GONADOTROPHINS IN SECONDARY AMENORRHOEA

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SUMMARY

The role of gonadotrohin estimation in the investigation of patients with secondary amenorrhoea was determined. A single high serum FSH more than 40 mIU/ml was diagnostic of primary ovarian failure. A high LH/FSH ratio of more than 3:1 was seen in 85% of patients with polycystic ovarian disease and was normal only in those patients of PCOD who were obese with no signs of androgen excess. Serum LH levels more than 30 mIU/ml with normal FSH levels were seen in cases of PCOD who were obese with signs of androgen excess. Based on the response to progesterone withdrawal, a single FSH, LH and when required prolactin estimation, patients with secondary amenorrhoea could be classified into four groups for diagnostic and management purposes.

Introduction

Secondary amenorrhoea is the end of the spectrum of anovulation. It indicates a deranged hypothalamo-pituitary-ovarian-uterine axis to such an extent as to cause an inhibition of cyclical menstruation. The pituitary being at the centre of this axis would reflect derangements either in the ovary, by elevation of gonadotrophins, in the pituitary, by low levels of gonadotrophins, and in the hypothalamus by low gonadotrophin levels with hyperprolactinemia or by an abnormal gonadotrophin ratio. This study was designed to determine the value of gonadotrophin estimation in the investigation of secondary amenorrhoea patients and to draw out an investigative format based on our findings utilizing the minimal number of investigative tests, since these are expensive and not easily available at many centres.

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Accepted for publication on 23/1/1990.

Materials and Methods

85 women with secondary amenorrhoea attending the gynaecology out patient clinic of Safdarjang Hospital, formed our study group. Secondary amenorrhoea is defined as the cessation of menstruation for no physiological reasons for six or more months in women in the reproductive age group. After a detailed history and clinical examination serum was tested for FSH, LH and prolactin levels. The sera were stored at –20° C till the time of assay. Assay was done using standard RIA techniques.

Progesterone withdrawal with 5 mg of medroxy – progesterone acetate daily orally for 5 days was given, and oesterogen progesterone withdrawal with oral contraceptives, to those patients with no response to progresterone alone. Patients were divided into 5 groups according to gonadotrophin levels. All patients underwent an ultrasound examination, laparoscopy with or without open biopsy, to determine the uterine and ovarian index and presence or absence of follicles, or confirm the diagnosis of PCOD. Patients with normal and low gonadotrophins levels also had thyroid function tests and neurological investigations to rule out intracranial space occupying lesions.

Gonadotrophins levels were also studied in patients with hyperprolactinemia, prolactin more than 20 ng/ml, to determine the co-relation of gonadotrophin levels with elevated serum prolactin levels.

Serum levels of gonadotrophins were co-related with the final diagnosis of these patients, to determine the sensitivity and specificity of elevated, normal and low values of these hormones in the diagnosis and management of these patients.

Results

Twelve of the 84 patients had no withdrawal bleeding with estrogen and progesterone, indicating a uterine cause

TABLE - I
CLASSIFICATION OF SECONDARY AMENORRHOEA PATIENTS ACCORDING TO GONADOTROPHIN LEVELS

Classification	*No. of Patients*	*Other Investigations Required*	*Diagnosis*	*Number*
GROUP I				
Normal FSH & LH	15	Serum Prolactin if high Serum, TSH	1) Poly cystic Ovarian Disease	4
			Idiopathic	5
			2) Hyperprolactinemia 20-40 ng/ml	
			Hypothyroidism	4
			3) Hyperthyroidism	2
GROUP II				
Normal FSH LH 30 mIU/ml	8	–	Polycystic Ovarian Disease with Androgen excess	8
GROUP III				
FSH & LH elevated 40 mIU/ml	18	–	Primary Ovarian Failure	18
GROUP IV				
Low FSH & LH 5 mIU/ml	17	Serum Prolactin, if 50 ng/ml R/o SOL	1) Hypogonadotrophic Hypogonadism	12
			Microadenoma	3
			2) Hyperprolactinemia 20 mIU/ml	
			Idiopathic	1
			Fracture Skull	1
GROUP V				
Increased LH/FSH ratio 3:1	22	–	Polycystic Ovarian Disease	22

of amenorrhoea and these did not require gonadotrophin estimation. The remaining 72 patients were divided into five groups depending on the serum gonadotrophin results.

Group I were patients with normal FSH and LH levels, these were 15 in number. Table I shows that 4 of these cases were found on ultrasound and laparoscopy to be cases of PCOD. 9 patients were found to have a mildly elevated serum prolactin between 20-50 ng/ml, of which 4 were found to have hypothyroidism and 5 mild hyperprolactinaemia with no detectable cause. 2 other patients were found clinically and on investigation to have hyperthyroidism.

Group II had 8 patients with normal FSH levels, but elevated LH levels more than 3 mIU/ml. All these patients were found on investigation to be cases of PCOD. 7 of these women were obese with signs of androgen excess. Table II and III. Thus an elevated LH value more than 30 mIU/ml was diagnostic of PCOD with androgen excess.

Group III patients were 18 and had elevated serum FSH and LH values more than 40 mIU/ml. 18 patients were found on ultrasound examination to have a small uterine and ovarian index, with no follicles detectable. Diagnostic laparoscopy revealed small shrunken ovaries, one patient having a unilateral streak ovary. Open ovarion biopsy done in 6 patients showed absence of follicles, indicating that these were cases of primary ovarian failure. None of the patients in the other groups had an FSH value of more than 20 mIU/ml, on the other hand 8 of the remaining 54 patients had an LH value more than 30 mIU/ml. (Group II patients).

Group IV patients were those with low FSH and LH levels both less than 6 mIU/ml. There were 17 patients in this group. 5 of these patients had hyperprolactinemia – 4 being more than 50 ng/ml, and one between 20-50 ng/ml (Table I).

TABLE - II
GONADOTROPHIN LEVELS IN PCOD IN NORMAL WEIGHT AND OBESE PATIENTS

	Number	*LH/FSH ratio >3:1*	*Normal FSH/LH ratio*	*LH >30 mIU/ml with normal FSH*
Obese patients	16	12	4	7
Normal weight	10	10	0	1

TABLE - III
GONADOTROPHIN LEVELS IN PCOD IN PATIENTS WITH AND WITHOUT ANDROGEN EXCESS

	Number	*LH/FSH ratio*	*Normal*	*LH >30 mIU/ml*
Androgen excess Hirsuitism+ Acne	14	14	–	7
No Androgen excess	12	8	4	1

3 of the patients with prolactin levels morethan 50 ng/ml were found to have a pituitary microadenoma on further investigation. One patient had hyperprolactinemia more than 50 ng/ml following head injury and treated fracture base of skull. The remaining 12 patients had normal serum prolactin levels and all other neurological tests were normal, these came under the group of hypogonadotrophic hypogonadism.

Group V were patients with an elevated LH/FSH ratio of 3:1 or greater. There were 22 patients in this group and it included all 8 patients of Group II with LH values more than 30 mIU/ml. All these patients showed cystic ovaries on ultrasound or diagnostic laparoscopy. Thus an LH/FSH ratio of 3:1 or greater was found to be very specific for the diagnosis of PCOD but it was not able to detect 4 patients in Group I with normal FSH and LH values. It was found that all 4 patients of PCOD with normal levels of gonadotrophins were obese with no signs of androgen excess.

Discussion

A positive response to progesterone induced withdrawal bleeding in a patient with secondary amenorrhoea indicates the presence of a normoestrogenic state, and an intact hypothalamopituitary-ovarian-uterine axis. Serum estrogens have to be at least 40 P gm/ml to respond to a progesterone challenge (Rajan 1988). Absence of withdrawal bleeding with progesterone alone indicates an estrogen progesterone test. Failure to withdraw is an indication for investigating local uterine factors. If withdrawal bleeding occurs it evidences a receptive endometrium and a hypoestrogenic state (Santer et al 1978). Thus progesterone withdrawal alone classifies these patients into eugonadal with normal estrogene status, and hypogonadal with low estrogen status. In the busy outpatient clinic, there is a tendency to neglect this simple test which gives so much information. It is stressed that it would be done before a D & Ç which may be indicated only in those patients with a uterine cause of amenorrhoea.

Normal gonadotrophin levels in Group I patients in this study would point at other endocrine disorders like thyroid dysfunction, hyperprolactinemia or polycystic ovarian disease as the cause of amenorrhoea (Table I). Obese non-hirsuit women in this group would be cases of polycystic ovarian disease if hypothyroidism is ruled out. It was seen that almost always patients in this group were found to have one of the above endocrine abnormalities. These patients should be screened for serum prolactin levels, and thyroid function if prolactin is high. Patients with normal prolactin levels would be cases of

TABLE - IV
GONADOTROPHIN LEVELS IN PATIENTS WITH HYPERPROLACTINAEMIA

Prolactin levels	*No. of patients*	*Low serum FSH and LH*	*LH/FSH ratio >3:1*	*Normal FSH & LH*
> 50 ng/ml	4	4	–	–
20-50 ng/ml	18	1	8*	9

*8 cases of PCOD with hyperprolactinemia

hypothalamo-pituitary dysfunction and treated with clomiphene.

Elevated LH levels in Group II patients in the presence of normal or low FSH values would indicate an increased positive feedback effect of estrogen which would have to be in the range of 200 p gm/ml to produce a positive effect on LH secretion with levels more than 30 mIU/ml. These high estrogen levels would be due to peripheral aromatization of ovarian or adrenal androgens and would indicate an excess of circulating androgens (Burger et al 1988). Single High LH value more than 30 mIU/ml in the presence of a positive progesterone withdrawal was found to be very specific for the diagnosis of PCOD with androgen excess. This would indicate treatment with dexamethasone 0.5 mg to 1 mg daily to suppress adrenal androgens, and thus decrease the circulating estrogen levels-and LH stimulation (Rajan 1988) Ovulation may be induced with dexamethasone alone or with clomiphene in these patients.

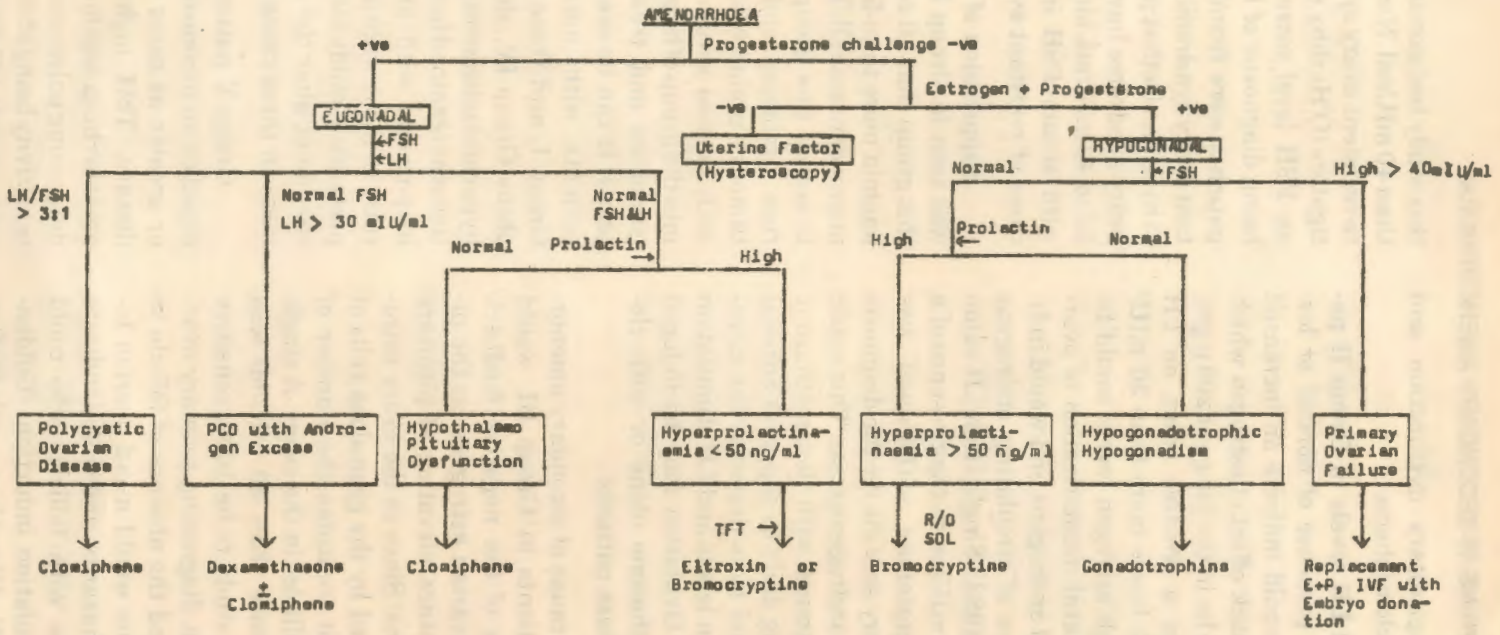
Ovarian cause of secondary amenorrhoea i.e. patients in Group III, would result in loss of the negative feedback influence of ovarian estrogens on the pituitary and hence elevation of pituitary gonadotrophins. Since in the ovary estrogen is produced by the granulosa cells of the follicles, it indicates the number of functioning follicles in the ovary. A single FSH value more than 40 mIU/ml was found in this study to be 100% sensitive and specific in diagnosing primary ovarian failure, and the absence of follicle in the ovary. This would avoid ovarian biopsy with its hazards, and would indicate those patients with follicles who could respond to ovulation induction. (Goldenberg et al 1973). All patients with POF in this study had gonadotrophin levels more than 40 mIU/ml. None was found to be due to resistent ovary syndrome. Other investigators (O'Herlihy et al 1980) have found an FSH level more than 20 mIU/ml as being diagnostic of POF but 16% of these patients were found to be cases of resistant ovary syndrome (ROS). It is tempting to hypothesisethat patients with resistant ovary syndrome have FSH levels between 20 to 40 mIU/ml, since we had no patient with serum FSH in this range, and no cases of resistant ovary syndrome.

Suppression of gonadotrophin levels was seen in Group IV patients. It was in this group that all cases of hyperprolactinaemia more than 50 ng/ml and pituitary microadenoma fell. Table I. It is important to screen this group of patients with serum prolactin and rule out pituitary tumour if prolactin levels are raised. Those with normal serum prolactin would fall into the group of hypogonadotrophic hypogonadism and treated with gonadotrophins. It can be seen from Table IV that patients with normal gonadotrophins, Group I, and those with low gonadotrophins Group IV, should be screened for hyperprolactinaemia. No added information was obtained by doing serum prolactin in patients with an increased LH/FSH ratio as these were all cases of PCOD, and presence of mildy elevated prolactin levels would not alter the diagnosis or management in these cases (Table III).

Group V patients could all be diagnosed by an increased LH/FSH ratio of 3:1 or greater as cases of polycystic ovarian disease. This high ratio in secondary amenorrhoea was found to be sensitive for diagnosing polycystic ovarian disease. The sensitivity being 85%. Patients with PCOD with normal LH/FSH ratio were found to

FIG. 1

INVESTIGATION OF SECONDARY AMENORRHOEA



be obese women in Group I with no signs of androgen excess. Other studies have shown similar findings (Franks 1988). The exact reason for this is not known, but it may be that obese women have less frequent LH spikes which may not be detected by a single gonadotrophin estimation. Inspite of the above an increased LH/FSH ratio of 3:1 or greater is sensitive enough to be utilized as a diagnostic test for PCOD. These patients being treated with clomiphene or dexamethasone if LH values were more than 30 mIU/ml.

Based on the findings of this study an investigative format has been drawn out using the progesterone withdrawal test, FSH LH levels, and when indicated serum prolactin levels. (Fig. I).

In conclusion gonadotrophin estimation is invaluable for the diagnosis and management of patients with secondary amenorrhoea.

1. Single elevated values of FSH >40 mIU/ml are diagnostic of primary ovarian failure.
2. LH values >30 mIU/ml in the presence of positive progesterone withdrawal indicate PCOD with androgen excess and treatment with dexamethasone ≥ clomiphene.
3. Increased LH/FSH ratio >3:1 indicates PCOD and treatment with clomiphene.
4. Low or normal gonadotrophin levels indicates the need for serum prolactin estimation.
5. Amenorrhoeic patients with low gonadotrophin values should be especially screened for pituitary adenomas.
6. Patients with normal gonadotrophin values should be screened for subclinical hypothyroidism.
7. Patients with secondary amenorrhoea can be classified and managed on the basis of gonadotrophin levels.

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