

Oocyte Freezing Following Ovulation Induction and Egg Retrieval in a 45x Teenage Girl with Hypergonadotropic Primary Amenorrhea, Estrogen Deficiency, and Sexual Infantilism

Jerome H. Check^{1,2*}, Brooke A. Neumann³, Danya Horwath² and Donna Summers²

¹Cooper Medical School of Rowan University Camden, NJ, USA.

²Cooper Institute for Reproductive Hormonal Disorders, Mt Laurel, NJ, USA.

³Inspira Health Network Vineland, NJ, USA.

*Correspondence:

Jerome H. Check, M.D., Ph.D., Cooper Medical School of Rowan University Camden, NJ, USA. 7447 Old York Road, Melrose Park, PA 19027, TEL: 215-635-4400, FAX: 215-635-2304.

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ABSTRACT

Although there have been some uncommon cases of spontaneous ovulation and even pregnancies in females with Turner's syndrome, most have been Turner mosaics, but some do have the 45x karyotype. However, in all cases these women had normal sexual development. There are techniques to restore sensitivity of follicles to FSH by up-regulating down regulated FSH receptors. This technique was tried on a 13-year-old with 45X Turner's syndrome with markedly elevated serum FSH, very low serum estradiol (E2) and sexual infantilism with the intent of banking an egg or two for future fertility purposes. Despite bilateral streaked gonads, she made a dominant follicle twice, once at age 13 and once at age 14. One egg was retrieved from each IVF cycle. The first egg was cryopreserved for the future whereas the second egg was discarded because it was degenerating. Thus, the FSH receptor up-regulation technique can even allow follicle maturation despite barely any ovarian tissue remaining on the urogenital ridges. Possibly, once considering the pros and cons, if the parents and child wanted to bank eggs despite Turner's syndrome, this should be considered at the youngest age possible.

Keywords

Turner syndrome, Streaked gonads, Follicular maturation, FSH receptor up-regulation, Egg banking.

Introduction

In the most common form of Turner's syndrome with a karyotype of 45X, the large majority of females present with not only primary amenorrhea but sexual infantilism. Sexual infantilism is related to accelerated depletion of ovarian follicles either during embryogenesis or during the first few years of life. Though a very small minority will undergo puberty and menstruate, and even more rarely even become pregnant, the majority of these uncommon cases have some form of mosaicism [1-6].

The large majority of this group of Turner mosaics who have menarche will eventually go into premature menopause. There has never been a published case of Turner's syndrome, either 45X or a Turner mosaic, who ovulated despite sexual infantilism. Obviously, that would seem impossible.

Forty years ago, in 1984, a technique was described where ovulation, and sometimes pregnancies, were achieved by up-regulating down regulated FSH receptors in women in apparent menopause [7]. The hypothesis was that some women with a paucity of follicles may still have some viable follicles left, but they are unresponsive to either endogenous or exogenous gonadotropins because the high serum levels of FSH down-regulated FSH receptors through internalization of the receptor.

The hypothesis was that if one lowers the serum FSH levels, there may be up-regulation of the FSH receptor leading to restoration of granulosa-theca cell function. This technique restores sensitivity to FSH stimulation either endogenous or exogenous [8,9].

The main agent used to lower the serum FSH was pharmacological dosages of oral estrogen with a preference for ethinyl estradiol (EE) 20 micrograms per day because not only is the dosage sufficient to lower serum FSH through negative feedback to the pituitary, but it has the advantage that ingesting this drug does not raise the serum estradiol (E2) level which allows more precise monitoring [10,11]. Sometimes a boost of FSH injection is needed to grow the follicle to full maturity once FSH receptor up regulation has been restored [12,13].

The younger the woman and the shortest duration from time of the hypergonadotropic estrogen deficiency state to the time of treatment, the higher the live delivered pregnancy rate [14,15]. Nevertheless, ovulation despite clinical overt ovarian failure and subsequent live deliveries in natural cycles have been achieved using this EE alone or EE plus a boost of gonadotropins even in women 45 and 46 years of age [16,17].

The concept that the main benefit of EE in inducing ovulation is merely the suppression of FSH to restore down-regulated FSH receptors, rather than some other mechanism, was supported by the demonstration and that ovulation can be achieved also despite apparent menopause by lowering elevated serum FSH with gonadotropin releasing hormone agonists or antagonists [14,18,19].

The large majority of females with Turner syndrome have just the presence of the urogenital ridge with no apparent ovarian tissue. Thus, to try to develop a mature follicle in a 45X early teenager with sexual infantilism would not seem possible. However, achieving ovulation and live delivery in women with premature ovarian failure and the presence of bilateral streaked gonads is not unprecedented [20,21]. Thus, when a mother brought her 13-year-old daughter with sexual infantilism to discuss the possibility of trying to use this FSH receptor up-regulation technique to allow follicular maturation with the objective of retrieving an egg or eggs with cryopreservation for a future pregnancy, we decided, after a meeting with our own ethics committee and acquiring positive feedback from a child psychologist that this teenager wanted to have oocyte cryopreserved performed and was not coerced, we attempted to use the FSH receptor up-regulation technique to try to create a mature follicle hoping there were still some antral follicles present even though they were not evident by transvaginal sonography, and we could thus mature the follicle to the dominant stage containing a metaphase II oocyte.

Case Report

EE was given to a girl aged 13 with estrogen deficiency and very high serum FSH (67.2 mIU/mL) with a serum E2 of <15 pg/mL and a diagnosis of Turner's syndrome (45X). If the FSH would dip too low, then a boost of low dosage FSH would be given. The

objective would be to perform egg retrieval and cryopreservation if a dominant follicle was achieved.

After 40 days of EE, a serum E2 of 251 pg/mL was attained with a dominant follicle averaging 18 mm by ultrasound. No gonadotropins were given [10,12,13,17]. 10,000 IU human chorionic gonadotropin was given the next day when the serum E2 increased to 355 pg/mL. One metaphase II oocyte was retrieved and vitrified. The EE technique was tried a second time when she was age 14. The E2 increased to 205 pg/mL and the follicle measured 16.6mm. Freezing was not performed because the retrieved egg was degenerating.

Discussion

This case helps to support the concept that development of a dominant follicle, despite ovarian failure, can be achieved by lowering elevated serum FSH by treatment with EE based on the fact that two times in a row follicular maturation was achieved despite streaked gonads. This clearly shows that the success was related to the EE treatment per se, and not merely fortuitous spontaneous ovulation. This is the first demonstration that achievement of a dominant follicle, and a metaphase II oocyte, is possible even in a girl with Turner's syndrome with sexual infantilism, although, as mentioned, ovulation induction and even pregnancy was previously achieved in two women with streaked gonads, and premature menopause, but normal chromosome analysis and normal sexual development [20,21].

Before attempting this procedure, the patient and her parents were explained that about 50% of patients with Turner's syndrome who had spontaneous conception were reported to have miscarriages [2,4]. They were made aware that, if the fetus was a female and delivered alive, that 50% of her offspring would have Turner's syndrome. They were also made aware that if the fetus had Turner's syndrome, that because of the 45X karyotype the child would be at increased risk of heart, kidney, and other organ defects. We advised her that if the egg fertilized and she conceived, or even if later conception occurred with the use of donor eggs, she would have some increased risks herself e.g., aortic dissection [22,23]. For a further discussion on the pros and cons on whether patients with Turner's syndrome should be encouraged to carry their own children or use a gestational carrier, we recommend reading the comments of Soderstran-Anttila and Pinborg (both pro) and Karnis and Reindollar (both con) [24]. Besides aortic dissection, they were advised of an increased risk of hypertensive disorder during pregnancy [25].

Hopefully, in the future we will publish the first case of oocyte banking, long-term storage, subsequent fertilization and successful uncomplicated pregnancy following embryo transfer in a 45x Turner patient with sexual infantilism whose menopause was temporarily reversed. Obviously, for this to happen if a potential future child with the same gene pool as the mother is desired, the earlier in the child's life that oocyte cryopreservation is attempted, the greater the chance for success.

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