PRIMARY OVARIAN FAILURE

(A Clinico Pathological and Cytogenetic Study)

by

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The problem of the absent, anomalous or prematurely failing gonad has recently attracted greater interest on the part of gynaecologist and Pathologist. This interest has been enhanced by a flurry of reports campaigning for the continual administration of substitutive hormone therapy, both in the prematurely and physiologically failing ovary. Better techniques of chromosome analysis and gonadal biopsy and more widespread use of culdoscopy have aided in the elucidation of these facinating problems.

It is the purpose of this paper to study the frequency and importance of this syndrome to the practicing gynaecologist.

Material and Methods

We are reporting here 50 cases of Primary amennorrhea studied in 2 year period during 1973 and 1974. Out of these, 20 cases had their gonadal biopsies made by laparatomies and had detailed histopathological studies done to assess the primary ovarian failure. All these cases were associated with primary amennorrhea. All had elevated urinary gonadotrophin castrate levels. All had chromosomal karyotypes taken from cultures of blood lymphocytes. Additional endocrine investigations included maturation indices by cytology, adrenal and thyroid function wherever necessary, together with X-Rays of sella turcica.

Results

Classification: We have followed the classification of Kinch *et al* (1965) of primary gonadal failure with female phenotype and found it very useful. It is based on clinical, endocrinal, chromosomal karyotype and mainly on gonadal morphology and histopathology. It is more comprehensive than the functional classification of Keettel and Bradbury (1964) and less complicated than that of Jones *et al* (1963). Data is given on Table I and number of cases in each class as follows:

(1) Pure gonadal agenesis (40 XY) 2 cases;

(2) Gonadal dysgenesis (a) Turners syndrome (45 XO) 3 cases; (b) Turner's Mosaic (45 XO/46 XX) 1 case;

(3) Ovarian agenesis with enuchoid features (46 XX) 1 case;

(4) Ovarian dysgenesis (46 XX) (a) afollicular ovarian dysgenesis 5 cases; (b) follicular ovarian dysgenesis 7 cases;

(5) Ovarian hypoplasia (46 XX) 1 case.

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Accepted for Publication on 4.5.1976.

TABLE I
Analysis of 50 Cases of Primary Amenorrhea

S. No.	Condition	Karyotype	Number of cases
1.	Pure gonadal agenesis	(46 XY) (Swyer's syndrome)	2 cases
2.	Gonadal dysgenesis	(a) Turner's syndrome (45 XO)	3 cases
		(b) Turner's mosaicism 45 XO/ 46 XX	1 case
3.	Ovarian agenesis with enuchoid features	(46 XX)	1 case
4.	Ovarian dysgenesis	(46 XX)	
		(a) Afollicular ovarian dysgenesis	6 cases
		(b) Follicular ovarian dysgenesis	7 cases
5.	Ovarian hypoplasia	(46 XX)	1 case
6.	Mullerian anatomical dysgenesis with functioning ovaries	(46 XX)	8 cases
7.	Mullerian agenesis or aplasia with functioning ovaries	(46 XX)	7 cases
8.	Congenital atresia of cervix with haematometra	(46 XX)	1 case
9.	Testicular feminisation syndrome	(46 XY)	8 cases
10.	Congenital adreno-genital syndrome	(46 XX)	2 cases
11.	Pituitary failure	(46 XX)	2 cases
12.	Hypothalamic hypophyseal gonadal failure due to Cranio-pharyngioma	(46 XX)	1 case
			50 cases

Pure Gonadal Agenesis: These individuals are genetically male but phenotypically female and no breasts. They are tall, destined to become male. They have no gonadal tissue at all and ovaries are "streak like" showing fibrous tissue with few smooth muscle fibres and contain mesonephric tubules, absent cortical stroma or oocytes. Chromosomally XY (Fig. 2). We had 2 such cases in our series forming 4%.

Gonadal Dysgenesis: One of short stature with webbing seen in 2 cases out of 4. They are of short stature, below 120 cm in height, primary amenorrhea, failure of development of secondary sex characters. Polydactyly was seen in 1 case, typical 45/XO karyotype in 3 cases and Turner mosaicism of 45 XO/46 XX in 1 case. We had gonadal biopsy taken in all and it showed only 'streak gonads' consisting of fibrous tissue. This formed 8% in our series (Fig. 1). We are of the opinion that to qualify as gonadal dysgenesis the individual must either have a 45 XO Karyotype or be an XO mosaic. They are all of short stature.

Ovarian Agenesis with Enuchoid Features: We have one case of this type forming 2%. These women have primary Amenorrhea, tall stature with enuchoid features typical of young girl castrated prior to puberty with span greater than height, generally married, with slight breast development with hypoplastic external and internal genitalia and an atrophic endometrium. Laparotomy revealed streak ovaries and karyotype was 46/XX and low 17-Ketosteroid and intermediate smear, streak ovaries showed slight spilling of cortical

DETAILS OF 20 CASES OF PRIMARY OVARIAN FAILURE

Name	Age	Ht cm.	Span in cm.	Karyo-type	Biopsy	Laparotomy findings	Sec. Sex features
CLASS I. XY pure Gonadal Dysgenesis:							
K.A.	20	155	160	46/XY	Rete testes tubules with fibromuscular tissue.	Streak gonads both sides Uterus knob like F-tubes on both sides.	No breasts, female phenotype.
B.Y.	19	150	152	46/XY	-do-	-do-	No breasts, female phenotype.
CLASS II. XO Gonadal Dysgenesis. Turner's syndrome:							
G.A.K.	19	123	125	45/XO	Fibrous tissue both gonads.	Streak ovaries small uterus +	Short stature. No breasts, Flat chest, Short neck. Prominent carrying angles. Infantile genitalia.
M.R.	18	110	115	45/XO	Fibrous tissue both sides.	Streak ovaries—Small knob like ut. both fall. tubes +	Flat chest, Short No sexual hair, infantile genitalia.
K.S.	20	121	123	45/XO	Fibrous tissue both gonads.	-do-	Breasts Bud stage, polydactilism, short chest neck, infantile genetalia.
Turner's Mosaic:							
V.S.P.	17	125	127	45/XO/ 46XX	Fibrous tissue left side. Germinal epithelium with band of cortical stroma Rt. side.	Streak ovaries both sides. Infantile uterus and tubes.	Flat chest, short infantile genitalia.

Name	Age	Ht cm.	Span in cm.	Karyo-type	Biopsy	Laparotomy findings	Sec. Sex features
CLASS III: Ovarian Agenesis with Enuchoidal Features:							
K.A.K.	20	155	160	46/XX	Fibrous tissue with germinal inclusion cyst (Rt) Thin band of fibrous tissue with cortical stroma Lt. side.	Streak ovaries both infantile uterus without stretched F. tubes.	Tall enuchoidal, female phenotype small breasts +
CLASS IV. Ovarian Dysgenesis: (Afollicular type)							
5 cases		18-25 yrs.	140-155 cm	46/XX	Well developed germ epithelium ovarian stroma dense. No primary follicles medulla is seen.	Small ovaries with bulbous ends of 1 cm uterus Hypo-plastic normal tubes.	Normal stature breasts +, female phenotype.
7 cases		20-25 yrs.	145-160 cm	46/XX	Hypoplastic ovaries with primary and secondary follicles. No corpora lutea or albicantia. No developing Graaf. follicles seen.	Hypoplastic ovaries small uterus and tubes normal.	Normal stature. Breasts + Well developed, female phenotype.
CLASS V. Ovarian Hypoplasia:							
K.L. 22		145 cm	150 cm	46/XX	White thick ovaries follicular cysts anovular type with granulosa and Theca lining. No albicantia No corpus luteum.	Hypoplastic ovaries Uterus and tubes Normal.	Normal stature well developed breasts, female phenotype.

stromal cells with predominantly fibrous tissue (Fig. 2).

Ovarian Dysgenesis

This group formed the maximum incidence in our series. Out of 50 cases, 13 belonged to this pattern, forming 26%. Of this 5 cases belonged to

(a) afollicular dysgenesis forming 12%
(b) follicular dysgenesis totalling 14% (7 cases). Their average age was 18-25 years and average height of 150 cm—160 cm and all were with primary amenorrhea. 50% of them were married. They were otherwise normal for all purposes with normally directed well developed libido. They did not suffer from hot flushes. They were intensely female with female bodily habits with definite breast development and female sexual hair. Chromosome karyotype was 46 XX, and MI of intermediate type in most of them. Laparotomy showed small ovaries with bulbous end of 1 cm length.

The histology of the ovary was of two types. The afollicular ovarian dysgenesis —there is well developed germinal epithelium on the surface, Tunica is normal and below that the ovarian cortical stroma is dense and there are no oocytes or primary follicles or developing follicles. There are no corpora lutea or albicantia to indicate previous follicular development. Vascular tissue resembling medulla is present in all. These gonads are characterized as ovaries identified by germinal epithelium, tunica alluginea, cortex and medulla. The absence of oocytes, primary follicles and follicular derivatives is a striking feature (Fig. 3), and they are described as afollicular dysgenesis.

The pathogenesis of these eggless ovaries, particularly in view of the several challenging observations, indicating that absence of germ cells with a trisomic autosomal defect or with simple gametogenic deletion of an X-chromosome is possible. Whatever the cause of their origin, the hormonal inutility and reproductive futility of such egg free ovarian streaks are readily apparent and they have no biologic future.

From the clinical point of view it is no longer sufficient to differentiate victims of primary ovarian failure by their stature alone, be this short, average or tall. It is the precise state of the ovaries that counts, hence laparotomy or culdoscopy is very essential to study the ovaries of all these cases. Early recognition enables proper planning of the patient's future life. If culdoscopy uncovers ovaries of relatively normal appearance biopsy should be mandatory before agents to stimulate ovarian function are employed. If there are no ova such therapy is useless; similarly the therapy of azoospermic males rests upon the finding of testicular biopsy. Unfortunately ovaries are not as accessible as testes. Proper bilateral ovarian biopsy requires laparotomy.

We had 7 cases of follicular ovarian dysgenesis. The gonad has the general structure of a hypoplastic ovary with an atrophic germinal epithelium, cortex and medulla. The tunica is thin, numerous primary follicles are present near the junction of cortex and medulla. No developing follicle is noted and no corpus luteum. This ovary differs from the preceeding group by the presence of follicles (Fig. 4). This ovary has adequate number of primary germ cells. However, no development of its germ cells is noted and for some reason they may be refractory to stimulation, development and ovulation. This group is called as gonadal dysgenesis frequently affects sisters, while XO gonadal dysgenesis is rarely affected with a family history. The follicles may

be only of primary follicles, anovular follicles or antral type (Fig. 5).

Ovarian Hypoplasia: These patients also had primary amenorrhea in our series and we met with 1 such case forming 2%. She was married, of average height and well built. There were no signs of virilization and breasts were well developed. Pelvic findings were that of a nulliparous woman. They appeared to have greater ovarian function and number of follicular cysts. The chromosome karyotype was 46 XX. The 17-Ketosteroid and thyroid functions were normal. The ovaries on laparotomy were like those of steinleventhal syndrome with smooth white thickened tunica and subcapsular regimented cysts. Wedge resection was done in this case. The endometrium was atrophic. This was thought of as "prepubertal-Stein leventhal syndrome". These features suggest to us a running down ovary but the presence of follicular cysts lined with granulosa cells suggest an ovary capable of function (Fig. 6).

Discussion

We have attempted a classification of primary gonadal and ovarian failure in the phenotypic female based on Kinch *et al* studies (1965). This leads from the XY fibrous streak of gonadal agenesis through XO gonadal dysgenesis to XX ovarian agenesis and dysgenesis with ovarian like stroma with or without primordial follicles, finally to ovarian hypoplasia. Beyond gonadal agenesis might be placed male pseudohermaphroditism on one end and at other end the polycystic disease of the ovary. Jacobs states that atleast 28% of cases with primary amenorrhea will prove to have a chromosomal anomaly. Similarly, in our series 28% of cases showed chromosomal disorders with 8 cases of testicular feminisation syndrome, 16%, which is very high.

Pure XY gonadal dysgenesis seems to correspond to Jost's experiments on I.U. castration of the male embryo.

XO gonadal dysgenesis is due to the failure of the primitive germ cells to arrive in the genital ridge during the normal development of the human embryo, prior to 16-18 days. They suggest that it is the X chromosome which controls the competent germ cells to induce ovarian cortical development.

In many cases XO gonadal dysgenesis and XX afollicular ovarian dysgenesis have the same histological appearance in the gonad. However, the latter are of normal or tall enuchoidal stature without congenital anomalies. This situation would be due to specific destruction of germ cells after migration and development by some agent such as a virus (Keettel and Bradbury, 1964).

These patients with XX "Streak ovaries have the enuchoid bodily habits of the young girl castrated before puberty. These with XX ovarian dysgenesis have a feminine bodily habits and tend toward enuchoidism. Other authors report similar findings in cytogenetic studies of gonadal dysgenesis. It is rare to find an XX ovarian dysgenesis with dwarfism.

Studying these lively intensely feminine young women, all with high urinary Gonodotrophin excretion, yet none exhibiting hot flushes tempts to a question, the validity of the established concepts of the menopausal syndrome.

It is important that a definitive diagnosis should be made in this class so that these young women can plan their lives and cease their futile search for fertility by going from one doctor to the other. There is no help from human pitutary gonadotrophines as there appears to be

an end organ failure, clomiphene is ineffective in the absence of endogenous oestrogen.

As a biological phenomenon these individuals are a puzzle. They bear their physical and psychological handicaps cheerfully and philosophically. These are the cases that require ovarian transplants. So that this group of women be forced to flower to physiological normalities.

Summary

1. Out of 50 cases of primary amenorrhea, 20 cases belonged to primary ovarian failure.

2. The ovaries were histopathologically studied in detail and classified according to the classification of Kinch *et al* and analysed.

3. The importance of cytogenetics and histopathology of gonads were discussed.

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See Figs. on Art Paper XIII-XIV