Primary Amenorrhoea

A Review of Five Cases

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Regular menstruation is a feature of the reproductive physiology of only some primates. The cyclical nature of normal menstruation is a result of a complicated stimulatory and negative feed-back system of hormones secreted by an endocrinological axis composed of the hypothalamus, pituitary gland and ovaries in that order. The menarche is the time of onset of regular menstruation and is a result of a period of increasing hypothalamic stimulation through releasing factors, upon the axis. The pituitary and ovaries in turn respond by secreting their own respective hormones each of which exerts a negative feed-back mechanism on its stimulatory hormone. It usually takes about 2 to 3 years for menstruation to become established regularly and a number of these cycles will be anovulatory. The menarche is to be differentiated from the puberty which is a longer process starting a number of years before the menarche and involving both striking physiological changes and important psychological aspects. We may consider the menarche to be only one part of the process of development that occurs during the puberty. Primary amenorrhoea is the failure of onset of menstruation. Although normal menstruation should be established by the age of sixteen there is no established age at which primary amenorrhoea should be investigated. In a patient with normal secondary sexual characteristics eighteen is often a reasonable age. Alternatively patients may be investigated four years after the development of the breasts. The breasts normally start to develop two years before the menarche. If amenorrhoea is associated with sexual infantilism, patients should be investigated at 15 to 16 years o even earlier. Primary amenorrhoea is not an uncommon problem facing gynaecologists. A good working classification of the aetiology of primary amenorrhoea is provided by Dewhurst (1981).

Classification of Primary Amenorrhoea

Dewhurst (1981).

1. Chromosomal
   - (i) Turner's Syndrome
   - (ii) XY female
2. Gonadal
   - (i) True hermaphrodite
   - (ii) True gonadal agenesis
   - (iii) Absent anti-Mullerian factor
3. End-organ resistance
   - (i) Testicular feminizing
   - (ii) 5 α reductase deficiency
4. Hypothalamus pituitary
   - (i) Panhypopituitarism
   - (ii) Craniopharyngioma
   - (iii) Asexual ateliotic dwarfism
   - (iv) Laurence-Moon-Biedl syndrome
   - (v) Olfacto-genital syndrome
   - (vi) Hypogonadotrophic hypogonadism
   - (vii) Prepubertal polycycstic ovaries
5. Adrenal hyperplasia
6. Gynaetresia
   - (i) Mullerian agenesis
   - (ii) Cryptomenorrhoea
7. Delayed menarche

The following five cases are being presented becuase of the different aetiological factors.

Case 1

A sixteen year old patient presented complaining of primary amenorrhoea. Her past family and social history did not present any relevant facts. On examination the patient had the appearance of a normal female with normal breast formation and pubic and axillary hair.

Investigation revealed a Chromatin positive smear, a 46XX Karyotype and a normal IVP[1]. Urinary steroids were not performed. At EUA[2], the vulva was normal with a short blind vagina and no cervix. At laparoscopy no uterus could be visualised, though both tubes and ovaries were noted to be present.

A diagnosis of Mullerian agenesis of the lower part of the Mullerian duct system was made (Mayer - Rokitansky - Hauser Syndrome).

Case 2

A seventeen year old patient presented complaining of primary amenorrhoea. The elder sister of the patient reported that when the patient was one year old she was operated twice in the abdomen at six months' interval. The records of the operation showed that the patient was born with a bilateral inguinal hernia and a herniotomy was performed on each side at six months' interval. Immature testicular tissue was present in the hernia on both occasions. The patient had been brought up as a female. It was reported that another sister was married for nine years with no children, had had similar problems with her period, lacked body hair and was also tall. On examination the patient was tall, there was poor

breast development and no axillary or pubic hair. Over the lower abdomen three scars were present. The lateral ones for the herniotomy and the central for an exploratory laparotomy done at the same time. Investigation showed a chromatin negative smear, and a 46XY Karyotype. At EUA, the vulva and vagina were found to be well developed, the vagina was about 4 to 5 cm long. The hymen was present. No cervix was visualised. At laparoscopy no internal genital organs were visualised, rudimentary utero-sacral ligaments were present. The diagnosis in this case was one of Testicular Feminization Syndrome. (Morris 1953).

Case 3

A 13 year old patient presented primarily complaining of back pain since one week. On subsequent history taking, she admitted to not having been in her menarche yet. She had had a tonsillectomy 2 years previously. Her family history was not relevant.

On examination a firm, mobile, irregular mass in the RIF[3] was palpable. VE[4] was not performed. A right ovarian cyst was queried. A plain abdominal X-ray was reported as normal while the ultrasound scan confirmed the presence of a large cystic mass behind the bladder. The uterus was not visualised. An ovarian cyst was again queried. Patient was booked for an EUA with a view to have a laparotomy if the provisional diagnosis was confirmed. At EUA, an imperforate hymen was found. A cruciate incision was performed. The cervix was visualised and an abundant amount of chocolate-coloured fluid drained. The patient was treated post-operatively with antibiotics. Her recovery was satisfactory and regular menstruation subsequently commenced.

Diagnosis: Imperforate hymen

Case 4

This patient was seen at the age of 33 years with a history of marked hirsutism dating back to adolescence. The severity was such that she needed repeated shaving and electrolysis. On systematic enquiry she gave a history of primary amenorrhoea. She however admitted to having a male psychy, being attracted to females. On examination the secondary sexual characteristics were those of a male, with no breast development, a male pattern of pubic and axillary hair besides the general hirsutism. The voice was deep and the blood pressure normal (120/70). Chromosome studies showed a male (46 XY) Karyotype. The genital examination revealed a large phallus and an absent vagina. Bilateral genital swellings were present, the right being larger than the left. A wedge biopsy of the right genital swelling was reported histologically to be testicular tissue with morphological evidence of depression of spermatogenesis. The patient was subsequently referred for plastic surgery where liberation of the penis from the bilateral genital swelling and reconstruction of the scrotum was performed in two stages.

Diagnosis: Gross hypospadias and bifid scrotum.

Case 5

A seventeen year old girl presented with primary amenorrhoea. She was a well developed and attractive girl, of average intelligence. On examination she was tall, there was no webbing of the neck and no ulnar deformity. Her breasts were well developed, pubic and axillary hair was normally present. There was complete absence of the vagina. Investigations revealed a normal female karyotype (46 XX). 17 oxy- and hydroxysteroids were normal. ß -oestradiol level was normal. Her IVP was also normal. At laparoscopy two vestigial uteri separated from each other were seen. Each uterus had a normal Fallopian tube and a normal sized ovary on each side. Follicles were seen on the right ovary. No evidence of any cervix on either uterus and no continuation with an upper vagina.

Diagnosis: Congenital absence of the vagina and two rudimentary uteri. This patient was subsequently treated surgically when an artifical vagina was created (Mc Indoe and Reed Technique).

Discussion

The female genital organs arise embryologically from the Mullerian (paramesonephric) ducts which are derived from invaginations of the cylindric coelomic epithelium of the lateral side of the mesonephric ridge, at the level of the 3rd and 4th thoracic segments. These ducts are situated bilaterally and grow downwards towards the urogenital sinus. In doing so, their caudal ends approach the midline and fuse. This latter part then develops into the uterus, cervix and upper two-thirds of the vagina. The upper, unfused, portions give rise to the fallopian tubes. The fused part is, in fact, a solid cord at first, but later canalises.

Developmental defects in the Mullerian System results in a spectrum of abnormalities ranging from complete absence of the uterus and vagina to unilateral agenesis resulting in a unicornuate uterus. Only the former will give rise to primary amenorrhoea. Failure of canalisation of the Mullerian duct system particularly of the lower vagina can give rise to congenital absence of the vagina or an imperforate hymen. These will give rise to cryptomenorrhoea in the presence of a functional uterus. The aetiology of the Mayer-Rokitansky-Hauser Syndrome is a multifactorial one involving genetic susceptibility and environmental factors. The fallopian tubes are much less often effected and this is possibly due to a greater susceptibility of those parts of the Mullerian ducts which give rise to the uterus and vagina to exogenous agents.

An intersex may be defined as an individual in whom there is conflict at any level between the chromosomal sex, gonadal sex, external genital sex, internal genital sex or sex of rearing. The sex of an individual is based on these five criteria. The causes of intersex may briefly be listed as follows.

— an abnormality in the sex chromosones e.g. Turner's Syndrome (45 XO).
— a gonadal defect in the presence of normal chromosomes.
— gonadal mixture or true hermaphrodite.
— gonadal agenesis and partial/complete end-organ resistance e.g. testicular feminization syndrome.
— external genitals of female infant may be modified by the effect of increased levels of circulatory androgens (adrenogenital syndrome).
— behavioural intersexuality.

The testicular feminization syndrome results from a deficiency of the 21-hydroxylase enzyme, converting testosterone to the biologically active hydroxy-testosterone. This results in end-organ resistance to the effect of testosterone. Masculinization of the genitalia does not occur, nor do the other secondary sexual characteristics appear. It is postulated that testosterone is the mullerian regression factor responsible for the normal development of the external genitalia in males. A similar clinical picture is produced in these cases where the defect lies in the hormone receptors of target tissues. In both the latter and in the case of the testicular feminization syndrome, massive doses of testosterone will produce no effect. In the testicular feminization syndrome the testes are hormonally competent as shown by the complete regression of the mullerian duct system. The condition is familial, X-linked recessive or autosomal dominant and may be seen in 'sisters'.

In the development of the external genitalia the male organs develop from a primarily female condition. The clitoris enlarges into a penis, the labia fuse, to give rise to part of the shaft of the penis and to the scrotum. Therefore, in the absence of a stimulus for this development (produced by testosterone), the individual will have what appear to be female external genitalia. This development may also be defective rather than absent and give rise to various degrees of hypospadias and a bifid scrotum. Case 4 described, had such a gross defect that he was labelled as a female at birth. In the development of the external genitalia, the female form may be regarded as the neutral or asexual form (Jost's postulate 1958).

Management

Initial management of a case of primary amenorrhoea should consist of a good history particularly with reference to pubertal changes and of a thorough clinical examination. The stature, the development of the breasts, the presence and pattern of axillary and pubic hair and the blood pressure all reflect the endocrinological status of the individual. A genital examination is performed to exclude obvious anatomical malformations.

In the absence of any abnormality a period of observation is all that is necessary since most of these cases will have their menarche in the subsequent months. A diagnosis of delayed puberty can then be confirmed.

A few cases will persist and these cases together with those cases where an abnormality was detected (or suspected) at the first visit, further investigation is justified. While the development of the gonad is seperate from that of the genital organs, the Mullerian and Wolffian ducts are closely related. Embryological anomalies in the genital organs may be associated with anomalies in the urinary tract and the latter have to be excluded. Also gross anatomical malformations may be associated with defects in the sex-chromosome make up of the individual.

A step-wise approach to investigation is best adhered to and this should include: chromosome studies (karyotyping), urinary oxy- and hydroxy-steroids, radiography (HSG[5] and IVP), laparoscopy and occasionally exploratory laparotomy.

Very often management depends upon the attribution of an appropriate sex to the individual. In this respect, perhaps the most important single consideration is the sex of rearing. It is on this more than anything else, that the psychosexual orientation of the individual will depend (Money 1968). The case of an imperforate hymen presents the simplest solution. Here there is no question of the sex and treatment consists of a simple cross-shaped incision. Larger degrees of atresiae will require grafting to avoid long term post-operative stenosis. Antibiotic therapy post-operatively is an essential part of the treatment as exposure of the uterine cavity with its draining haematometra (due to retrograde menstruation) to the heavily contaminated vagina may easily result in ascending pelvic infection with possible consequent sterility.

The other cases i.e. cases 1,2,4 and 5 required a decision on the appropriate sex to be adopted. The important contribution of the sex of rearing in this decision was particularly evident in cases 2 and 4. Whereas case 2 a female intersex, was well adopted to a female role and the attribution of a female sex was obvious, case 4 a male intersex was not well adopted psychologically. The attribution of a male sex even at the age of 33 years can be justified by his better psychological outlook as a male. If a decision is taken to attribute a female sex to an intersex one has to ensure the presence of an adequate vagina that will permit satisfactory coital function for both the patient and her partner. This applies also to those patients suffering from a congenital anomaly of their genital organs. Case 2 had a moderately developed vagina and current opinion is in favour of avoiding plasty operations and lengthening the vagina with the regular use of dilators together with the application of oestradiol cream locally. This can result in a truly elastic vagina with a moist surface and good practical results. Another aspect of the management is oestrogen replacement therapy in the form of oestradiol 4 mg daily initially adjusting the dose according to response later on. This will stimulate female secondary sexual characteristics, particularly important being the

development of the breasts. Case 5 required the creation of an artificial vagina. The standard technique is Mc Indoe's Operation, first introduced by Mc Indoe and Reed (1936). The timing is best deferred till the patient is sexually active as regular intercourse is the best treatment against post-operative stenosis.

The technique consists of cutting a split skin graft from the medial or lateral aspect of the thigh and fixing it to a hollow plastic mould, its raw surface outermost. An adequate cavity is created by blunt dissection between the bladder and rectum and the skin covered mould is then sutured in situ. Six months later the mould is removed. The regular use of dilators may also be employed to avoid stenosis but this may be a psychological burden on the patient especially if sexually unmotivated. In experienced hands Mc Indoe's operation has a very good success rate. Mc Indoe and Reed themselves presented a series of 50 cases with only a few failures, mostly because the mould was removed too early following operation. Counsellor from the Mayo Clinic reported a series of 76 cases with a perfect result in 68% and no failures.

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1. IVP = Intra Venous Pyelography
2. EUA = Examination Under Anaesthesia
3. RIF = Right Inguinal Fossa
4. VE = Vaginal Examination
5. HSG = Hystero Salpingo Graphy