Case Report

Primary amenorrhea

Varied etiology

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ABSTRACT

Investigation of primary amenorrhea is usually initiated by the age of 14 years if there is delayed puberty (absent secondary sexual characteristics and absent menses), or no menstruation within 4 years of the onset of adrenarche and thelarche. We established diagnosis in our 3 cases on the basis of chromosomal analysis, hormonal analysis, diagnostic laparoscopy, and histopathological examination of the samples biopsied. We identified 3 varied etiologies.

Saudi Med J 2005; Vol. 26 (9): 1453-1455

Approximately 30% of patients with primary amenorrhea have an associated genetic abnormality. The syndrome of gonadal dysgenesis, or Turner's syndrome, and its variants, represents the most common form of hypogonadism in women. Determination of the presence or absence of secondary sexual characteristics is useful to detect the cause of amenorrhea.[1] Evaluation of 3 cases of primary amenorrhea, in our setting, after subjecting them to various laboratory investigations and diagnostic laparoscopy revealed 3 different etiologies. Chromosomal study identified 2 cases as 46 XX and the third case as 46 XY.

Case Report. ***Patient 1.*** A 19-years-old unmarried female, weighing 76 kgs with negative sickling test, presented as primary amenorrhea with normal external genitalia, well-developed breasts and normal hair distribution. Her hormonal profile indicated normal levels of follicular stimulating (FSH), leuteinizing hormone (LH), serum estradiol, prolactin and thyroid function tests (TFT). She was advised on weight reduction and subjected to the progesterone challenge test (progyluton) with no resulting bleeding per vaginum. Her history elicited surgery for bilateral inguinal hernias at the age of 4 months. On ultrasound, uterus and ovaries were infantile, otherwise, normal. Uterus measured 25 x 7 x 25 mm, right ovary measured 18 x 11 mm and left ovary measured 17 x 10.5 mm. Chromosomal study revealed 46XY, suggestive of androgen insensitivity syndrome (testicular feminizing syndrome). She underwent diagnostic laparoscopy and examination under anesthesia (EUA). The EUA showed well-formed female external genitalia and intact hymen. Per rectal examination showed presence of a blind vaginal pouch with empty pelvic cavity. On laparoscopy, no central uterus was found, right side was empty, and on the left side small fibrous tissue looking like epididymis going to the left inguinal canal on one side and the other side directly connected to ovarian/testicular tissue **(Figures 1 & 2)**. A biopsy of the tissue taken depicted a thick capsule overlying immature testicular tubules with interstitial tissue showing Leydig cells consistent with immature testicular tissue. Considering the

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Received 19th March 2005. Accepted for publication in final form 12th June 2005.

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higher risk of gonadal malignancy associated with 46 XY and immature testicular tissue; she has been offered surgery for removal of testicular tissue and maintenance of female phenotype.

Patient 2. A 20-year-old married female was referred from the hospital polyclinic with a history of primary amenorrhea with no coital problems. She had underdeveloped breasts and normal hair distribution. Her external genitalia were normal; speculum and vaginal examination showed a small nulliparous healthy cervix and a small retroverted uterus. Ultrasound showed infantile uterus with streak ovaries. Laboratory investigations showed high FSH (39.05 IU) and LH levels (84.9 IU). Serum prolactin and TFT were within normal ranges. She was 46 XX on chromosomal analysis. Diagnostic laparoscopy showed small uterus with normal tubes and bilateral streak ovaries, the left being smaller than the right **(Figure 3).** Biopsy of the tissue revealed primary, secondary follicles and corpora albicantia with small follicles showing cystic dilatations and attenuation of the cortex, suggestive of streak ovary (gonadal dysgenesis). She was subjected to progesterone challenge test, which was positive, and was started on hormonal treatment (estrogen and progesterone) for the rest of her life, with a recommendation to undergo assisted reproductive techniques (ART) for conception.

Patient 3. A 20-year-old unmarried female, presented with history of primary amenorrhea. On examination, secondary sexual characteristics were found to be not well developed. Ultrasound showed small nodule like uterus with streak ovaries. Laboratory investigations showed FSH and LH levels of 0.28 and 0.00 IU. Serum prolactin and TFT were within normal ranges. She was 46 XX on chromosomal analysis. She initially refused diagnostic laparoscopy, and was started on estrogen and progesterone (progyluton). She responded to the above treatment and was experiencing regular withdrawal bleeding. She later agreed to undergo diagnostic laparoscopy, which revealed a small central uterus with small tubes, bilateral normal looking ovaries from which biopsy was taken **(Figure 4).** A section from the ovary showed numerous primordial follicles on histopathological examination. She continues to be on progyluton.

Discussion. It is well known that by the age of 20 years, women have established remarkably regular and persistent patterns of menstrual cycle length with little variation on an individual basis. Gonadal dysgenesis is an important cause of primary amenorrhea, which can occur with either a 46 XX or a 46 XY karyotype.[1] Despite a 46 XY karyotype and gonads with the typical appearance of testes (perhaps altered similarly to those with cryptorchidism), a feminine gender assignment is unquestionable due to completely feminine

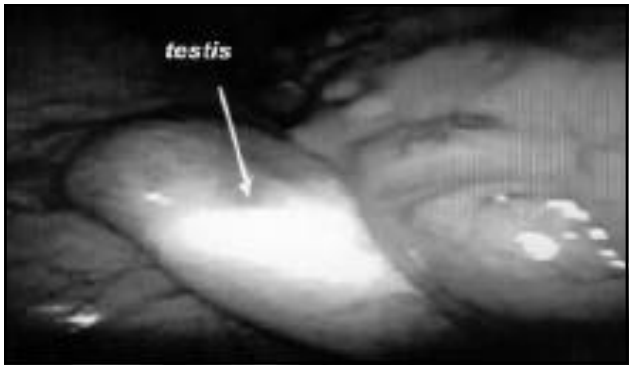

Figure 1 - Testis in the phenotypic female.

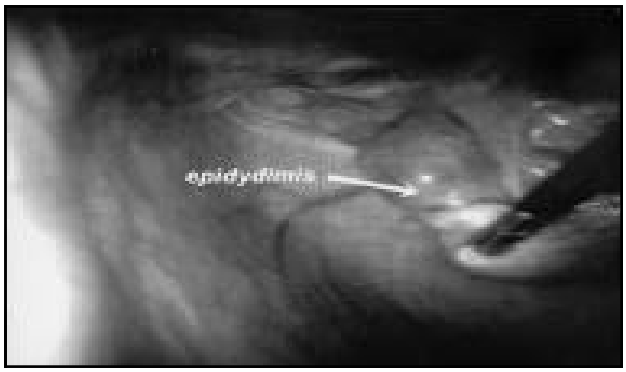

Figure 2 - Epididymis in the 46 XY phenotypic female.

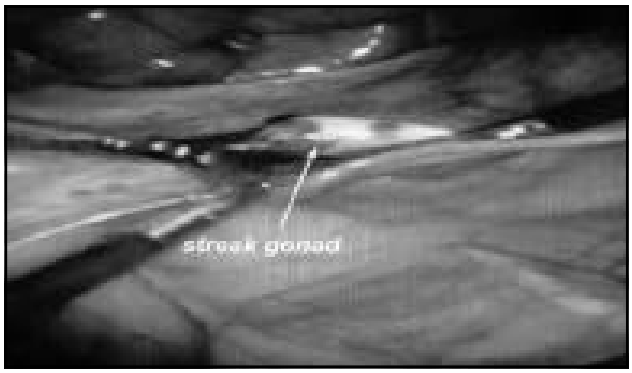

Figure 3 - Streak gonad in 46 XX female.

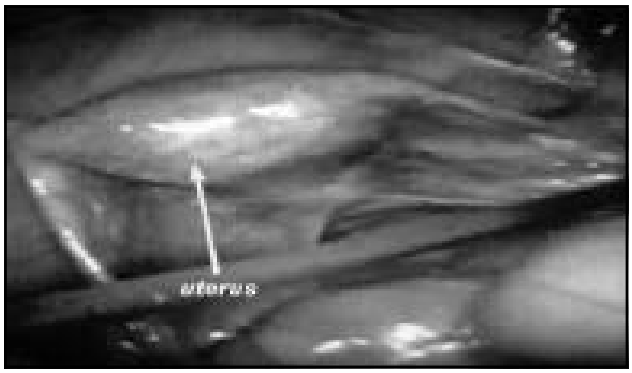

Figure 4 - Infantile uterus in 46 XX female.

phenotype and as end-organ failure prevents endocrinologically produced masculinization. Confirmation of the diagnosis is crucial as the syndrome is associated with a significant incidence of gonadal malignancies.[2] Keeping this in view, laparotomy is being planned for patient one to remove the immature testicular tissue to avoid gonadal malignancy. It is important to elicit previous history of surgery for inguinal hernias in such patients as inguinal hernias are reported to be common in testicular feminization. Failure to identify an internal mullerian structure in a phenotypic female with an inguinal hernia should always raise the possibility of testicular feminization.[2] If not detected in this fashion, diagnosis usually is not made until puberty, when the patient presents with amenorrhea. Our patient had a history of surgery at the age of 4 months for bilateral inguinal hernias, but the diagnosis was not made until puberty when she presented with primary amenorrhea. The biopsy report of this patient depicted a thick capsule overlying immature testicular tubules with interstitial tissue showing Leydig cells consistent with immature testicular tissue. This is consistent with the findings of **Rutgers and Snyder**[3], who in their study of 43 patients with complete androgen insensitivity syndrome, found immature tubules and prominent Leydig cells in the stroma on histopathological examination. The single most common cause of delayed puberty in all prior delayed puberty series reported by Reindollar et al,[4] has been primary ovarian failure. Forty-three percent of all 326 patients reported by Reindollar et al[5] had hypergonadotropic hypogonadism.

Patient 2 had hypergonadotropic hypogonadism with streak ovaries (a streak gonad is dysgenetic and resembles ovarian stromal tissue, no germ cells are present). Bilateral streak gonads appearing as ovarian stroma without oocytes, usually is not recognized in newborns as the phenotype typically is completely female. Patients tend to present at puberty as in our case, at which point, they do not undergo normal pubertal changes. Neither Turner's syndrome nor the XX type of pure gonadal dysgenesis appears to be associated with increased risk of gonadal malignancy. Therapy in these children (from an intersex standpoint) primarily is limited to appropriate estrogen and progesterone support.[2] Similar treatment was advocated to this patient.

Patient 3 had hypogonadotrophic hypogonadism with normal prolactin and TFTs. No apparent cause was revealed by history or general physical examination that suggested an idiopathic etiology. A number of irreversible disorders are found in patients with hypo-gonadotropic hypogonadism, some of those are associated with fractional or complete pituitary insufficiency; the majority is not. Previously, this later group was categorized as idiopathic hypogonadotropic hypogonadism (IHH), of which many patients were felt to have isolated deficiency of gonadotropin-releasing hormone. A number of other genetic defects have been found to cause hypogonadotropic hypogonadism including congenital forms of hypopituitarism, genetic disorders such as Prader-Willi syndrome, the coloboma of the eye, heart defect, atresia of the choanae, retardation of growth, genital hypoplasia, ear abnormalities (CHARGE) syndrome, and Laurence-Moon and Bidel-Bardet syndromes.[6-10]

Possessed with the knowledge that most women with premature ovarian failure have ovarian follicles on ultrasonography, we eagerly await the next therapeutic landmark namely, the application of the preservation or in-vitro maturation of ova.

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