Case Report

A Rare Case of Swyer Syndrome in Two Sisters with Successful Pregnancy Outcome in Both

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Abstract

Swyer syndrome is a disorder of sex development characterized by gonadal dysgenesis in a phenotypic female with normally developed Mullerian structures but a 46XY karyotype resulting from failure of testicular development in the early embryogenesis. It can have X-linked, Y-linked, or autosomal inheritance. We had a case of two sisters who presented with primary amenorrhea and primary infertility. On investigation, both had hypergonadotropic hypogonadism, 46XY karyotype, and streak gonads. They conceived following *in vitro* fertilization (IVF) with ovum donation. Prophylactic gonadectomy has been done in one and advised in other due to the increased risk of gonadoblastoma which is as high as 15%–35%. Such patients should be counseled that despite hypoplastic uterus, successful pregnancy can be achieved through IVF and ovum donation.

Keywords: *Gonadal dysgenesis, hypergonadotropic hypogonadism, primary amenorrhea, Swyer syndrome*

Introduction

Swyer syndrome was first described by Jim Swyer in 1955 and is a disorder of sex development characterized by gonadal dysgenesis in a phenotypic female with normally developed Mullerian structures but a 46XY karyotype. It has an incidence of 1 in 80,000[1] and results from failure of testicular development in the early embryogenesis, for which several genes have been implicated. The condition comes to light when there is delayed puberty and primary amenorrhea. Most cases are sporadic but some familial cases have also been described.[2] We had two sisters who presented with primary infertility and conceived following *in vitro* fertilization (IVF) with ovum donation. An informed consent was taken for case reporting.

Case Report

Mrs. P, 25-year-old female, presented with primary infertility of 2 years. She gave a history of menarche at 18 years and irregular menses every 3–4 months lasting for 2–3 days for the initial 2–3 years. Thereafter, she had only withdrawal bleeding after sequential E + P therapy. She had undergone laparohysteroscopy at another center which was suggestive of small-sized uterus with normal fallopian tubes and bilateral small ovaries. She had undergone two cycles of ovulation induction with clomiphene and gonadotropins and one cycle of IVF with ovum donation, which were unsuccessful.

She had normal female external genitalia and breast development Tanner Stage 3. Her hormone levels were as follows: follicle-stimulating hormone (FSH) – 43.14 mIU/ml, luteinizing hormone (LH) – 36.23 mIU/ml, thyroid-stimulating hormone – 3.08 μIU/ml, prolactin – 3.21 ng/ml, anti-Müllerian hormone (AMH) – 0.27 ng/ml, and testosterone – 0.52 ng/ml. A provisional diagnosis of premature ovarian failure was made, and the patient was counseled for IVF with ovum donation. However, her karyotype showed 46XY pattern. On further counseling, she revealed that she had primary amenorrhea and menses only after E + P withdrawal since beginning and had withheld this information due to perceived stigma associated with primary amenorrhea. She was counseled

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regarding her diagnosis and its implications on her long-term health. She did not want this information to be disclosed to her husband, and hence, it was withheld from her partner to avoid marital discord.

She was advised gonadectomy followed by IVF with ovum donation due to risk of gonadoblastoma in such cases. She did not opt for gonadectomy at this stage because of social pressure to conceive and opted for IVF with ovum donation. For endometrial preparation, she received tablet estradiol (E2) 2 mg 8 hourly and E2 gel 8 hourly. Her fresh embryo transfer was unsuccessful. She conceived following frozen embryo transfer and had an otherwise uncomplicated pregnancy and delivered a healthy male child at 37 weeks with a birth weight of 2.9 kg and exclusively breastfed the baby up to 6 months. She has been counseled regarding need for gonadectomy and is currently on follow-up.

One year later, her younger sister presented with primary infertility and primary amenorrhea with menses on E + P withdrawal. Her ultrasound showed a hypoplastic uterus with bilateral small ovaries. Her hormone levels were as follows: FSH – 93.05 mIU/ml, LH – 25.29 mIU/ml, and AMH – 0.05 ng/ml. Her karyotype was 46XY, and she was diagnosed as a case of Swyer syndrome.

She was counseled and advised laparoscopic bilateral gonadectomy followed by IVF with ovum donation. On laparoscopy, there were bilateral streak gonads and small uterus. It has been suggested that complete removal of gonads can be better accomplished by removal of adnexa, especially when gonads are elongated, attenuated, or in close approximation to fallopian tubes.[3] In our case only, gonadectomy was done, and tubes were conserved as it did not compromise complete removal of gonadal tissue. Histopathological examination showed dysgenetic gonads [Figures 1 and 2].

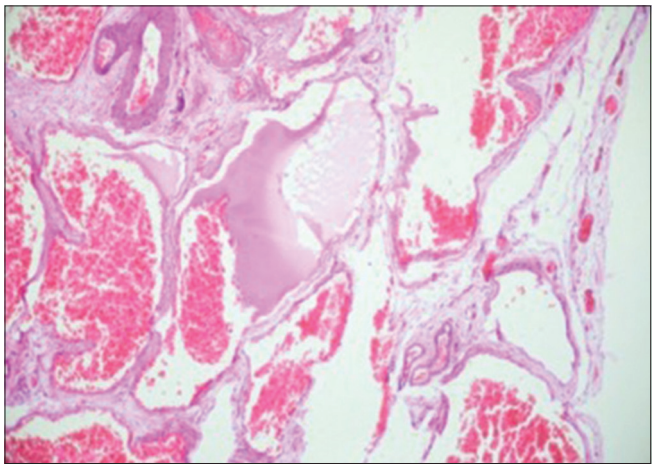

Figure 1: Gonadal biopsy: H and E, ×100 showing vascularized fibrosis

Two months later, IVF with ovum donation was done after endometrial preparation with estrogen replacement. She conceived following a fresh embryo transfer and is currently 14-week pregnant with an uneventful pregnancy till now.

Discussion

Swyer syndrome is a relatively uncommon condition, and only few familial cases have been reported.[2,4,5] It can be inherited as Y-linked, X-linked, and autosomal dominant or recessive disorder.[6] The most commonly accepted mechanism is that a protein produced by sex-determining region Y (SRY) gene present on Y chromosome is responsible for differentiation of primitive gonad into testes. Mutations in SRY gene lead to production of a defective protein, which results in streak gonads and persistence of Mullerian structures in a fetus with 46XY karyotype. SRY gene mutations have been implicated in 10%–15% cases of Swyer syndrome.[7] In other cases, role of genes located on autosomes or X chromosome which affects sex differentiation has been suggested.[4]

In our case, the sisters have a healthy unmarried younger brother. There was no history of consanguinity or similar history in the family. A report by Hines *et al*. examined the presence of mosaicism in sperm DNA (paternal gonadal mosaicism) and described how a normal father can have two populations of sperms with one normal population and another population carrying mutation in SRY gene.[5] This can explain how the same father can produce two XY sex-reversed siblings and one XY "normal" sibling. Genetic tests such as arrayCGH, WES, and microdeletion studies in SRY gene have been described to identify pathogenic mutations. As both sisters declined further genetic testing, exact molecular event responsible for sex reversal could not be identified.

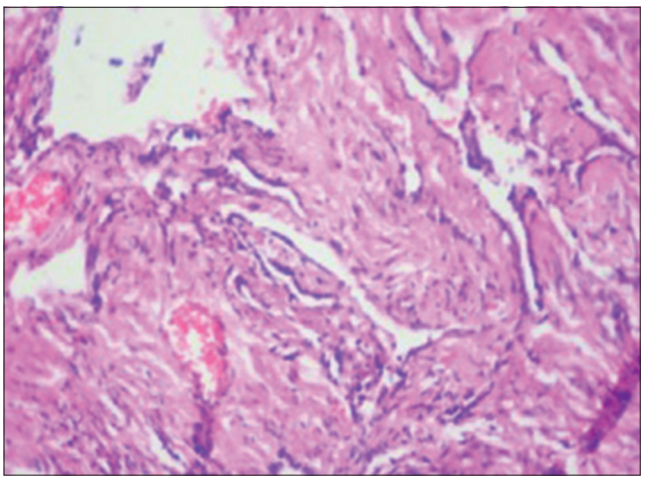

Figure 2: Gonadal biopsy: H and E, ×400 showing fibrous stroma with no evidence of testicular differentiation. Epithelial structures with irregular anastomosing tubules are seen

We want to highlight the importance of timely diagnosis of Swyer Syndrome and need for early prophylactic gonadectomy as incidence of gonadoblastoma in these cases is as high as 15%–35% and increases with age.[8]

Furthermore, such patients should be counseled that despite an underdeveloped uterus, they can have successful pregnancies with IVF and ovum donation. Although there is some evidence that transvaginal ultrasound guidance during embryo transfer may increase success rates, we found that in experienced hands, embryo transfer under transabdominal guidance has excellent results.[9] Available literature suggests that except for a higher incidence of cesarean section which may be due to either anatomical properties of such uteri which may not permit normal dilation and labor or due to associated physician and patient anxiety, such pregnancies are otherwise similar to other IVF pregnancies.[10]

After delivery, hormone replacement therapy should be started for preservation of bone health in all such patients.

Declaration of patient consent

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

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