A CLINICAL AND PRACTICAL APPROACH TO EVALUATION OF PRIMARY AMENORRHOEA

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SUMMARY

This study highlights the current decisive diagnostic role of pelvic ultrasonography in primary amenorrhoea. Based on sonographic finding the patients are divided into 3 major categories: (i) those with 'absent uterus'; (ii) those with infantile uterus and gonads and (iii) those with normal uterus and ovaries. Those with 'absent uterus' could be further subdivided into two groups : (i) ovaries depicted at sonogram; and (ii) ovaries not identifiable at sonogram.

These sonographic classifications with the clinical back-up which includes (i) stature; (ii) secondary sex development (iii) obesity; (iv) galactorrhoea; (v) evidence of tuberculosis and (vi) somatic anomalies such as pelvic kidney (identified at ultrasound scan), should provide a clear diagnosis. This diagnostic protocol will identify two clinically significant categories: (i) genetic cause of primary amenorrhoea with no reproductive capability (68.18%); and (ii) endocrine or anatomic disorders with excellent chances for reproductive salvage (31.82%).

Pelvic sonography discredits the role of vaginal and rectal examinations, makes laparoscopy and IVP obsolete, and selects the few subjects who deserve to be further investigated by cytogenetic and endocrine studies.

Primary amenorrhoea is not an infrequent menstrual symptom of adolescent subjects visiting the gynaecologists. Patients with rudimentary streak gonads, sexual infantilism and primary ovarian failure constitute an increasing number of subjects complaining of primary amenorrhoea. McDonough and Byrd (1977) report 42% gonadal dysgenesis among subjects with primary amenorrhoea, and among them 60% possessed structural or chromosomal deletion of sex chromosome (such as mosaic Turner) and the other 405 represented phynotypically normal 46, XX and 46, XY females with streak gonads and primary ovarian failure.

While the primary amenorrhoea of gonadal dysgenesis etiology remains an irreversible disorder, 34% of primary amenorrhoea subjects have an endocrine

Accepted for publication on 16/2/1990.

basis and hence a reversible pathology. Another 9% have a functional uterus with obstruction (McDonough and Byrd, 1977). These two latter categories have excellent prognosis for improved reproductive function. A carefully selected investigative protocol should enable the physician to identify the gonadal dysgenesis and androgen insensitivity groups from the clinically important groups of endocrine disorders and obstructive pathologies.

The usual clinical protocol employed includes (i) stature; (ii) secondary sex development; (iii) systematic examination (e.g. CVS); (iv) pelvic-abdominal masses; (v) external genetalia and (vi) obvious endocrine pathology (e.g. galactorrhoea). Cytogenetic study could identify chromosome anomalies, and discriminate the group into XO mosaic, structural privation of sex chromosomes or normal phenotype (XY or XX). Endocrine study should identify the gonadal function, discriminate the tests from the ovaries and locate pituitary or other endocrine tumors, which should be differentiated from enzymatic disorders. Diagnostic laparoscopy could identify the uterus and intra-abdominal gonads. I.V.P. has been employed to locate the kidneys and possibly supra-renal pathologies. Ultrasonography is a recent addition to the armamentarium, which could in majority of situations replace a diagnostic laparoscopy or an IVP. Since the uterus, ovaries, and normal and distended vagina could be clearly imaged at sonography the need for the cumbersome vaginal and rectal examinations could be avoided. After a detailed inspection of the external genitalia a pelvic sonography (trans-abdominal) should give more precise informations in an amenorrhoeic subject than the vague informations derived at vaginal or rectal examinations. Moreover, none of the other investigations can provide accurate informations about the uterine cavity, nature of the pelvic mass, and ovarian cyclic changes, as compared to the non-invasive sonographic study.

In this communication we describe the practical diagnostic strategy employed by us to differentiate the different types of gonadal dysgenesis, endocrine disorders and obstructive conditions presenting with primary amenorrhoea.

Investigative Protocol for Primary Amenorrhoea

The initial survey includes identification of nature of second sex developments, stature and systemic examination of the subject reporting with primary amenorrhoea. This is followed by inspection of external genetalia and abdominal and inguinal palpation. Attempts at vaginal and rectal examinations are totally avoided. We hold that a vaginal examination should be reserved for adolescent subjects reporting with complaints of vaginal bleeding or abnormal vaginal discharge; because, without a proper vaginal examination a correct diagnosis cannot be arrived at. By contrast, in amenorrhoeic subjects, whatever information that could be gathered by vaginal or rectal examination could be discerned at transabdominal sector sonography. Moreover, details that could not be collected at vaginal or rectal examinations (such as nature of uterus, delineation of uterine cavity, recognition of dynamic changes in the ovaries) could be more clearly discerned at sonography. Rather, sonography is certainly more informative than the other two examinations.

Initially, presence of uterus is ascertained at sonography, and if present

whether normally developed or infantile. An infantile uterus with vagina, in a subject with absent secondary sex development or minimal iso-sexual development denotes gonadal dysgenesis. If the subject is short-statured, the diagnosis is more in favour of Turner syndrome. This diagnosis is further authenticated if somatic anomalies of classical Turner phenotype, such as pelvic (horseshoe) kidney, congenital heart disease, lymphedema or webbed neck, are located. We routinely scan the kidneys in all such subjects and have located to subjects with pelvic kidney. However, the most common form of mosaicism involves involves the 45,X/46,XY karyotype.

If the uterus is normally developed the diagnosis is more in favour of endocrine disorders or anatomic alterations (obstructive conditions). Identification of normal ovaries, particularly, evidencing cyclic changes, and normal endometrial morphology, in a subject with normally developed secondary sex characters could indicate a functional endocrine disorder such as delayed menarche. Possibility of genital tuberculosis should be considered with family or personal history. Subjects with upper body obesity or hirsuitims will sway the diagnosis towards PCOD. However, severe hyperandrogenism, such as adrenal hyperplasia will present with clitoral enlargement and other hyperandrogenic features. A careful examination of the breast for galactorrhoea could evidence hyperprolactinemia which should be confirmed by endocrine study.

In this group with normal uterus and developed secondary sex characters, ovarian and endometrial morphology, as delineated by sonography, could give a clue to endocrine diagnosis. Inactive ovaries with unstimulated endometrium will indicate hypoestrogenic state associated with hyperprolactinemia or hypogonadtropic hypogonadism. However, proliferative or hyperplastic endometrium, particularly with polycystic ovarian changes could indicate PCOD.

Subjects with gynetresias (Obstructive pathology) usually present with normal uterine and secondary sex development. The diagnosis becomes evident when hematocolopos or hematometra are observed at sonography. A non-canalised vagina with a normal uterus and ovaries could also be identified at scan.

Primary amenorrhoea subjects with infantile uterus and absent or poorly developed secondary sex characters could present with normal high. Such subjects are XX or XY gonadal dysgenesis group who are cytogenetically competent with no deletion or privation of genetic material. Among them those who evidence limited ovarian function (minimal secondary sex development or even occasional menstruation) have XX cell line and hence the risk of neoplasm of the intraabdominal XY streak gonad does not arise. The incidence of pure gonadal dysgenesis (XX) in siblings is striking. Those with XY cell line (mixed gonadal dysgenesis) could present with heterosexual development and intra-abdominal or inguinal testis.

Primary amenorrhoea subjects with absent uterus form another important category who could have either XX or XY phenotype, though obviously presenting with developed female secondary sex characters. Sonographic identification of ovaries, evidencing ovarian follicles in different stages of maturation, weights more in favour of a diagnosis of mullerian

agenesis in an XX phenotpye. By contrast, inability to locate a female gonad will be the indication for further evaluation to identify a male gonad (which may not be discerned at sonography) (TFS). Presence of an inguinal swelling, blind or shallow vagina and endocrine and cytogenetic studies should confirm the diagnosis. Ambigual external genitalia or pubertal masculaization in subjects with absent uterus, also indicates XY phenotype, either androgen resistant syndrome or incomplete TFS.

Data Analysis

TABLE - I
ETIOLOGY OF PRIMARY AMENORRHOEA (22 PATIENTS)

Those with no reproductive future		15 (68.18%)
Gonadal dysgenesis (XX or XY) :	5	
Classical Turner syndrome (XO) :	5	
Mullerian agenesis (XX) :	7	
Testes feminising syndrome (XY) :	1	
Those with good reproductive capability		7 (31.82%)
Hematocolpos :	3	
Delayed menarche :	2	
Polycystic ovarian disease :	1	
Hyperprolactinemia :	1	

Among the 46 patients investigated for adolscent teenage problems 22 patients had reported a symptom of primary amenorrhoea (47.83%). Genetic factors linked to gonadal dysgenesis and androgen insensitivity (TFS) were located in 8 subjects and mullerian agenesis in 7 subjects. Thus, a total of 15 among the 22 primary amenorrhoea subjects had no reproductive future (68.18%). The remaining 7 subjects (31.82%) had either an endocrine disorder or obstructive lesion which could be corrected to restore the future fertility of the subject.

Patients with sexual infantalism, primary gonadal failure and short stature were diagnosed to have Turner karyotype; and there were 2 subjects with pelvic kidney, and hence could be assigned to the classical Turner syndrome group.

Subjects with dysgenesis with normal stature were provisionally diagnosed to be either normal XX or XY phenotype (5 patients) Among them 2 subjects evidenced minimal isosexual development indicating the possibility of XX cell line, and another 2 subjects were sisters which again indicated greater possibility of XX cell line. These subjects with XX cell line dono need gonadal extirpation.

Among patients with absent uterus mullerian agenesis (XX cell line) is encountered more often (7 patients) as against TFS (XY cell line) in one subject. This discrimination was made on sonographic location of the ovaries and nature of the vagina. A blind or shallow vagina is diagnostic of TFS.

Obstructive lesions with hematocolpos was recognised in 3 subjects, among whom one subject had hematometra as well. This indicates that hematometra is not an uncommon finding in subjects with hematocolpos.

There were 4 subjects with endocrine factors responsible for the primary amenorrhoea, of whom PCOD and hyperprolactinemia constituted one each and the other two subjects had delayed menarobe.

Discussion

The focus is on a clinical and practical evaluation of primary amenorrhoea, so much so, such of these few patients who will need detailed endocrine or cytogenetic evaluations could be picked up from the large number of amenorrhoric sub-

jects. This study also highlights the promising role of transabdominal sonography (sector scan) for sorting out the possible diagnoses without a recourse to invasive diagnostic measures such as laparoscopy. Laparoscopy which was enjoying a prominent diagnostic role in primary amenorrhoea is seldom indicated in modern practice employing sonography. We also highlight the specific advantages of avoiding vaginal or rectal examinations in subjects with primary amenorrhoea. Sonographic identification of kidney makes I.V.P. an obsolete diagnostic aid in primary amenorrhoea.

The stragegies of differentation of various forms of gonadal dysgenesis are highlighted. Location of pelvic kidney has been specific to diagnosis of classical Turnover in a subject with short stature and sexual infantalism. Among the subjects with normal height, where both XX and XY gonadal dysgenesis are possible, a clue to identifying XX phenotype is obtained in subjects with minimal iso-sexual development. Because, limited ovarian function is possible in subjects with XX phenotype and not in subjects with XY cell line (Reindollar and McDonough 1987).

In normal females with constitutionally delayed puberty, the demonstration of normal ovaries and normal endometrial morphology on sonography can help assure the patients that pubertal changes are probably imminent, as was observed in 2 of our subjects. This will avoid unnecessary and exhaustive investigations.

Sonographic identification of subjects with 'absent Uterus' (normal iso-sexual development) could further be diagnosed as subjects with mullerian agenesis (XX) as proved by the presence of normal ovaries at sonography. This observation was made in 87.5% of the 8 subjects with absent uterus. Here the sonographic depiction of normal ovaries could avoid the need for cytogenetic study or laparoscopic diagnosis. Only if the ovaries could not be recognised at scan there is the need for further investigations for ascertaining the cell line of the gonad, and remove the intra-abdominal gonad if it has XY cell line.

If sonography depicts normal uterus, endometrial lining and ovaries, one could make a search for endocrine disorders based on clinical findings such as obesity or galactorrhea, and suggest appropriate endocrine study, as was observed in 2 of our subjects.

Conclusion

There should be a simple and practical method of differentiating the primary amenorrhoea subjects into 2 groups: (i) those who have a genetic background with no reproductive capability and (ii) those with endocrine or anatomic abnormalities with excellent prospects for reproductive performance. pelvic ultrasonography has recently emerged as a highly informative diagnostic aid in this respect. By employing sonography in conjunction with clinical findings we could identify 68.18% of subjects with primary amenorrhoea had no reproductive future, and 31.82% could be confidently treated for excellent reproductive performance. This discrimination could be achieved without a recourse to diagnostic laparoscopy and I.V.P.

References

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