seemed ill-advised to the treating physicians, she was able to achieve a live birth. This case demonstrates that continuing to offer treatment in the setting of very poor prognosis can be

acceptable when appropriate counseling has been provided, and may even result in success.

Had we used growth hormone, DHEA, sildenafil, or CoQ-10, the success in this patient might be interpreted as an endorsement of those adjunctive treatments. That was not the case. Our patient was treated with what our clinic considers to be a “very poor responder” protocol, which includes clomiphene citrate to stimulate FSH and LH secretion from the pituitary, and a high dose of hMG. When the GnRH antagonist is administered, we add a dose of 100 IU of hCG to compensate for the diminished secretion of gonadotropins from the pituitary resulting from the antagonist blockade of the pituitary. We have found this adjunctive treatment to be helpful in very poor responders, whose follicle development may stop when the GnRH antagonist is used. Doses of hCG up to 200 IU daily have previously been used in the late follicular phase to complete follicle stimulation without luteinization or premature ovulation [17–19]. It is tempting to speculate that the hCG boost helped this patient achieve follicle maturity in spite of her high baseline gonadotropin values.

It is interesting to note that reports of pregnancies in women of advanced reproductive age using autologous oocytes have recently appeared [7–9]. Many would argue that the ages reported would previously have been considered “futile.” Fertility treatment success rates are rising every year, and it is possible that treatment that was previously considered futile may simply represent another poor prognosis situation. An alternative explanation might be that as more IVF cycles are performed, the numerators may be catching up to the denominators. This patient may simply have remained in treatment long enough to overcome her statistically low chances, and a sufficient number of oocytes to finally obtain a euploid embryo may have eventually been reached.

Compliance with ethical standards

Informed consent Informed consent was obtained from the individual discussed in this case report.

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