

# Pregnancy following *in-vitro* fertilization and embryo transfer in a patient with gonadal dysgenesis

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### ABSTRACT

Gonadal dysgenesis is a congenital condition in which there is gonadal dysfunction as a result of anomalies of sex chromosomes or mutations in the genes involved in the development of the indifferent embryonic gonads. It usually remains undiagnosed until when puberty fails to occur in patients. There is absence of development of female secondary sexual characteristics and primary amenorrhea. Infertility is an important manifestation of this condition, and this has a significant impact on the quality of the reproductive and family life of the patients, especially in areas where importance is placed on childbirth in marriages. This case is that of a woman with pure 46, XX gonadal dysgenesis with primary infertility who was able to achieve conception following IVF (*in-vitro* fertilization) with donor oocyte at our facility. This has helped to buttress the fact that with proper evaluation and effective application of hormone replacement therapy and assisted reproductive techniques, women with such cases can be helped to achieve conception and give birth.

**Key words:** Gonadal dysgenesis; *in-vitro* fertilization; pregnancy.

### Introduction

Gonadal dysgenesis is a subset of disorders of sexual development characterized by incomplete or defective formation of the gonads due to either structural or numerical anomalies of the sex chromosomes or mutations in the genes involved in the development of the gonads.<sup>[1]</sup> It is a congenital disorder of the development of the reproductive system with usual gynecological manifestations of primary amenorrhea and infertility. There is usually no suspicion until puberty fails to occur and patient does not menstruate as at when expected.<sup>[2]</sup>

Gonadal dysgenesis is characterized by nonfunctional streak ovaries with variable degree of hypoenestrogenism depending on the level of gonadal development. It is associated with high levels of follicle stimulating hormone (FSH) and luteinizing

hormone (LH) with poorly developed secondary sexual characteristics.<sup>[2]</sup> Though the cause is unclear, mutations in the SRY-gene and abnormalities in FSH-receptor have been implicated.<sup>[3]</sup>


It can be classified based on the gonadal morphology into complete (pure) gonadal dysgenesis in which there is a female phenotype with no gonadal differentiation, and partial gonadal dysgenesis in which there is incomplete testis differentiation with an external phenotype that depends on the degree of testicular function.<sup>[4]</sup> Based on the karyotype, the variants include Turners syndrome (45, XO), XX gonadal dysgenesis (46, XX),

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Swyer syndrome (46, XY), and the mixed gonadal dysgenesis (45, X/46, XY) mosaicism.<sup>[5]</sup> This is a case of a nulliparous Nigerian woman with pure 46, XX gonadal dysgenesis who has been previously managed for primary amenorrhea and thereafter presented at our center on account of primary infertility.

## Case Report

Mrs. A.F. was a 34-year-old married woman who lived together with her husband for 6 years without achieving conception despite satisfactory unprotected sexual intercourse 2–3 times per week. She had history of primary amenorrhea and had to use oral contraceptive pills to initiate and induce menses since 19 years of age. She attained adrenarche at 15 years and thelarche at 19 years.

She had no anterior neck swelling, heat or cold intolerance, palpitations or fine tremors. There was no recurrent frontal headache, changes in sense of smell, or abnormal milky nipple discharge. There was no increasing acne, deepening of voice, or abnormal male hair pattern, and also no history of anosmia or deafness. She could not ascertain the use of diethylstilbestrol (DES) in-utero. She did not consume alcohol nor smoked cigarette.

She had laparoscopy for the evaluation of primary amenorrhea at a teaching hospital in 2000 where poorly developed ovaries were found. She was not a known hypertensive, diabetic, peptic ulcer disease, or asthmatic patient. There was history of use of antipsychotics, risperidone, and quetiapine fumarate. She had also used bromocriptine due to hyperprolactinemia.

She was married in a monogamous family setting to a 37-year-old building contractor. Her husband was able to initiate and sustain erection and he ejaculated normally. He did not wear tight underwear. He was not a known hypertensive or diabetic. There was no previous scrotal trauma, groin surgery, or mumps orchitis. He consumed alcohol occasionally but did not smoke cigarette.

Examination revealed a middle-aged woman with the following anthropometric measurements: weight: 62 kg; height: 1.64 m; BMI: 23.1 kg/m<sup>2</sup>.

Examination of the head, neck, cardiovascular system (CVS), and respiratory system did not reveal any abnormalities. She had rudimentary breast development-Tanner stage III, with well-developed axillary hair, no palpable lumps or nodules in the breast, and no nipple discharge.

The abdomen was flat, moved with respiration, well-developed female pattern of pubic hair.

No areas of tenderness and no ascites were seen. Bowel sound is normoactive. Vaginal examination revealed small female external genitalia, short vagina, rudimentary cervix, and an anteverted uterus that sounds to 7 cm with some difficulties encountered at the level of the internal cervical os.

Based on the history and examination findings, an assessment of primary infertility secondary to gonadal dysgenesis was made. She was counseled on the diagnosis and its implications with regard to menstruation and fertility. She was placed on hormone replacement therapy and was advised to go for IVF using donor oocytes.

She did several investigations with results as follows:

FSH = 56.0 IU/L (3.9–12.0)

LH = 28.0 IU/L (1.5–8.0)

Prolactin = 16 mg/dL (5–35)

Estradiol = 23 pg/mL (30–100)

Day 21 progesterone: 1.6 ng/mL (2.0–25.0)

Testosterone: 0.4 ng/mL (0.2–1.0).

Cytogenetics Report: 46 XX

Pelvic ultrasound showed a small uterus measuring 56 mm by 38 mm by 20 mm. Husband's seminal fluid analysis revealed normal findings.

She was subsequently scheduled for in-vitro fertilization (IVF), egg donation, and embryo transfer. She had a failed IVF cycle using donor oocyte in 2015. In January 2017, she was booked for a repeat IVF and was commenced on IM estradiol valerate 10 mg weekly for 2 weeks, and thereafter, IM progesterone-in-oil 100 mg stat was given. She had withdrawal bleeding after 1 week and this was repeated for the next 2 months. Endoscratch was done, and the endometrium was then built up with weekly IM estradiol valerate.

She had IVF and Day 3 embryo transfer on February 14, 2017. Two embryos were transferred into the endometrial cavity with the aid of a Labotech catheter under ultrasound guidance. First attempt at transfer was unsuccessful, but the second attempt was successful. She was then placed on luteal phase support with IM progesterone in oil 100 mg daily, IM estradiol valerate 10 mg weekly, and PO folic acid 5 mg daily.

Fourteenth-day post-transfer, pregnancy was biochemically confirmed with positive serum PT and hormonal support was continued until 12 weeks of gestation. Transvaginal ultrasound done at 5 weeks of gestational age also confirmed pregnancy showing a gestational sac with an identifiable fetal

pole. She had prophylactic cervical cerclage using McDonald Technique at gestational age of 13 weeks following and ultrasound scan that revealed a short cervical length of 20 mm.

She booked for antenatal care at gestational age of 16W + 0D and she received two doses of tetanus toxoid and intermittent preventive therapy for malaria at 16W + 0D and 20W + 0D, respectively. Pregnancy remained uneventful until 37 weeks 4 days of gestational age when she was admitted for elective cesarean section.

She was delivered of a live singleton male baby weighing 3.5 kg with APGAR scores of 10<sup>1</sup> and 10<sup>5</sup>. An intraoperative finding of poorly formed ovaries was made, although the fallopian tubes appeared grossly normal bilaterally. Cervical cerclage was removed immediately after the surgery. Postop condition was uneventful with a postop packed cell volume (PCV) of 32% and mother was discharged on third postoperative day. Baby was commenced on immunization according to the extended program for immunization. Six weeks postdelivery, both mother and baby were seen in a satisfactory condition.

## Discussion

The case presented above is that of a Nigerian woman with complete gonadal dysgenesis (Karyotype 46, XX). In patients with 46, XX gonadal dysgenesis, there is a homozygote or heterozygote mutation of the FSH receptor gene.<sup>[3,6]</sup> This results in a female phenotype in the absence of secondary sex characteristics. It is a form of pure (complete) gonadal dysgenesis characterized by absence of well-differentiated gonads, but with normal internal and external genitalia. Patients have delayed puberty as well as primary amenorrhea as a result of ovarian insufficiency and they also have infertility. Hormone replacement therapy is needed for the initiation of female genital development.<sup>[7]</sup>

This patient typically had delayed development of secondary sexual characteristics and primary amenorrhea until the commencement of estrogen replacement therapy with oral contraceptive pills (OCPs) at the age of 19. This was as a result of the primary ovarian insufficiency.<sup>[3]</sup> As seen in this patient, there was also incomplete development of breasts due to low levels of circulating estradiol. There was however development of pubic and axillary hair probably due to the normal production of androgens by the adrenal gland.<sup>[8]</sup>

Gonadal dysgenesis is usually associated with an elevated level of FSH and LH and a low estrogen level.<sup>[9]</sup> From the laboratory findings, the level of the gonadotrophins was

expectedly elevated, and estradiol level was also low. As they have defective gonads with complete germ cell deficiency and hypoplastic uterus, infertility is commonly seen. IVF with the use of donor oocytes is therefore often offered as an option to circumvent the challenge of infertility.<sup>[2,3]</sup>

Researchers<sup>[2,10]</sup> have postulated that the uterus in patients with gonadal dysgenesis though hypoplastic can be stimulated with exogenous hormones to carry pregnancy successfully and this was further confirmed by this study. However, the hypoplastic uterus may lack the receptors and the capacity to dilate and contract as expected during the process of labor.<sup>[2,10]</sup> It has also been suggested that there is reduced response of the uterus to induction of labor in such group of patients.<sup>[11]</sup> The choice of cesarean section as the mode of delivery was influenced by these reports as well as maternal choice following discussion of the options of delivery.

Prophylactic cervical cerclage was placed at 13 weeks as a result of an ultrasound finding of short cervical length of 20 mm. This was combined with progesterone supplementation. They have both been shown to reduce preterm birth and its associated complications in singleton pregnancies with short cervix.<sup>[12,13]</sup>

During the cesarean section, streak ovaries were observed. Though gonadectomy is often recommended in women with dysgenetic gonads, it was not necessary for this patient as the increased risk of ovarian malignancies in this group of patients has been particularly attributed to the presence of Y chromosome.<sup>[4,14]</sup> The presence of GBY region as well as the testes-specific protein gene on Y chromosome have been identified as prerequisites for malignant transformation.<sup>[7]</sup>

The need for early diagnosis in patients with gonadal dysgenesis cannot be overemphasized, as the long-term lack of estrogen is associated with several neurological, metabolic, psychological, and cardiovascular health problems. They are also at risk of early bone loss and osteoporosis.<sup>[9]</sup> Infertility, which is a consequence of the primary ovarian insufficiency in them, has been shown to be treatable through IVF with donor oocytes; therefore, patients should be identified early for prompt management.<sup>[8]</sup>

In conclusion, early presentation, in-depth evaluation, adequate counseling, and early institution of management can help women with gonadal dysgenesis resume their menstrual cycle and assume a good reproductive life. The effective use of hormone replacement therapy and application of assisted reproductive treatment techniques can

help them to circumvent the monstrous challenge of infertility associated with this condition, especially in an environment like ours where marital success is a factor of the woman's ability to conceive and give birth.

### 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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