Case Report

Pregnancy in a lady with premature ovarian failure following dehydroepiandrosterone (DHEA) treatment

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ABSTRACT

Poor responders are real challenges for infertility physicians, as they produce lesser numbers of oocytes after ovulation stimulation. Fertility begins to decline after 30 years of age in women. Hence, in elderly women, diminution of ovarian reserve is a reality. Diminished ovarian reserve (DOR) may be found in young women as well. Ovarian reserve test (ORT) are many, but among them, estimation of follicle-stimulating Hormone (FSH), antral follicle count (AFC) by ultrasound, and estimation of anti-Müllerian Hormone (AMH) are far more standardized. In recent years, one of the androgens called dehydroepiandrosterone (DHEA) has been tried to elevate ovulatory response in DOR patients. DHEA mostly brings the sleeping follicular pool to functional pool and prevents apoptosis of many follicles, thereby, promoting ovulatory response of ovaries with diminished ovarian functions. One such case with premature ovarian failure (POF) has been presented here, who conceived after DHEA treatment. Though escape ovulation can happen in postmenopausal patients, here the lady conceived with DHEA treatment 7 years after achieving premature menopause, during which she suffered from complete secondary amenorrhea.

Keywords: Dehydroepiandrosterone (DHEA), diminished ovarian reserve (DOR), infertility, premature ovarian failure (POF)

INTRODUCTION

The demand of pregnancy in elderly reproductive age group is increasing day by day due to late marriage, career building, divorce, and remarriage. This leads to dealing with women having age-related diminished ovarian reserves (DOR). Women whose ovarian reserves have been compromised by different diseases or surgery additionally present real problem during ovulation stimulation. DOR of indeterminate etiology pose significant challenge in reproductive medicine by adversely affecting pregnancy outcome. The mechanism for this response is complex, and multiple factors may interplay in inducing this factor in individual patients. Poor response in ovarian stimulation prevails in fertility clinics between 9% and 24% in women undergoing controlled ovarian hyperstimulation (COH). Many molecules have been tried as adjuvant to augment the effects of Gonadotropin (Gn) stimulation and thus increase *in vitro* fertilization (IVF) outcome. Dehydroepiandrosterone (DHEA) looks like a breakthrough therapeutic agent in improving the ovarian responses in poor responding patients. The postulated mechanism of benefits of DHEA have been summarized as—increased intraovarian androgen level, increased numbers of preantral and small antral follicles, increase in insulin-like growth factor 1 (IGF-1) level, improvement of the quality of oocytes and embryo ploidy. All these together lead to the development of more healthy oocyte-containing follicles.

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CASE REPORT

Mrs. A. C., a 27-year-old, attended our clinic in the year 2007 with history of primary infertility for 6 years. She stopped menstruating a year back and used to get withdrawal bleeding initially with progesterone, but subsequently required an estrogen and progesterone combination to induce vaginal bleeding. She was little obese with no other symptom, except a little bit of dryness of the vagina. On examining her serum hormones, follicle stimulating hormone (FSH) was found to be 52 mIU/mL and anti-Müllerian hormone (AMH) was 0.2 ng/mL. She did not have much of menopausal symptoms such as hot flush, night sweats, or urinary problems. As she was looking for a baby, we could offer only oocyte donation (OD) to her. She was not very happy at our proposal and left the clinic. In the year 2012, with persisting secondary amenorrhea since her last visit, she did not have any withdrawal bleeding as well. We again estimated her hormone levels. The FSH level was found to be as high as 87 mIU/mL this time, and her AMH level was <0.1 ng/mL. As she did not have her periods, these hormones were tested randomly. Her thyroid profile was normal, and she did not have hyperprolactinemia (HP). The estradiol (E2) level was extremely low. We told her that she requires IVF through OD. However, we came to know about DHEA by that time along with benefits and we explained the molecule to her and she was extremely happy to go with DHEA. DHEA 25 mg thrice daily was prescribed her. We asked her to come back after 4 months. However, she came back to us after 3.5 months of taking DHEA, with complaint of weakness, sick feeling, and reeling of the head, which she thought to be complications of the medicine. We performed transvaginal ultrasonography (TVS) on her and to our utter surprise, detected a 5-week gestational sac (GS) with a live embryo in it, having flickering heart. She was delighted with this news, and we gave her advice about early pregnancy and started usual antenatal care. She went home and tested her urine the next morning and found urine pregnancy test (UPT) as positive, which she informed us over the phone on the same day, in a delighted voice. She repeated ultrasound (US) after 3 weeks and found a 8-week-old live fetus inside. She was put on usual antenatal care. Her first trimester screening with ultrasonography (USG) and double marker test was found to be normal. We did her triple marker test, and the report came out to be normal as well. However, anomaly scan performed at nearly 18 weeks of her pregnancy detected abnormality, as follows: "Single, live fetus at breech presentation with anhydramnios. The fetus was in a flexed position, with less fetal movement". She had another USG performed before the said anomaly scan at 14 weeks, revealing a 14-week-old fetus with normal amount of liquor. The patient was referred to fetal medicine center for a review USG that revealed a 20-week-old fetus with almost anhydramnios and though there was a restricted view, the overall fetal anomaly was found to be normal. The fetal kidneys were seen, but fetal bladder and stomach were not visible during USG. The fetal lungs were visible, but USG commented a strong chance of pulmonary hypoplasia. We were a bit upset with this report and offered her termination of pregnancy (TOP), which she refused straightaway. Repeat anomaly scan was performed again at 22 weeks of pregnancy that indicated 22-week-old fetus with anhydramnios along with hypoplastic fetal chest and empty urinary bladder. There was possibility of single umbilical artery. The lady was counseled once more in favor of TOP, which she again disagreed, as she said that she wanted to enjoy the taste of motherhood, for which she waited for 10 long years. Not only the patient, but her husband and other members of family were counseled as well for medical termination of pregnancy, but the expectant mother disagreed to do so on all the occasions. The pregnancy continued. She was admitted at 34-weeks of pregnancy with a threatened preterm labor that subsided with conservative management, and she went back home. She was readmitted at 36 weeks of pregnancy with complaint of preterm premature rupture of membrane (PPROM) along with dysfunctional labor. We counseled the patient for a vaginal delivery, which she disagreed. We reinforced that this baby would not be delivered anyway in neonatal period, but she insisted for the birth of a living baby, at least alive for a few hours following delivery such that she could have a feeling of holding a newborn in between her hands. Cesarean section (CS) was performed subsequently. She delivered a baby with ambiguous external genitalia and deformed chest [Figure 1]. The baby's breathing pattern was irregular as well. The baby gasped one or two times after birth, but did not cry. He was immediately intubated and put on mechanical ventilation, along with other treatments. The baby started desaturating after few hours of delivery. Straight x-ray of the chest performed in between, revealed pulmonary hypoplasia. Ultimately, the baby expired within 24 h with respiratory distress. The parents were a bit upset and the mother said, holding her baby at this terminal stage with eyes full of tears, that at least she could ultimately become a mother. The karyotype performed with the baby's skin was found to be normal [Figure 2]. The story, however, does not end here. She came back to us after a year, asking for treatment again. Again, we checked her

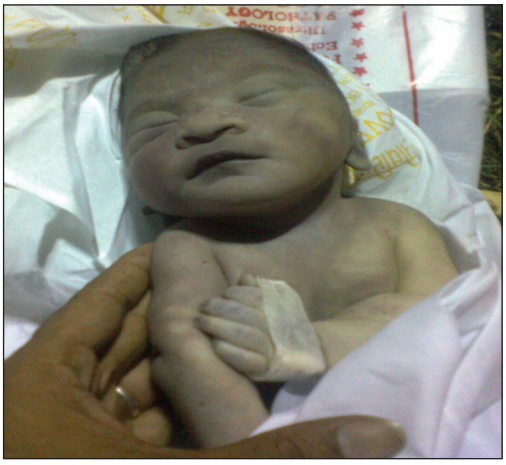

Figure 1: Deformed chest

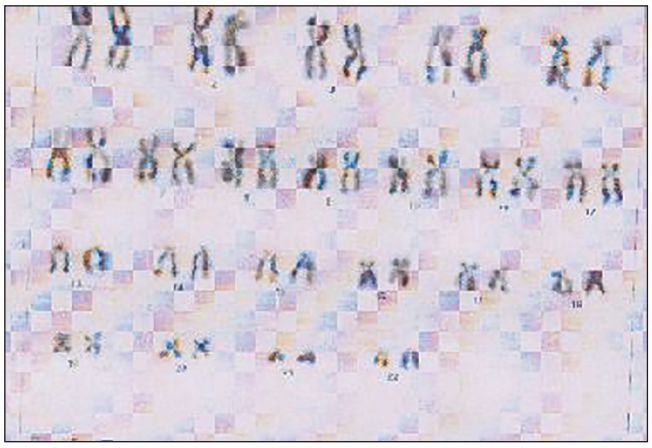

Figure 2: Normal karotype

FSH and AMH levels, and similar results were obtained. She was put again on DHEA 75 mg daily dose, as she was working at that time. After starting DHEA, she came to us after 2.5 months and asked to get her follicular development checked, as she said that she was getting a bit wet. We put her on TVS folliculometry, which revealed a single developing follicle. For the last 1 year, she developed a single mature follicle and she ovulates three times and average follicular development took about 3 months each time. The E2 value was estimated when matured follicle was of 18 mm diameter and found to be between 150-200 pg/mL on these three occasions. She had her period spontaneously almost each time on three occasions. Though she has not conceived till date, she is still hopeful to do so.

DISCUSSION

Androgens have a role to play in early phase of follicular development, before follicles become Gn-sensitive. Androgen inhibits apoptosis and enhances the FSH action in Gn-sensitive follicles. The androgen level falls with advancing age, and that is why in elderly women, higher FSH dose and longer duration of administration are required for proper folliculogenesis. The patients with DOR undergoing assisted reproductive technology (ART) may be boosted by androgen, leading to more recruitment of follicles. This can be accomplished by DHEA or transdermal testosterone gel preceding ovarian stimulation. Pretreatment with DHEA for 2-3 months, before instituting Gn-stimulation has become a practice in ART cycles in poor responders. Its benefits such as more numbers of oocytes, matured fertilized oocytes, and good quality embryos as compared to the controlled groups, are shown in randomized controlled trial (RCT) groups.[1] Gleicher in a review had summarized that DHEA supplementation in a dose of 75 mg per day started 2 months prior and continued throughout COH increase pregnancy chances and lowers aneuploidy and miscarriage rates.[2] In addition, it has been suggested that DHEA beneficially affects the aging ovarian environment. DHEA is a relatively safe drug, administered orally. The main side effects may be nausea or vomiting and occasional gastric problems. Sometimes, it can induce heavy menstrual bleeding and rarely drowsiness, which are not major side effects.

The mechanism of DHEA action is mentioned elsewhere in details. To summarize, development of healthy oocytes with euploid embryos are two main beneficial effects induced by DHEA. It had been shown by Mamas of Greece that five women, who were postmenopausal for certain period of time, delivered living children on treatment with DHEA.[3] Our case, that is, of Mrs. A. C., 34 years of age, can be added to the same list, as she was postmenopausal as well for some period of time and conceived following treatment with DHEA, and it was a spontaneous pregnancy. Even today, the mainstay of achieving pregnancy in a menopausal lady is oocyte donation (OD) with IVF. This case may be an exception and not many premenopausal ladies even today with premature ovarian failure (POF) will have the same good luck. Barad *et al*. showed that DHEA supplementation in women with DOR significantly improved the overall clinical pregnancy of 10.9-28.1%, and half of the pregnancy in treatment group occurred spontaneously.[4] Fussi *et al*. had corroborated the above finding, showing spontaneous pregnancy in women with DHEA supplementation prior to IVF, indicating that DHEA can improve the chance of not only ART but spontaneous pregnancy as well,[5] as our mentioned case and Mama's case demonstrate. It is to be kept in mind that stray ovulation or escape ovulation is a possibility as well in postmenopausal women to give rise a pregnancy. In case of Mrs. A. C., who conceived following DHEA administration after 7 years of premature menopause, during which no stray ovulation occurred, and she did not have her periods either. So, it is hard to believe that this was a pregnancy following a stray ovulation, instead of a pregnancy following induced ovulation by DHEA and clomiphene citrate (CC).

CONCLUSION

The fertility physicians are now working more and more with DOR either in elderly or young women as mentioned before. This may be either constitutional as found in young age, or may be due to late marriage etc., as found in elderly women. It has become the demand of the day to manage these women efficiently, for which many newer molecules are under trial, for treating women with DOR. The case presented above shows a young lady facing premature menopause due to poor ovarian reserve, but gave birth to a child after DHEA treatment, though the baby did not survive. This lady is still hopeful for conceiving, and there is possibility of her getting pregnant again. This is a burning example of the triumph of modern medicine to fight many conditions that were thought to be irreversible a few years back.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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