Case Report

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# Swyer syndrome (46, XY complete gonadal dysgenesis): A rare case of primary amenorrhea

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**Abstract:**

Swyer syndrome is a type of gonadal dysgenesis wherein a 46,XY karyotype presents with a female phenotype. It is a rare cause of disorder in sexual development that occurs in 1:100,000 births. Local studies are currently limited to few case reports. Sex-determining region on the Y chromosome gene mutation is the root cause of nonfunctional gonads with no hormonal or reproductive potential. They are born with normal female external genitalia but not suspected until puberty when menses do not occur or if secondary sexual characteristics do not develop. This report presents the case of a 23-year-old phenotypically female presenting with primary amenorrhea and hypogastric discomfort. Ultrasound revealed an infantile cervix and uterus with streak left ovarian tissue and a cystic mass on the right pelvic area. Gonadotropin levels were elevated, and the karyotype showed a normal male 46,XY. Laparoscopic bilateral gonadectomy with salpingectomy was done, which revealed dysgerminoma on bilateral ovarian tissues. In conclusion, this report describes a rare case of Swyer syndrome associated with ovarian dysgerminoma. Accurate and prompt diagnosis, using a systematic approach in evaluating primary amenorrhea, is crucial in initiating treatment. Our goal is to ensure hormonal replacement, fertility preservation, psychosexual and emotional stress reduction, and overall patient survival.

**Keywords:**

Disorders of sexual development, dysgerminoma, gonadal dysgenesis primary amenorrhea, Swyer syndrome

## Introduction

Sexual determination is genetically and hormonally controlled. Differentiation begins with the genetic or the chromosomal sex (XX or XY), acquired during fertilization when the ovum and sperm unite. This causes the primitive gonad to develop into a testis or an ovary, defining the gonadal sex. Subsequently, gonadal differentiation and function determines the phenotypic sex and secondary sexual characteristics during puberty.[1]

During early embryonic life until the 6th-week age of gestation, sexual difference is indistinct. The undifferentiated gonads are identical at this stage and can develop into either an ovary or testes.[2] Multiple genes are involved in this process, but the presence of the Y chromosome is known to be the single most consistent determinant of maleness. The sex-determining region on the Y chromosome (SRY) gene acts as a binary switch that dictates the course of development.[3] Initially, both the Wolffian and Müllerian ducts are present. In the male gonadal course, the developing testis is arranged into two compartments – the Sertoli and Leydig cells. Testosterone is secreted by the Leydig cells, stabilizing the Wolffian ducts that develop to the epididymis, vas deferens, and seminal vesicle. It also undergoes peripheral conversion to dihydrotestosterone via 5a-reductase that causes the development of the external male genitalia. On the other hand, the Sertoli cells secrete anti-Müllerian

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hormone (AMH), which induces the dissolution of the Müllerian ducts. In the absence of testosterone and AMH, the Wolffian duct regresses, the external female genitalia develop, and the Müllerian duct develops into the fallopian tubes, uterus, cervix, and upper vagina.[4] External or internal factors can modify this normal development process leading to chromosomal or gonadal abnormalities that may or may not be apparent at birth.

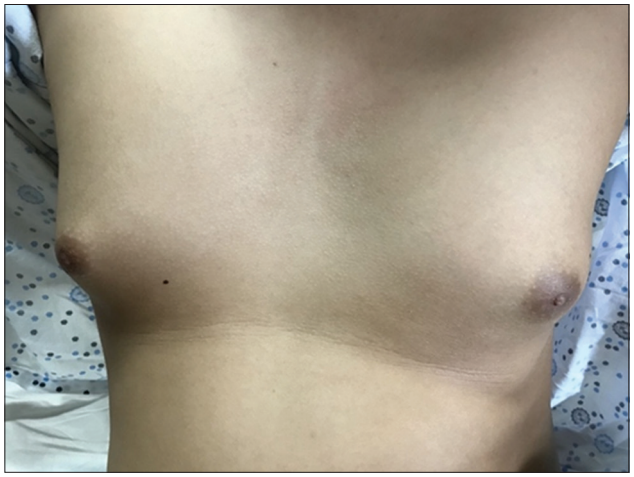

**Figure 1:** Breast development of the patient. There is breast enlargement but without separation of the contours of the areola from the breast representing Tanner Stage 3

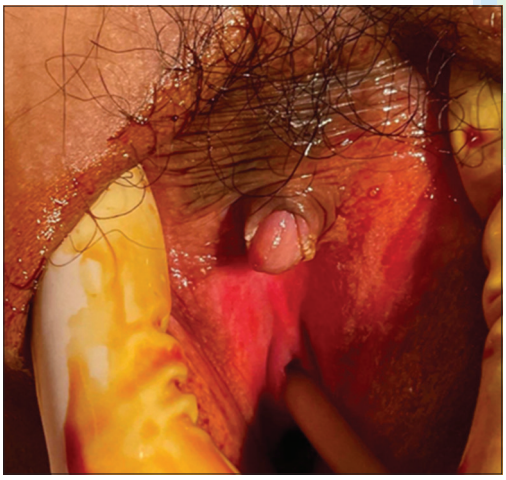

**Figure 2:** Intraoperatively, examination of the external genitalia revealed a grossly normal vagina; the clitoris was noted to be slightly enlarged

Congenital conditions wherein the chromosomal, gonadal, or anatomic sex is atypical define the disorders of sexual development (DSD).[5] Advances in genetics have replaced the traditionally used terms "pseudohermaphroditism" and "hermaphroditism." Based on the Chicago Consensus,[5] the new nomenclature is based on the primary genetic defect that may be either sex chromosome DSD, 46,XX DSD, or 46,XY DSD. Gonadal dysgenesis refers to conditions that cause impaired gonad differentiation. One type is Swyer syndrome or 46,XY complete gonadal dysgenesis. It is a rare cause of DSD with an incidence of 1:100,000 births.[6] G.J. Swyer first described this disorder in 1955 and is believed to be caused by an error in sex determination during embryogenesis, causing a failure in gonadal progression. A female phenotype with nonambiguous genitalia, normally developed Müllerian derivatives, bilateral streak gonads, normal XY karyotype, and elevated gonadotropin with decreased estradiol levels (hypergonadotropic hypogonadism) usually characterize patients with this syndrome.[7] Diagnosis is usually delayed since it does not become apparent until puberty, when primary amenorrhea occurs. A retrospective study done on 102 patients with primary amenorrhea revealed a 20.5% prevalence of gonadal dysgenesis, 4.9% of which was diagnosed with Swyer syndrome through cytogenetic studies.[8] In 20%–30% of cases with dysgenetic gonads, association with germ cell malignancies is found, so the current practice is to proceed with gonadectomy once the diagnosis is made. On review of local case reports, there are six reported cases of Swyer syndrome in the Philippines,[9-13] one of which was previously reported from our institution.[14] Half presented with primary amenorrhea, while the others with an abdominal mass. The mean age of diagnosis is at 20 years of age (14–28 years old). All had a 46, XY karyotype with normal female phenotype and streak gonads. Of the cases reported, one (16%) was diagnosed

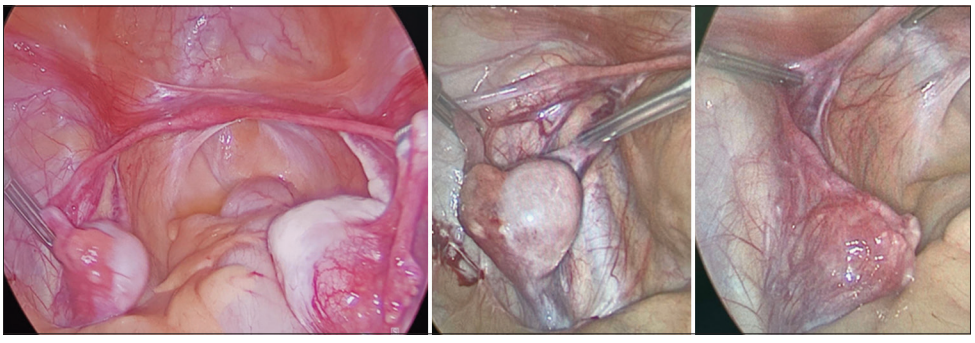

**Figure 3:** Laparoscopic view of the uterus and gonads (left), right adnexal mass (middle), left ovarian tissue

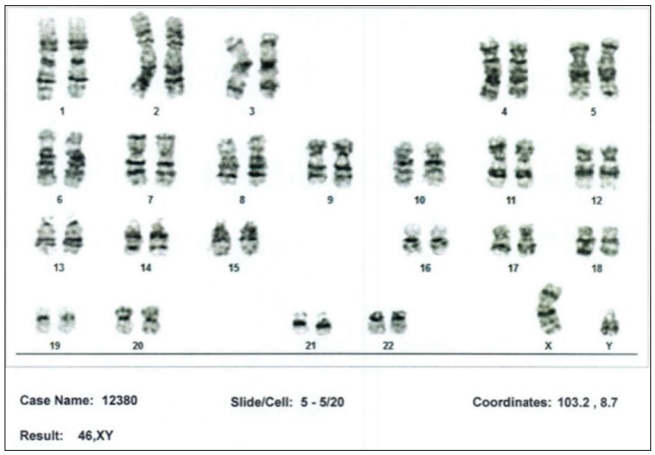


**Figure 4:** Karyotype of the patient, showing a normal male 46,XY karyotype

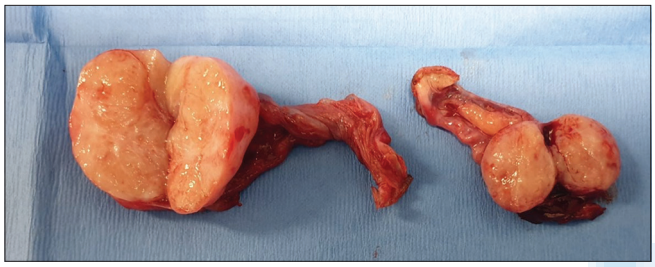

**Figure 5:** The gross specimen on the cut section. The left adnexal mass (right) measured 2 cm × 2 cm × 1.5 cm with a tan, smooth, soft to medium consistency solid mass on the cut section. The right adnexal mass (left) was cystically enlarged to 3.5 × 3 × 2 with a tan-yellowish, firm, trabeculated pattern

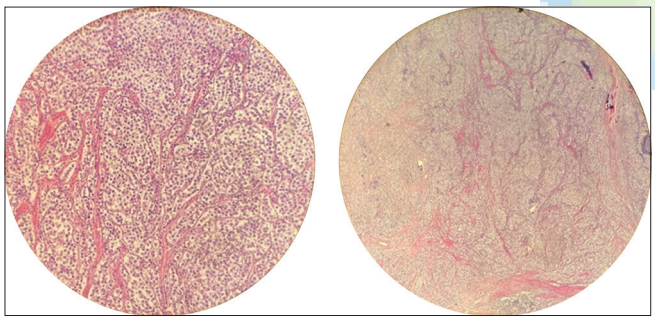

**Figure 6:** Histopathology findings. There are sheets or nests of large, uniform polygonal cells with clear or eosinophilic cytoplasm and distinct squared-off cell membranes. The tumor is separated by fibrous septa containing cytotoxic lymphocytes and epithelioid histiocytes. Stroma is loose and delicate with numerous mitotic figures

with dysgerminoma, one (16%) with yolk sac tumor, one (16%) with gonadoblastoma, and two (33%) with mixed germ cell tumor.

This report discusses the rare case of a 23-year-old female with primary amenorrhea diagnosed as Swyer syndrome. Here, we discuss the approach and management of patients presenting with primary amenorrhea and why accurate and prompt diagnosis is crucial to initiating treatment in patients at high risk for developing gonadal malignancy.

## Case Report

This is a case of a 23-year-old, phenotypically female, single, presenting with primary amenorrhea. She was born with grossly normal female genitalia. Childhood history was unremarkable, and there was no report of neurodevelopmental delay. Growing up, she was raised as a female, and gender identity never became a problem for the patient. No previous sexual contact was reported, but the patient has expressed her desires and hopes to have children in the future. She sought consult due to primary amenorrhea with accompanying hypogastric discomfort. There were no associated vasomotor symptoms, mood changes, headache, bowel, or urinary symptoms. On physical examination, the patient is seen phenotypically female, with a height of 1.61 m (5 feet, 3 inches) and a weight of 69.5 kg (body mass index of 26 kg/m$^2$). The skin was not dry, and no hirsutism was noted. Breast development was at Tanner Stage 3 and pubic hair development at Tanner Stage 2 [Figure 1]. There was no midline hair or abdominal masses palpable; the abdomen was soft and nontender. The external genitalia were grossly female, but with flattened labia majora, the clitoris was not enlarged [Figure 2]. On digital rectal examination, there was a tight sphincteric tone without palpable masses or nodularities.

Transrectal ultrasound was done on initial evaluation, which showed an infantile cervix and uterus with thin endometrium (0.9 cm), nonvisualized right ovary, and streak left ovarian tissue. A cystic mass was noted on the right pelvic area with mixed echogenicity and no color flow measuring 3.3 cm × 2.9 cm × 2.8 cm. Within this cystic mass is an echogenic structure that demonstrateees acoustic shadowing measuring 1.4 x 1.1 x 1.4 cm. Hormone levels revealed elevated follicle-stimulating hormone (FSH) at 50.72 mIU/mL and luteinizing hormone (LH) at 14.02 mIU/mL. Thyroid-stimulating hormone (TSH), serum prolactin, and free testosterone levels were within the normal range. A pelvic *magnetic resonance imaging* was requested for further evaluation and confirmed the presence of an underdeveloped uterus located midline within the pelvic cavity measuring 1.2 cm × 1.8 cm × 3.6 cm, with an approximate volume of 4cc (normal volume for age is 62.4 cc); the vagina and cervix are likewise underdeveloped. Ovoid structures were seen on both sides of the pelvic cavity, superolateral to the uterus, measuring 3.1 cm × 2.2 cm × 3.7 cm on the right and 2.2 cm × 1.9 cm × 2.4 cm on the left. Both ovoid foci are found in keeping with normally positioned ovaries. A karyotype study was advised due to suspicions for congenital Müllerian anomalies and revealed a normal male 46, XY [Figure 4]. Ovarian tumor markers were requested for further evaluation of the adnexal masses. Normal cancer

antigen 125 (11.20 U/mL), carbohydrate antigen 19-9 (23.99 U/m), alpha-fetoprotein (AFP) (<1.3 ng/mL), lactate dehydrogenase (LDH) (164 U/L), and serum total beta-human chorionic gonadotropin (hCG) (<2 mIU/mL) were noted.

She was referred to reproductive medicine and gynecologic oncology for further management. The patient underwent laparoscopic bilateral gonadectomy with salpingectomy. Pelvic examination under anesthesia revealed a patent vaginal canal of approximately 7 cm, with an underdeveloped cervix measuring around 1 cm × 1 cm; the uterus was small with no palpable adnexal mass. Intraoperatively, the uterus appeared flattened and infantile in size, with a pink serosal surface [Figure 3]. The left adnexal mass (gonad) measured 2 cm × 2 cm × 1.5 cm with a tan, smooth, soft to medium consistency solid mass on the cut section. The right adnexal mass (gonad) was cystically enlarged to 3.5 × 3 × 2 with a tan-yellowish, firm with a trabeculated-like pattern [Figure 5]. The left and right fallopian tubes appeared grossly normal. The liver, appendix, and the rest of the pelvo-abdominal organs were grossly normal [Figure 6]. The final histopathology result was dysgerminoma with a pathologic stage of pT1b; On the whole abdominal *computed tomography* (CT) scan done, the liver is not enlarged with smooth margins, no discrete enhancing mass lesion was identified; the spleen and both adrenal glands are normal in size without focal lesion. There is no evidence of significantly enlarged retroperitoneal, mesenteric, pelvic, or inguinal lymph nodes, negative for ascites or extraluminal free air. On chest and mediastinum CT scan, no discrete pulmonary mass or nodule, no enlarged mediastinal and hilar lymph nodes were appreciated. According to FIGO, (2018) the final staging is Stage IB (T1b, N0, M0). She was started on hormonal therapy with monitoring every 3–6 months and subjected to chemotherapy with bleomycin.

## Discussion

Primary amenorrhea occurs if menses are absent by the age of 15 or if no menstruation occurs within 5 years of breast development if occurring by age 10.[15] Our patient was seen at 23 years old but has not menstruated ever since. Evaluation starts with a thorough history and physical examination. Workup first involves ruling out pregnancy, then a systematic evaluation of the five major factors involved in the regulation of menstruation – the anatomic patency of genital tract, normal female chromosomal pattern (46,XX), the synchronized regulatory feedback mechanism of the hypothalamic–pituitary–ovarian (HPO) axis, support by the thyroid and adrenal cortex, and a responsive endometrium. A problem in any one or more of these factors can lead to amenorrhea.[16] Clinically, the causes of primary amenorrhea can be divided according to the presence or absence of secondary sexual characteristics (e.g., development of breast, pubic hair, and axillary hair) and the presence or absence of the uterus. A simplified clinical evaluation of the etiology of primary amenorrhea is presented in Table 1.[16]

Tanner staging for breast development is a reliable indicator of estrogen production. In our patient, her breasts were consistent with the normal breast development among 10–15-year-old females at Tanner Stage 3. An arrest in breast development suggests a disruption in the HPO axis. Examination of the external genitalia revealed grossly normal vagina with pubic hair at Tanner Stage 2. The growth of pubic hair reflects androgen exposure; however, it is not as reliable as the breast staging in assessing pubertal development because of the independent maturation of the adrenal axis.[17] Imaging was done to determine the presence or absence of the uterus. Our patient had an infantile-sized uterus with thin endometrium and streak left ovarian tissue on transrectal ultrasound, which are signs of hypoestrogenism. Hormonal assays revealed elevated serum FSH and LH, thus confirming a hypergonadotropic-hypogonadic state. This points to ovarian failure, wherein the ovaries fail to produce enough estrogen leading to the absence of negative feedback on the hypothalamus and pituitary gland. Serum prolactin, if elevated, could point to a pituitary tumor that could lead to hypoestrogenemia, but it was normal in our patient. TSH levels rule out subclinical hypothyroidism, even if the patient does not present with thyroid-associated problems. Given these findings, what clinched the diagnosis was the chromosomal analysis showing a 46, XY complement. Females with 46, XY complete gonadal dysgenesis have female external genitalia, a small uterus, and streak gonads, the same as our patient. This should be distinguished from patients with androgen insensitivity syndrome who also present with amenorrhea and an XY karyotype; however, the absence of breast development and the presence of a uterus in our patient exclude this possibility.

Our patient had the typical signs of Swyer syndrome (46,XY complete gonadal dysgenesis): average height, underdeveloped breasts, and axillary and pubic hair present. The absence of secondary sexual characteristics occurs because the streak gonads cannot produce estrogen and androgens at normal levels. The adrenal glands are not affected by the syndrome and can still secrete small amounts of androgens. This stimulates pubic hair growth, and its conversion to estrogen in adipose tissues promotes breast and female genitalia to develop. However, since only small amounts of androgens are produced, only a moderate amount of pubic hair grows. Her uterus is infantile in size

**Table 1: Clinical evaluation of the etiology of primary amenorrhea**

| Group I<br>Breast (+)<br>Uterus (+) | | Group II<br>Breast (+)<br>Uterus (–) | Group III<br>Breast (–)<br>Uterus (+) | | Group IV<br>Breast (–)<br>Uterus (–) | |
|---|---|---|---|---|---|---|
| **Outflow tract obstruction** | **No outflow tract obstruction** | | **Gonadal failure** | **Hypothalamic failure due to inadequate GnRH release** | **Pituitary failure** | |
| Imperforate hymen<br>Vaginal agenesis<br>Transverse septum<br>Cervical agenesis<br>Uterine didelphys with blind vagina | PCOS<br>Adrenal cause (CAH, Cushing syndrome)<br>Androgen-secreting tumor<br>Hyperprolactinemia<br>Thyroid disease<br>Tubercular endometritis | Mullerian agenesis/ MRKH (46,XX)<br>Androgen insensitivity syndrome (46,XY) | Turner syndrome (45,X)<br>46,XX (partial) or 46,XY (complete) gonadal dysgenesis<br>17a-hydroxylase deficiency with 46,XX | Kallmann's syndrome (inadequate GnRH synthesis)<br>Congenital anatomic defects in the CNS<br>Craniopharyngioma | Pituitary neoplasm<br>Isolated gonadotropin insufficiency (thalassemia major, retinitis pigmentosa)<br>Mumps<br>Encephalitis<br>Newborn kernicterus | 17, 20-desmolase deficiency<br>Agonadism<br>17a-hydroxylase deficiency with 46,XY karyotype |

CAH: Congenital adrenal hyperplasia, PCOS: Polycystic ovarian syndrome, GnRH: Gonadotropin-releasing hormone, CNS: Central nervous system, MRKH: Mayer-Rokitansky-Küster-Hauser Syndrome

due to a lack of sufficient estrogen stimulation. The gonads are dysgenetic with no hormonal function, that is, why the hormonal assay would show a hypergonadotropic-hypogonadic state.

How come the patient presents as phenotypically female even if with a nonfunctioning gonad? Despite having a Y chromosome, the phenotype presents as female because the dysgenetic gonads fail to produce AMH and androgens. In 10%–15% of Swyer syndrome cases, it was found that an inactivating mutation in the SRY gene is the root cause. The absence or mutation in the SRY gene causes the development of the female reproductive organs. Identification of gene mutation utilizes a particular test called fluorescent *in situ* hybridization because the karyotype test usually misses it. In this case, however, it was no longer done as the management of the case will not change whether an SRY mutation was found or not.

Early diagnosis is necessary due to the high possibility of developing gonadal malignancy. The most common tumor of dysgenetic gonads is gonadoblastoma and dysgerminoma, with a 15%–35% risk in patients with Swyer syndrome.[18] Our patient had an incidental ultrasound finding of a cystic mass on the right pelvic area, which raised suspicions for a possible gonadal malignancy. A panel of ovarian tumor markers was requested. Serum CA 125 is the most common marker used in assessing ovarian masses.[19] AFP, hCG, and LDH are germ cell tumor markers.[20] CA 19-9 assesses mature cystic teratomas, while carcinoembryonic antigen is an independent prognostic factor for mucinous ovarian cancer.[21] Our patient had normal results for all tumor markers, so the initial consideration for the right adnexal mass is gonadoblastoma. Gonadoblastomas arise from the undifferentiated gonadal tissue within the dysgenetic gonad. Although benign, it can develop into invasive germ cell tumors, the pathogenesis of which is still not known.[22] Immediate gonadectomy is the procedure of choice to exclude malignancy with absolute certainty.[23] This was explained to our patient, and she agreed to the planned surgical procedure. Intraoperative findings show an infantile uterus and small gonads. The right adnexal mass (gonad) was cystically enlarged, and bilateral fallopian tubes appeared grossly normal. The final histopathology result revealed dysgerminoma on bilateral gonads, with a pathologic stage of pT1b, which means that the tumor was only confined to the ovaries without gonadal and fallopian tube surface involvement.

Dysgerminoma is the most common malignant germ cell tumor of the ovary.[24] It contains germ cells that have not differentiated into embryonic or extraembryonic structures. About 65% are Stage I at diagnosis, with 85%–90% confined to one ovary, while 10%–15% are found bilaterally. Dysgerminoma is the only germ cell malignancy that has this significant rate of bilaterality.[25] Although malignant and rapidly growing, they are often not aggressive and are highly sensitive to adjuvant chemotherapy, particularly with bleomycin, etoposide, and cisplatin given for three to four cycles. The survival rates of patients with XY gonadal dysgenesis and dysgerminoma are similar to the survival rates of XX individuals with malignant ovarian germ cell tumors.[26] In both types, survival rates are mainly dependent on the tumor stage. Our patient's prognosis is good since Stage I tumors are found to have a survival rate as high as 96.9%.[27] A previous case report of Da Silva Rios *et al*. in 2015 reported a Swyer syndrome patient with advanced-stage dysgerminoma, yet had a survival time of 23 years, with no recurrence of the disease.[26]

Adequate sex hormone production at puberty has a necessary action on bone mineral content, metabolism, and breast development and improves uterine size for possible future pregnancy.[28] Initiation of hormone replacement therapy is therefore warranted. A daily dose of 0.625–1.25 mg conjugated equine estrogen is given for 3–6 months to achieve pubertal development. Maintenance therapy should then be given once breast and pubic hair development is achieved. Since the patient came to us with primary amenorrhea at 23 years old, an investigation on her bone integrity should also be warranted. A baseline dual-energy X-ray absorptiometry scan can be done to document the presence of osteopenia or osteoporosis. In some studies, the bone mass of women diagnosed with hypogonadal amenorrhea was 20%–30% lower than menstruating women of the same age.[29] Hormone therapy and calcium supplementation are the mainstays of treatment.

Generally, patients with dysgerminoma are good candidates for fertility-preserving surgery because of their excellent response after chemotherapy, even with advanced-stage disease. This is good for our patient, given her desire to have children in the future. Rates of relapse after radical surgery compared with conservative surgery for the ovaries and the uterus were not different.[30] Successful pregnancies in Swyer syndrome have been reported since 1988[28] through advanced reproductive technology with oocyte donation and embryo transfer, and so could be an option for our patient later on.

Another controversial issue is disclosing the patient's true gender. This involves not only the patient but her family as well. Psychosocial management to promote positive adaptation is essential, and counselors or psychologists with expertise in DSD should provide adequate care. After discussing with the patient all the treatment plans and options, she was given the opportunity to discuss her sentiments regarding her condition, how she understood it and what it means to her. Moral support from family members and health-care professionals is crucial to avoid depression and suicidal thoughts and enhance satisfactory sexual functioning in adulthood.

Genetic counseling is an essential part of management in this case. This aims to help the patient and her family assess the risk for this genetic condition and know the possible inheritance patterns and chances of recurrence. If done, it can increase our understanding of the condition, its course, and associated comorbidities and help us better discuss the options regarding management and risks and benefits. In summary, the management of patients with disorders in sexual development, as in our case, is complex and involves a multidisciplinary approach. The endpoint is to give the patient, and her family, reassurance as this case is a manageable condition, and though associated with a gonadal malignancy, a long, disease-free, and productive life is achievable.

## Conclusion

This is a rare case of 46, XY complete gonadal dysgenesis or Swyer syndrome presenting as primary amenorrhea and delayed secondary sexual characteristic development at the age of 23. The diagnosis and management are complex, and optimal care requires a specialist center with a multidisciplinary team. A thorough investigation of primary amenorrhea is crucial for early diagnosis to identify individuals with a Y chromosome who will require timely prophylactic gonadectomy to avert degeneration of dysgenetic gonads into malignancy. This will ensure the preservation of fertility, reduction of psychosexual and emotional trauma, and improvement in overall patient survival. Proper counseling should also be done on the psychological aspects of the disease. Moral support from family members and professionals is crucial. Providing the patient, the proper knowledge regarding her condition would limit the risk of psychological problems and is important for satisfactory development into adulthood.

### Declaration of patient consent

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

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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