

Primary amenorrhoea – a single centre experience of 38 cases

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Abstract

Introduction: Primary amenorrhoea is defined as absence of menstruation by the age of 14 in absence of secondary sexual characteristics & by age 16 regardless of the presence or absence of secondary sexual characteristics. It occurs in around 1-4% of women in reproductive age group. The common causes of primary amenorrhoea include outflow tract disorders or uterine abnormalities, ovarian disorders, pituitary dysfunction, and hypothalamic dysfunction. The data of primary amenorrhoea from our country is limited due to poor reporting and frequent loss to follow up. Hence we undertook this prospective study to determine the etiology for primary amenorrhoea based on clinical examination and laboratory investigations. **Methodology:** This prospective study was done in Gynecologic Clinic of Sunrise Hospital between August 2013 to May 2015. The work up of primary amenorrhoea patients comprised of 1) History taking 2) Physical examination 3) Laboratory investigations. Patients were classified into 5 groups based on the compartment of organs involved. I- End organ failure/ outflow tract obstruction, II- Gonadal failure, III- Pituitary cause, IV- Hypothalamic cause, V- Other causes. **Results:** In our study, the 2 most common etiologic factors of primary amenorrhoea were müllerian agenesis (65.78%) and gonadal dysgenesis (21.05%). Hypogonadotropic hypogonadism was noted in 10.52% of cases. Range of average age of the patients when they first consulted the physician was 14 to 33 years. **Conclusion:** Prompt reporting and awareness of available treatment options based on the etiology can make a huge difference in this often underreported disorder.

Key words: Primary Amenorrhea, Müllerian Agenesis, Gonadal, Dysgenesis .

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Introduction

Primary amenorrhoea is defined as absence of menstruation by the age of 14 in absence of secondary sexual characteristics & by age 16 regardless of the presence or absence of secondary sexual characteristics [1]. Maturation of hypothalamus, anterior pituitary, ovary & reproductive tract results in establishment of normal menstruation. Amenorrhoea results due to break in one or more places in this chain. The causes of primary amenorrhoea include outflow tract disorders or uterine abnormalities, ovarian disorders, pituitary dysfunction and hypothalamic dysfunction. The absence of secondary sexual characteristics indicates either hypothalamic-pituitary axis dysfunction or gonadal dysgenesis. Amenorrhoea occurring in the presence of normal secondary sexual characteristics points to a problem with menstrual outflow such as imperforate hymen or absence of uterus or vagina.

The prevalence of Primary Amenorrhoea is around 1-4

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% of women in reproductive age group [2,3,4]. Despite the low prevalence of primary amenorrhoea, a prompt, comprehensive assessment by a consultant in reproductive medicine is warranted, as amenorrhoea is often the presenting sign of an underlying reproductive disorder. A delay in diagnosis and treatment may adversely impact the long-term future of such patients.

Although primary amenorrhoea has long been recognized, there are not many studies on large numbers of patients. Majority of papers are case reports and some are based on a small series of patients. Apart from these the etiologic causes may vary from area to area due to different racial group of patients. Since there are few large series on this topic from our country, the present study was undertaken to determine the etiologic factors responsible for primary amenorrhoea.

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To determine the etiologic factors responsible for primary amenorrhoea on the basis of clinical examination and laboratory investigations.

Material & Methods

This prospective study was done in a private setting among patients who attended the Gynecologic Clinic of Sunrise Hospital between August 2013 & May 2015. The study protocol was approved by the Institutional Ethics committee. The work up of primary amenorrhoea patients comprised of 1) History taking including chief

complaint, present history, past history & family history; 2) Physical examination including general examination, rectal and/or pelvic examination & transabdominal pelvic ultrasonography; 3) Laboratory investigations depending on the provisional diagnosis derived from history & physical examination. Patients were classified into 5 groups based on the compartment of organs involved.

- I- End organ failure/ outflow tract obstruction
- II- Gonadal failure
- III- Pituitary cause
- IV- Hypothalamic cause
- V- Other causes.

Results

During the study period, 38 cases of primary amenorrhoea were analyzed. Two most common etiologic factors were mullerian agenesis (65.78%) and gonadal dysgenesis (21.05%). Hypogonadotrophic hypogonadism was noted in 10.52% of cases. Hyperprolactinemia was noted in 1 case. Range of average age of the patients when they first consulted the physician varied between 14 to 33 years. Karyotyping was done on 8 cases of gonadal dysgenesis and 46 XX karyotype was found in 75% and 45 XO in 25% of analyzed cases.

Distribution of Primary Amenorrhoea

CAUSES	No.
GROUP I- END ORGAN FAILURE/ OUTFLOW TRACT OBSTRUCTION	
Mullerian Agenesis	25
Transverse vaginal septum	0
Tuberculous endometritis	0
Male pseudo hermaphroditism - complete testicular feminization	0
GROUP II- GONADAL FAILURE	
Gonadal dysgenesis (46XX)	6
Gonadal dysgenesis (45XO, Mosaic)	2
Agonadism	0
Post chemotherapy.	0
GROUP III- PITUITARY CAUSE	
Hyperprolactinemia	1
Prolactinoma	0
GROUP IV	
Hypogonadotrophic hypogonadism	4
Hypothalamic dysfunction	0
OTHERS	
Primary hypothyroidism	0
Congenital adrenal hyperplasia	0
Androgen secreting tumour	0

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Discussion

Amenorrhoea is not a diagnosis but a symptom of a physiological or pathophysiological process. Physiological causes of primary amenorrhoea include pregnancy and late puberty and these will not need treatment. As for gynaecological reasons, congenital and acquired anomalies in the structure of the uterus and vagina can cause pathological amenorrhoea. The prevalence of Primary Amenorrhoea is around 1-4 % of women in reproductive age group [2,3,4].

The pathophysiology of a normal menstrual cycle is complex involving multiple axes including the hypothalamus, pituitary, ovary, uterine smooth muscles and arterioles of the endometrium. The hypothalamus secretes GnRH, which travels down the anterior portion of the pituitary via the hypophyseal portal system and binds to receptors on the secretory cells of the adenohypophysis. In response to GnRH stimulation these cells produce LH and FSH, which activates the ovaries to produce estrogen and inhibin which regulate the menstrual cycle and ovarian cycle [5,6]. When all the axes including the hormonal secretions by target organs are maintained, amenorrhoea can be secondary to loss of vascular integrity in the spiral arterioles of the endometrium.

The pathophysiology of primary amenorrhoea can be better understood by the embryologic development. The uterus, cervix and upper two thirds of the vagina are formed from the coelomic derived paramesonephric ducts in the third month of development. In the absence of anti-Müllerian hormone the paired paramesonephric structures adhere and connect to the sinus tubercle. The ducts fuse together from their caudal tops forming a single lumen known as the uterovaginal canal. The uterovaginal canal develops into the uterus and superior section of the vagina, while the cranial unfused tips form the fallopian tubes with the infundibula at the open ends of the ducts. The reason and mechanism behind the failure of the paramesonephric ducts to fuse or develop in some women is not clearly understood. Various hypotheses have been suggested including teratogenic insult and maternal infection. Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome) affects about 1 in 5,000 newborn females [7].

The etiologic factors of primary amenorrhoea include

Group I- End organ failure/ outflow tract obstruction

- a) Müllerian agenesis
- b) Transverse vaginal septum
- c) Tuberculous endometritis
- d) Male pseudo hermaphroditism- complete testicular feminization.

Group II- Gonadal failure

- a) Gonadal dysgenesis (46XX, 45XO, Mosaic)
- b) Agonadism
- c) Post chemotherapy.

Group III- Pituitary cause

- a) Hyperprolactinemia
- b) Prolactinoma.

Group IV

- a) Hypogonadotropic hypogonadism
- b) Hypothalamic dysfunction.

Group V

- a) Primary hypothyroidism
- b) Congenital adrenal hyperplasia
- c) Androgen secreting tumour

The most common cause of primary amenorrhoea in our study population was Müllerian agenesis. About 65.78 % cases of primary amenorrhoea had Müllerian agenesis which was higher than the studies by Quorrata et al., [8] & Prasong et al., [9] who reported Müllerian agenesis in 36.3% & 39.7% of cases of primary amenorrhoea respectively. Müllerian agenesis was also the most common cause of primary amenorrhoea in studies by Rattanachaiyanont M et al., [10], Rao K et al., [11] & Kumar A et al., [12]. Müllerian agenesis patients present with primary amenorrhoea, and are usually found to have an absent or rudimentary vagina, and an absence of the uterus and fallopian tubes. Ovarian function is normal and patients have normal development of secondary sexual characteristics.

Gonadal dysgenesis was noted in 21.05 % of our cases of primary amenorrhoea which was comparable to 29.05 % in the study by Quorrata et al [8] & 35.3 % in the study by Prasong et al, [9]. Reindollaret al. in his study showed that the most common cause of primary amenorrhoea in the American population was gonadal dysgenesis (48.5%) [13].

We noted hypogonadotropic Hypogonadism in 10.52 % of our cases which was similar to the study by Prasong et al., [9]. Karyotyping was done on 8 cases of

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gonadal dysgenesis. 46, XX karyotype was found in 75% of analysed cases, as compared to 50% in the study by Quorrata et al., [8] and 45 XO was noted in 25% as compared to 10% in the study by Quorrata et al., [8] & 35.59% in the study by Prasong et al., [9]. The most common cause was chromosomal abnormality (24%) in a study by James H Evans et al.,[14]. Range of average age of the patients when they first consulted the physician was between 14 to 33 years which was comparable to the study by Quorrata et al.,[8].

The approach towards primary amenorrhoea starts with a carefully obtained History. Physical examination focusing on body composition (weight), the presence or absence of breast development and the presence of a uterus is important. Additional laboratory examination and imaging (ultrasound and/or laparoscopy) help in prompt management.

Conclusion

The etiologic causes of primary amenorrhoea in our study are different from earlier reports. Racial and environmental differences, facilities for diagnostic tools may contribute to these differences. As diagnosis based on inadequate data may be misleading, both clinical examinations & laboratory investigations have to be completed before final diagnosis of primary amenorrhoea is established. Early recognition of the definite etiology and institution of the appropriate treatment will minimize late complications.

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