Occasional Review

Primary amenorrhoea: the ambiguous non-entity

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Summary

Hypothalamic-pituitary activity was investigated in 20 women with primary amenorrhoea, in whom gonadal dysgenesis and lower Müllerian duct anomalies had been excluded. There was no specific or uniform pattern of response to luteinising hormone-releasing hormone and no evidence of a common defect at pituitary-hypothalamic level to account for the absence of spontaneous menstruation. Six women had hyperprolactinaemia; of these five had radiological evidence of pituitary enlargement.

The conventional distinction between "primary" and "secondary" amenorrhoea should be abandoned, and, in common with current practice for other endocrine glands, primary amenorrhoea should indicate an abnormality of the gonad itself and secondary amenorrhoea an abnormality that results from hypothalamic-pituitary dysfunction.

Introduction

Amenorrhoea is conventionally classified as "primary" or "secondary"; primary amenorrhoea indicates a failure to start menstruation at puberty while secondary amenorrhoea indicates a later failure, once menstruation has occurred, even if only once in adult life. This classification, however, varies from that used for the other endocrine glands. Primary hypothyroidism, for example, denotes thyroid insufficiency due to disease of the thyroid gland alone, whereas secondary hypothyroidism indicates dysfunction of pituitary or hypothalamic control of thyroid activity, the thyroid gland remaining capable of endocrine activity when stimulated.

Apart from those women with genetic gonadal anomalies that preclude the spontaneous onset of menstruation, however, most women with primary amenorrhoea apparently have normal ovarian tissue, both structurally and functionally. The reason why these women do not menstruate spontaneously is unknown, but primary gonadal dysfunction is not the cause, since after appropriate treatment with gonadotrophin stimulants they menstruate and may conceive and carry successfully to term. The defect in such patients is therefore at pituitary-hypothalamic

level. But we do not know whether it is due to lack of gonadotrophin-releasing hormone from the hypothalamus, inability of the pituitary gonadotrophs to respond to the releasing hormone, or absence or malfunctioning of pituitary gonadotrophins from some other cause.

We investigated 20 women with so-called primary amenorrhoea in whom gonadal dysgenesis or Müllerian duct anomalies had been excluded to determine whether there was a specific defect—a common abnormality at hypothalamic-pituitary level. We were particularly interested to determine whether the development of secondary sex characteristics was related to endocrine responses and whether pituitary or other factors played any part in preventing spontaneous menstruation.

Patients and methods

CLINICAL FEATURES

Clinical details of the 20 women studied (all aged over 16) are given in the table. None had ever menstruated spontaneously but all had ovarian tissue, as indicated either at laparoscopy or gynaecography or by menstruation in response to gonadotrophin stimulant treatment (cases 4 and 16). No patient had evidence of thyroid or adrenal dysfunction. In the nine women in whom chromosomal studies were performed there was no abnormality, the karyotype being 46 XX in each case; in the remainder Barr bodies were observed in the buccal smear. Five girls (cases 7, 13, 16, 17, and 20) had radiological evidence of enlargement of the pituitary fossa but the remainder had no apparent abnormality on skull radiography.

The patients were seen over several years and some subsequently left the district. Hence not all the tests were performed in each patient. The number tested in each case is noted.

Sense of smell—This was assessed in 16 cases (nasal patency having first been shown) by testing the patient's ability to (a) detect any odour, and (b) identify peppermint, oil of cloves, eucalyptus, vinegar, and ammonia.

ENDOCRINE ASSESSMENT

LH/FSH-RH test—This was performed in all 20 women. Luteinising hormone/follicle-stimulating hormone-releasing hormone (LH/FSH-RH), 100 µg, was given by rapid intravenous injection, and venous blood samples were taken at 0, 20, and 60 minutes.

Prolactin—Basal serum prolactin was measured in 16 women, and their levels were also measured after thyrotrophin-releasing hormone (TRH) injection.

TRH test—TRH, 200 µg, was given by rapid intravenous injection to 16 women and venous blood samples were taken at 0, 20, and 60 minutes for estimating thyrotrophin and prolactin concentrations.

Clomiphene stimulation test—Twelve patients underwent this test to assess pituitary-hypothalamic responsiveness. Clomiphene citrate was given by mouth in a dose of 2 mg/kg/day to the nearest 20 mg for seven days, as in a previous study.¹ Blood LH and urinary pregnanediol or plasma progesterone concentrations were determined on days 3 and 21. In case 5 the procedure was repeated with a larger dose of 200 mg/day.

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Gonadotrophin treatment—Ovarian responsiveness to gonadotrophins was tested in 13 women by giving human menopausal gonadotrophin (HMG) intramuscularly on alternate days in doses of up to 10 ampoules (75 units). Human chorionic gonadotrophin (HCG), 10 000 units, was injected after urinary oestrogen had reached concentrations of 110-440 nmol/24 hours. In seven women gonadotrophin was given to assess ovarian responsiveness and in six to induce ovulation for conception.

Hormone assay techniques—Serum LH and FSH concentrations were measured by double antibody radioimmunoassay as previously¹; the lower limits of detection of the assay were 1 U/l for LH, and 0.25 U/l for FSH. Thyrotrophin and prolactin were also measured by double antibody radioimmunoassay using antisera and labelling material supplied by the National Pituitary Agency (USA); the

Medical Research Council, and Tenovus Institute for Cancer Research, Cardiff.

Results

CLINICAL FEATURES

Secondary sexual development—Seven girls (cases 1, 11, 15, 16, 18-20) had developed adequate breasts and pubic or axillary hair without oestrogen or progestogen treatment. Three of these (cases 1, 18, and 20) had normal-sized uterus and ovaries, while three (cases 11, 15, and 19) had normal-sized ovaries and in each case a small uterus (see table). The seventh girl refused laparoscopy. Two girls

Details of 20 women with "primary" amenorrhoea

Case No	Height (cm) weight (kg)	Born	Secondary sex characteristics	Genital tract		Sense of smell	LH-RH response	Prolactin	Other
				Laparotomy (L) or gynaecography (G)	Findings				
1	163 66.6	1951	Normal	L	Normal uterus and ovaries, subcapsular fibrosis and primordial follicles	Normal	Flat	Normal	Mentally subnormal
2	160 65	1952	Breasts slight, normal secondary sex hair	G	Very small uterus and right ovary, left ovary not seen	Normal	Flat	Normal	
3	150 45	1956	Breasts slight, no secondary sex hair	G	Rudimentary uterus, small ovaries		Flat	Normal	Congenital sideroblastic anaemia
4	156 47.2	1952	No breasts, prepubertal, no secondary sex hair		Menstruated after gonadotrophins	Normal	Flat		Enlarged fossa: craniopharyngioma, head injury at 1½ years
5	160 47.2	1953	No breasts, prepubertal, moderate secondary sex hair	L	Small uterus and ovaries	Normal	Flat		
6	174 64.9	1948	No breasts, prepubertal, scanty secondary sex hair, infantile external genitalia	L	Uterus small, ovaries minute, subcapsular fibrosis, germinal follicles +	Impaired	Slight rise	Normal	Two HMG-induced pregnancies
7	165 62.2	1949	Poor breasts, scanty secondary sex hair, hypoplastic external genitalia	G	Uterus small, ovaries cystic but normal size	Normal	Low initially, rose normally	Raised	
8	163 64.8	1952	Poor breasts, scanty secondary sex hair	L	Small uterus and ovaries, subcapsular fibrosis, primordial follicles		Low initially, rose normally		
9	158 48	1951	Small breasts, sparse secondary sex hair	L	Small uterus, infantile ovaries, germinal follicles, subcapsular fibrosis		Mixed: LH rose FSH flat		One HMG-induced pregnancy
10	160 47	1947	No breasts or hair, prepubertal	L	Small uterus and tiny ovaries, primordial follicles	Normal	Low initially, delayed small rise	Normal	Head injury at 6 years, one HMG-induced pregnancy
11	165 59.5	1953	Normal	L	Small uterus, normal ovaries with small cysts, scanty follicles, subcapsular fibrosis	Impaired	Supranormal, LH rise	Normal	
12	166 71.2	1948	Poor breasts, scanty pubic hair only	L	Uterus small, ovaries minute		Supranormal LH rise		One HMG-induced pregnancy
13	168 63.5	1935	Poor breasts, scanty secondary sex hair	G	Small uterus and ovaries	Normal	Supranormal LH rise	Raised	Enlarged pituitary fossa
14	153 44	1954	Poor breasts, slight secondary sex hair	G	Small uterus, fair-sized ovaries	Normal	Supranormal LH rise	Raised	Cardiac murmur, ? atrioseptal defect
15	180 71.2	1944	Normal	L	Small uterus, normal ovaries, ripening follicles, subcapsular fibrosis	Normal	High basal LH with massive rise, FSH normal initially but supranormal rise	Normal	Two HMG-induced pregnancies
16	162 62.2	1943	Normally developed, became hirsute age 30, galactorrhoea for 4 years		Menstruated after gonadotrophins	Normal	Supranormal LH rise	Raised	Enlarged pituitary fossa
17	167.5 99.8	1955	Poor breasts, normal secondary sex hair, galactorrhoea	G	Uterus tiny, ovaries elongated and narrow	Normal	Low initially, delayed slight rise	Raised	Enlarged pituitary fossa
18	177 63.8	1961	Small breasts, slight secondary sex hair	L	Normal uterus and ovaries, primordial follicles, slight subcapsular fibrosis	Normal	High basal level, massive rise	Normal	
19	145.5 57	1955	Breasts and sex hair developed, widely spaced nipples, low set ears, low hair line, lymphoedema, ptosis, and variable squint	L	Small uterus, normal ovaries, developing follicles, subcapsular fibrosis	Normal	Large rise after LH-RH	Normal	Noonan's syndrome
20	167 59	1945	Moderate breasts, normal hair	L	Uterus and left ovary normal, right ovary cystic, few primordial follicles, no developing ones	Normal	Flat	Raised	Two HMG-induced pregnancies

(cases 6 and 12) with minute ovaries (less than 1 cm³) showed no development of pubic or axillary hair or of breasts until after hormone treatment. The girls with small ovaries had varying degrees of sexual development, but most developed pubic and axillary hair with small breasts before oestrogen-progestogen treatment. Subcapsular fibrosis was observed on ovarian biopsy in eight out of 12 patients.

Smell—Two of the 16 girls tested (cases 6 and 11) stated that their sense of smell had always been deficient. They could neither identify any of the test substances nor detect any odour, though vinegar and ammonia produced nasal discomfort. Both claimed to be able to taste normally. The remaining girls were aware of odours and identified two or more test substances correctly.

HORMONE RESPONSES

LH/FSH-RH tests

Responses of both LH and FSH in the 20 women varied widely but in no case was there a "normal" pattern of FSH and LH after LH-RH—that is, a response comparable to that evoked in menstruating women in the follicular phase of the cycle. Basal LH concentrations were low in nine of the patients, normal in 10 and raised in one (case 15) (fig 1). Basal FSH levels were low in 15 women and normal in five (fig 2).

The women could be grouped, according to their response to LH-RH, into those releasing amounts of LH and FSH comparable to or greater than those in menstruating women in the follicular phase and those releasing little or none. In all but one patient (case 9), in whom there was an excessive LH release but no appreciable output of FSH, the FSH response was similar to that of LH. The patient with a raised basal level of LH (case 15) also showed exaggerated LH and FSH responses after LH-RH.

Five of our patients had "isolated gonadotrophin deficiency," with low basal gonadotrophin levels and failure to respond to clomiphene but no evidence of other pituitary hormone abnormality (cases 1, 6, 8, 9, and 10). Their response to LH-RH was, however, variable. Two (cases 6 and 8) released "adequate" levels of LH and FSH, two (cases 1 and 10) showed a poor response to the releasing hormone in respect of both LH and FSH, and one girl (case 9) had a mixed response, with a good rise in LH but a poor FSH response.

Nine girls underwent LH-FSH-RH tests more than once, at intervals of up to two and a half years (fig 3). In each case their response showed no qualitative change; those with a "flat" pattern did not acquire the ability to respond to LH-RH and those responding

FIG 1—LH response to LH/FSH-RH (100 µg intravenously) in 20 women with primary amenorrhoea. Normal range is indicated by broken lines.

FIG 2—FSH response (U/l) to LH/FSH-RH (100 µg intravenously) in 20 women with primary amenorrhoea. Normal range is indicated by broken lines.

FIG 3—LH response to LH/FSH-RH (100 µg intravenously) in four women with primary amenorrhoea studied on two separate occasions.

to LH-RH initially showed a similar or enhanced response on the second occasion. There is thus no evidence that prolonged hypothalamic failure causes secondary failure of the pituitary gonadotrophs. Indeed, in one woman (case 6) who initially gave a "borderline" positive response FSH and LH release in response to LH-RH were increased after the second gonadotrophin-induced pregnancy compared with the response after the first pregnancy.

Response to clomiphene

LH levels normally rise after clomiphene administration, with a subsequent fall and a second preovulatory rise. None of the women

with primary amenorrhoea who were given clomiphene, however, showed a rise in LH or menstruated thereafter.

Response to gonadotrophin

Urinary oestrogen excretion rose in all those injected with HMG, and menstruation or pregnancy occurred after HCG administration. Gonadotrophin treatment has to date induced nine pregnancies in six of the women with primary amenorrhoea. In the other seven HMG was given to assess ovarian responsiveness and not to induce pregnancy.

Blood prolactin levels and response to TRH

Blood prolactin concentration was raised in six of the 15 women in whom it was measured, and in five of these it was as high as levels that we have seen in women with a functioning pituitary tumour (2000 mU/l).

The thyrotrophin response to TRH was normal in all those in whom it was tested. Prolactin rose in response to TRH injection in all except the five women with grossly raised prolactin concentrations, who showed no change after TRH.

Discussion

Our important finding was that there was no specific or uniform pattern of response to LH-RH in women with primary amenorrhoea. Some showed no response, some showed an exaggerated response, and eight women showed responses that were no different from those observed in so-called secondary amenorrhoea, as after oral contraception. There was therefore no evidence that our patients with primary amenorrhoea had the same pathological lesion at pituitary level. The division of amenorrhoea into primary or secondary has no aetiological, diagnostic, or therapeutic basis. Hyperprolactinaemia or sclerocystic ovarian change may in fact cause either primary or secondary amenorrhoea depending on the stage of development at which the abnormality first becomes manifest. Similarly, women with chromosomal abnormalities may present with secondary amenorrhoea. In the light of these findings we therefore suggest that the conventional distinction between primary and secondary amenorrhoea be abandoned. In common with current practice for other endocrine glands, primary amenorrhoea should instead indicate an abnormality of the gonad itself and secondary amenorrhoea an abnormality that results from hypothalamic-pituitary dysfunction.

Clinical examination in our patients appeared to give some guide to the size of the gonad present; if secondary sex characteristics had developed without exogenous oestrogen-progestogen treatment the ovaries were normal in size or small, but if there were no secondary sex characteristics the ovaries were minute. It is interesting to speculate on the development of secondary sex characteristics in women with primary amenorrhoea. Pituitary gonadotrophin stimulation might occur initially and later cease for some unknown reason. Zourlas *et al* have reported similar cases.² It may therefore be relevant that ripening follicles were noted in one patient (case 15) and corpora albicantia in another (case 1), both of whom developed secondary sex characteristics without treatment.

High gonadotrophin concentrations similar to those found in ovarian dysgenesis were found in case 6, which raised the possibility of the resistant ovary syndrome.^{3,4} Yet two successful pregnancies were readily achieved after gonadotrophin treatment. The fact that the LH-RH test performed after the second pregnancy showed an enhanced response suggested that the hypothalamic-pituitary ovarian axis was functional and that she might have had a premature menopause from ovarian exhaustion.

In view of the above and of the finding that clomiphene responsiveness may be induced after LH-RH treatment,⁵ women with a positive LH and FSH response to LH-RH should perhaps be treated with repeated LH-RH injections rather than with gonadotrophins.

Olfactory ability is worth testing. Two of the 16 girls tested in the present series seem to have had Kallmann's⁶ syndrome (agenesis of olfactory lobes and hypogonadotrophism) like the girl described by Mroueh and Kase.⁷ Their patient responded to HMG, as did ours, thus showing no evidence of the double defect reported by Bardin *et al*⁸ and Muller *et al*.⁹ Although Kallmann's syndrome is said to be commoner in men, the incidence in women is possibly underestimated: testing for smell is not a feature of routine clinical gynaecological practice, and patients do not spontaneously volunteer the relevant information. No generalised hypothalamic defect was evident in our two women with absence of smell. In view of the fact, however, that gonadotrophin concentrations increased after LH-RH but not after clomiphene, the defect in these two would seem to be at hypothalamic level or above. LH-RH injection may prove to be the treatment of choice in such cases.

The patient's weight may be a factor. Five girls in the present series weighed under 47.5 kg, the weight said to be required for menarche.¹⁰ None, however, had a history suggestive of anorexia nervosa, and none weighed under 44 kg or appeared to be emaciated. The response to LH-RH depends on body weight. Below 45 kg there is a restricted response, with FSH higher than LH—a prepubertal phenomenon; whereas above 45 kg the responses are normal.¹¹ When the underweight girls were tested with LH-RH three showed flat responses, and only one (case 14, weighing 44 kg) showed a good gonadotrophin response. In none of these were FSH concentrations higher than those of LH. Nevertheless, even with increased weight after refeeding, there was no spontaneous menstruation or clomiphene responsiveness.

The relatively large number of women with hyperprolactinaemia (six), in five of whom there was also radiological evidence of pituitary enlargement, is of interest. There was no consistent pattern of response to LH-RH in these particular women. With current treatment,^{12,13} such women should menstruate spontaneously and conceive without gonadotrophin treatment. In the remainder, a heterogeneous group, pregnancy may be induced with gonadotrophin treatment. Oestrogen replacement treatment will, however, also be needed in most cases.

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References

- Ginsburg, J, *et al*, *British Medical Journal*, 1975, **3**, 130.
- Zourlas, P A, and Comminos, A C, *Obstetrics and Gynecology*, 1971, **38**, 298.
- Seeger Jones, G, and de Moraes-Ruehsen, M, *American Journal of Obstetrics and Gynecology*, 1969, **104**, 597.
- Dewhurst, C J, de Koos, E B, and Ferreira, H P, *British Journal of Obstetrics and Gynaecology*, 1975, **82**, 341.
- Bohnet, H G, *et al*, *Clinical Endocrinology*, 1976, **5**, 25.
- Kallman, F J, Schoenfeld, W A, and Barrera, S E, *American Journal of Mental Deficiency*, 1944, **48**, 203.
- Mroueh, A, and Kase, N, *American Journal of Obstetrics and Gynecology*, 1968, **100**, 525.
- Bardin, C W, *et al*, *Journal of Clinical Investigation*, 1969, **48**, 2046.
- Muller, P, *Pathologie et Biologie*, 1963, **11**, 1273.
- British Medical Journal*, 1975, **2**, 52.
- Palmer, R L, *et al*, *Journal of Endocrinology*, 1974, **63**, 32P.
- Thornor, M O, *et al*, *British Medical Journal*, 1975, **4**, 694.
- Franks, S, *et al*, *Clinical Endocrinology*, 1975, **4**, 597.

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