by subcutaneous biopsy, and 19 samples of human breast milk were analysed quantitatively for D.D.E., D.D.T., total B.H.C. isomers, and dieldrin (H.E.O.D.). The material studied was derived from sources throughout England and Wales. Apart from one anomalous finding from a recent immigrant the levels in the fat ranged from 0.2 to 8.5 p.p.m. for total D.D.T.-equivalent (mean 3.3), from a trace to 1.0 p.p.m. for total B.H.C. (mean 0.42), and from a trace to 0.9 p.p.m. for dieldrin (mean 0.26). In human breast milk the corresponding figures were 0.075 to 0.170 for total D.D.T.-equivalent, 0.009 to 0.033 for total B.H.C., and 0.002 to 0.013 for dieldrin.

In the provision of samples for this study we have enjoyed considerable help and co-operation from the directors of four human breast milk banks and from numerous pathologists throughout the country—so many, in fact, that it is hoped that they will forgo being named individually. To all of them our gratitude is expressed collectively. Thanks are also due to Dr. J. M. Barnes and Mr. O. F. Newman for the benefit of discussions with them at all stages of this work.

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Association of Oligomenorrhoea, Hirsuties, and Infertility

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Brit. med. J., 1965, **2**, 69–72

A group of patients present with varying combinations of oligomenorrhoea, hirsuties, and infertility. They pose a number of aetiological and therapeutic problems. The following report concerns findings in a series observed at the North Middlesex Hospital in recent years.

Material and Methods

Altogether some 183 patients have been studied. Most of them attended at one gynaecological and one endocrine clinic complaining of oligomenorrhoea or hirsuties, or infertility found to be associated with one or other of these conditions. Minimal criteria demanded for a diagnosis of oligomenorrhoea were menstrual cycles exceeding 28 days by several days, occurring for a minimal period of one year ; in most instances, however, the cycles were much longer, ranging from five weeks to amenorrhoea for months or years, and the condition had been present for years or may even have dated from the menarche.

An attempt, not always successful, was made to complete a routine series of investigations in each patient.

1. A "hormonal" hair score was obtained according to the method of Ferriman and Gallwey (1961).

2. Basal temperature charts were kept for a minimum period of six months or three complete cycles—usually much longer, except in patients with prolonged periods of amenorrhoea.

3. Gynaecography was carried out after trans-abdominal induction of pneumoperitoneum. Some 900 ml. of air was introduced, and radiographs were taken with the patient lying prone and tilted head-downwards to an angle of 30 degrees with the horizontal, the *x*-ray tube being positioned 3 ft. (91 cm.) vertically above the perineum.

4. Twenty-four-hour excretions of 17-ketosteroids were estimated by the Medical Research Council (1951) method, and of pregnanetriol by James's (1961) method.

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5, 6, and 7. Endometrial curettage and culture for *Mycobacterium tuberculosis*, hysterosalpingography, and analysis of the husband's semen were carried out in patients complaining of infertility.

Cortisone 37.5 mg. daily was employed in a series of patients for the relief of infertility, and in others for the correction of oligomenorrhoea and anovulatory cycles. Wedge-resection was employed for the relief of infertility in some patients with enlarged polycystic ovaries.

The findings are presented under two headings—those bearing on the question of aetiology and those relating to the effects of treatment.

Aetiology

Some consideration must first be given to methods of analysis of the data if findings are to be intelligible.

Methods of Analysis

Analysis of the data we obtained would have been helped by a knowledge of the ranges of normality for the various parameters involved and by the existence of methods for distinguishing between physiological and pathological departures from average figures. Unfortunately, information on these matters is somewhat limited.

The length of the menstrual cycle appears to be a graded characteristic. Haman (1942) and Marshall (1963) have reported on series of apparently normal regularly menstruating women: cycles of up to eight weeks were recorded, but any above six weeks seem to be somewhat unusual. Body hair is another graded characteristic. Ferriman and Gallwey (1961) describe a simple method of assessment for clinical purposes ; in a control series of apparently normal women scores of from 0 to 4 were found in 89% and from 5 to 9 in 10%, but scores of 10 and upwards were found in only 1%. Anovulatory

cycles occur in normal women (Rubenstein, 1940 ; Morton and Hayden, 1941 ; Levan and Szanto, 1944), but the data are insufficient for any numerical conclusions to be drawn regarding their frequency. Every ratio of ovulatory to anovulatory cycles was observed in the present series from invariably ovulatory to invariably anovulatory cycles or complete amenorrhoea. Scrutiny of the data suggested that fertility was little affected unless the proportion of anovulatory cycles was comparatively high. Our search for evidence bearing on the size-range for the normal human ovary has been unsuccessful. It has not been possible therefore to calculate a range of measurements to be expected on gynaecography of normal human ovaries. Edwards and Evans (1963), however, produced evidence for the existence of two ovarian populations—one normal, and one of enlarged polycystic ovaries. Similar evidence is produced below.

There appear to have been no studies on the possible range of cystic changes in the normal ovary (M. Haynes, personal communication, 1964). Little consideration seems to have been given to the possibility that fertility is another graded characteristic, and we know of no studies directed specifically towards determining the normal range of human fertility. Some idea of this can be derived, however, from the findings of the Royal Commission on Population (1950) and of the 1951 Census, and from data concerning patients attending antenatal clinics (reviewed by Bender, 1952) and those attending infertility clinics (Westman, 1950 ; Grant, 1951 ; Bender, 1952 ; Barns *et al.*, 1953 ; Southam and Buxton, 1957 ; Sharman, 1958 ; Wilson *et al.*, 1959 ; Wyper, 1962). The material is somewhat heterogeneous and does not permit of precise conclusions. However, it would seem that somewhere around 80% of normal women conceive within the first year of uncontracepted intercourse, and a further 7.5% in the second year. Thereafter some 6.25% conceive before the end of reproductive life, half of these doing so before the end of the third year ; some of these pregnancies may be related to treatment for infertility, but a significant proportion probably occur naturally. Some 6.25% remain permanently infertile. Unaided conception is therefore infrequent after two years of uncontracepted intercourse and rare after three.

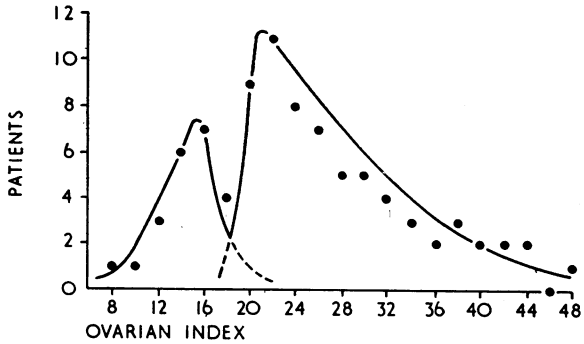
Since there is no clear line of demarcation in regard to any of these parameters, separation into groups for analysis has had to be made on an arbitrary basis. Patients were originally divided into three groups in respect to each of the parameters—apparently normal, frankly unusual, and intermediate. Little seemed to be gained by distinguishing intermediate groups, patients in these groups generally behaving like the apparently normal. Patients were therefore finally divided into two groups with respect to each parameter, which for convenience in presentation are referred to as normal and abnormal.

Patients have been classified as abnormal in respect of the various parameters as follows: those with menstrual cycles exceeding six weeks, those with hair scores of 10 or more, with ovarian indices (a measure of ovarian size—see next section) of over 20, those with ratios of anovulatory to ovulatory cycles of 2:1 or higher, and those with intervals between live births of three years or longer, allowance being made for periods of contraception, enforced separation, and the like.

Results of Analysis

The 24-hour excretion of 17-ketosteriods has been estimated in many patients, including 70 out of 82 with hair scores of 10 or over. It lay below 25 mg. in all but three. Two had excretions of 27 mg. and one of 28 mg.; palpation of the adrenals at laparotomy in one and intravenous pyelography in another showed no abnormality. The 24-hour excretion of pregnanetriol was estimated in 90 patients, including 55 with hair scores of 10 or over, and lay within the normal range of 0-2 mg. in all but two ; excretions in the latter were no more than 2.9 and 3.2 mg. and were increased to 4.6 and 6 mg. respectively only after stimulation with long-acting corticotrophin (80 units daily for three days). It is thought unlikely that any patients in the series were suffering from adrenal tumours or from congenital adrenal hyperplasia.

A crude index of radiographic ovarian size was determined for each patient by multiplying the length by the breadth in centimetres of each ovary separately, and adding the resulting two figures. The numbers of patients with each of the various indices were obtained ; the findings are presented graphically in the Chart. This indicates the possible existence of two ovarian populations—one of normal and the other of enlarged ovaries, with a dividing line at an ovarian index of around 20.



Distribution of ovarian indices among 85 patients

It has been possible to correlate measurements of the ovary at gynaecography with those obtained at laparotomy in 16 patients. The measurements found on gynaecography have been corrected for magnification by radiography ; geometrical considerations had suggested a correction factor of 9/16, but 2/3 gave a better match. The findings are shown in Table I. It can be seen that even with the correction actual ovarian size is significantly underestimated in a number of instances. This is not very surprising, since the ovaries will not always present with their major axes transverse to *x*-ray beams.

TABLE I.—*Comparison of Ovarian Indices (Length by Breadth in centimetres) Found at Gynaecography After Correction for Magnification, and at Laparotomy*

Gynaecography ..	12	15	20	20	22	24	24	24	24	24	25	29	32	36	37	38
Laparotomy ..	17	17	21	31	26	24	27	32	32	39	29	29	62	40	69	50

Inspection of the data for cycle length, hair score, ovulatory behaviour, size of ovary, and fertility in series of 183 patients reveals that some have presented with almost every possible combination of normal and abnormal forms of these

TABLE II.—*Correlation of Cycle Length, Hair Score, Ovarian Size, and Fertility in 66 Patients in whom Data in Relation to all these Parameters are Complete*

Cycle Length	Hair Score	Ovarian Size	Fertility	Patients
N	N	N	N	4
			A	4
		A	N	4
			A	14
	A	N	N	2
			A	4
		A	N	4
			A	5
A	N	N	N	1
			A	6
		A	N	3
			A	10
	A	N	N	1
			A	0
		A	N	0
			A	4

N = Normal. A = Abnormal (definition in section of methods of analysis). Figures relate to number of patients

parameters. An attempt to demonstrate this is made in Tables II and III. Cycle length, hair score, ovarian size, and fertility are all known in 66 patients; the numbers of patients in this group with each of the 16 possible combinations of these parameters are set out in Table II. Data for the remaining patients are less complete. In Table III, therefore, the numbers of patients with each of the four possible combinations of any two of the five parameters are set out for the entire series of 183 patients. The significance of the findings is considered in the discussion.

TABLE III.—*Correlation Between Cycle Length, Hair Score, Ovulatory Activity, Ovarian Size, and Fertility in 183 Patients*

		Hair Score		Ovulatory Activity		Ovarian Size		Fertility	
		N	A	N	A	N	A	N	A
Cycle length	N	54	60	77	11	20	41	31	39
	A	40	21	18	24	16	30	11	25
Hair score	N			48	21	23	41	23	42
	A			47	14	13	29	19	22
Ovulatory activity	N					21	41	25	33
	A					7	16	6	16
Ovarian size	N							8	14
	A							11	33

N = Normal. A = Abnormal (definition in section on methods of analysis). Figures relate to number of patients.

Treatment

Analysis has brought out several features bearing on treatment.

Relative Infertility.—Scrutiny of the data suggests that in the type of patient under discussion relative infertility is commoner than complete inability to conceive. This is illustrated in Table IV. Patients have been divided into fertile, relatively fertile, and completely infertile groups. A three-year interval between live births has been taken as the dividing-line between patients in the fertile and relatively infertile groups. Figures are given in these two groups for the total number of pregnancies, including those ending in abortion, and for those ending in live births only, together with the average interval between the conclusions of pregnancies in both instances. No stillbirths occurred in either group. The average duration of follow-up is given for the completely infertile group. It will be seen that the relatively infertile outnumber the completely infertile by a margin of nearly 50%.

TABLE IV.—*Data for Numbers of all Pregnancies, Including Those Ending in Abortion and Those Ending Only in Live Births, with Average Intervals Between Conclusion of Pregnancies, for Groups of Fertile and Relatively Infertile Patients, with Average Duration of Follow-up in the Completely Infertile Group*

Group	No. of Patients	Pregnancies		Live Births	
		No.	Interval	No.	Interval
Fertile	34	54	3·6 years	52	1·5 years
Relatively infertile	28			31	6·6 „
Infertile	20				5·5 „

Abortion.—Failure to maintain pregnancy in this series of patients was almost as important a factor as difficulty in conception. This also is shown in Table IV. Out of 54 pregnancies in the relatively infertile group no fewer than 23 (42.6%) ended in abortion.

Corticosteroids in Treatment of Infertility.—Table V shows the outcome of treatment of infertility by corticosteroids analysed with regard to hair score and ovarian size. Patients with hair scores of 10 or over fared better than the rest, and this is statistically significant, χ^2 being 7.169 and $P<0.01$. The figures suggest that patients with normal-sized ovaries (indices <20) fared better than those with large ovaries; but statistically the finding was not significant, χ^2 being 1.485 and $P>0.05$.

TABLE V.—*Relief of Infertility With Live Births Following Corticosteroids, Analysed in Relation to Hair Score and Ovarian Size*

		Success	Failure	Total
Hair score	0–9	2	21	23
	10+	6	7	13
Ovarian indices	−20	4	10	14
	20+	1	16	17

Corticosteroids and the Menstrual Cycle.—Table VI shows the effect of corticosteroids on patients with severe oligomenorrhoea (cycles longer than six weeks), amenorrhoea, or mainly anovulatory cycles, in relation to hair growth and size of ovary. Notable features are the proportion unaffected by treatment and the adverse effects noted in some; persistent menorrhagia was noted in several. Again there is a suggestion that patients with high hair scores and normal-sized ovaries fared best, but this finding was not statistically significant.

TABLE VI.—*Effect of Corticosteroids on Menstrual Behaviour in Patients with Severe Oligomenorrhoea or Infrequent Ovulation, Analysed in Relation to Hair Score and Ovarian Size*

		Improved	Unchanged	Worse
Hair score	0–9	4	11	3
	10+	6	5	1
Ovarian indices	−20	3	8	1
	20+	2	6	4

Wedge-resection.—This has been carried out in 16 patients with enlarged polycystic ovaries. Follow-up has reached one year in only nine—four with regular ovulatory cycles and five with oligomenorrhoea and anovulatory cycles. Only one pregnancy occurred—in a patient with ovulatory cycles—and then not until a lapse of one year from the time of operation.

Discussion

The data presented in Tables II and III indicate that normal and abnormal menstrual cycles, hair scores, ovulatory activity, size of ovary, and fertility may occur in almost every possible combination. It is particularly noteworthy that the presence of enlarged probably polycystic ovaries is consistent with ovulatory activity and fertility. Polycystic ovaries are found in a number of clinical conditions (reviewed by Sommers and Wadman, 1956; Ferriman, 1960; Goldzieher and Green, 1962); they almost certainly have a variety of causes, with a possible final common mechanism in excessive or continuous acyclic production of follicle-stimulating hormone. We believe that attempts to define entities based solely on combinations of these parameters are no longer very helpful. Somewhat similar conclusions have been reached by Ingle (1960), Goldzieher, and Green (1962), and Chamberlain and Wood (1964).

An aetiological approach to the problem may prove more fruitful. Little is known about causation, but there are a number of possibilities.

1. *Constitutional.*—Degrees of oligomenorrhoea, hirsuties, anovulatory behaviour, and infertility may be no more than extremes of physiological ranges.

2. *Hypothalamic.*—Psychological disturbances of hypothalamic centres.

3. *Pituitary.*—Disorders with manifestations confined to the underproduction of gonadotrophic hormones.

4. *Adrenal.*—Overproduction of androgenic compounds, leading to masculinization of hypothalamic centres similar to that produced experimentally in animals (Pfeiffer, 1936; Barraclough and Gorski, 1961).

5. *Ovarian.*—(*a*) Modified forms of gonadal dysgenesis with absence of the usual stigmata. (*b*) Enzyme defects in the synthesis of oestrogens (Lanthier and Sandor, 1960; Short and London, 1961; Warren and Salhanick, 1961; Axelrod and Goldzieher, 1962; Mahesh and Greenblatt, 1962; Short, 1961; Crooke *et al.*, 1963; Giorgi, 1963).

An aetiological classification is desirable, moreover, on therapeutic grounds. Rational treatment depends upon a precise knowledge of causes. Claims have been made for the efficacy of several lines of treatment, including wedge-resection of the ovaries, corticosteroids, pituitary irradiation, human follicle-stimulating and chorionic gonadotrophin combinations, and clomiphene. A better understanding of causation, and, in most instances, of the mechanisms through which these forms of treatment operate might permit a more effective choice of therapeutic agent.

Several factors must be borne in mind when evaluating the results of any particular form of treatment. The reports from infertility clinics cited in the section on aetiology indicate that a significant proportion of pregnancies, perhaps as high as 50%, may have occurred in the natural order of things and not as the result of treatment. It is true that much has depended upon aetiology. The groups who failed to consummate marriage or in whom no cause for infertility has been found have fared better than those with pelvic tuberculosis, tubal blockage, azoospermia, or persistent failure to ovulate. Nevertheless, in assessing the value of treatment allowance must be made for natural relief of infertility. Controlled trials in this field would be helpful. Much the same considerations apply to the relief of menstrual disturbance. Spontaneous relief of such disturbance occurs in a significant proportion of patients (Westman, 1958).

A number of authors have reported pregnancies after the use of corticosteroids in hirsute patients, both in those with and in those without polycystic ovaries (reviewed by Ferriman *et al.*, 1961). It is usually assumed that corticosteroids operate via a depression of adrenal androgen production. Jefferies (1960), however, has claimed benefit from corticosteroids in non-hirsute patients, and the possibility of another explanation should perhaps be borne in mind. Such an alternative is provided by Sohval and Soffer (1951) and by Brown (1956), who found alterations in the output of gonadotrophins following corticosteroids. On analysis our own data on pregnancies following use of corticosteroids, in relation to hair growth, are consistent with an effect on adrenal androgen production, but this finding must be accepted with a little reserve. The data also indicate a possible relation with ovarian size. The available data are insufficient for a statistical differentiation between the relative importance of these two factors.

It is generally believed that wedge-resection of polycystic ovaries is effective in the restoration of normal menstrual function and the relief of infertility. It is suggested, however, that the precise value of this operation remains to be determined. Relief of infertility does not invariably follow wedge-resection, and pregnancies may occur without any form of treatment. The mechanism of relief is little understood. A clearer understanding of the latter, and a better knowledge of the aetiological groups involved, may help to clarify the situation.

The Royal Commission on Population (1950) gives a figure of 7–11% of pregnancies ending in abortion for the population at large. Much higher figures are given for groups of infertile patients (Rubenstein, 1939; Rubin, 1945; Westman, 1950; Grant, 1951; Bender, 1952; Southam and Buxton, 1957; Sharman, 1958; Wyper, 1962), though Swyer (1959) has questioned the interpretation of these findings. No less than 42.6% of pregnancies in our infertile groups ended in abortion. It would seem that the management of threatened abortion may be as important as measures designed to promote conception in achieving relief of infertility in this group of patients.

Summary

Data are presented from the investigation and treatment of 183 patients attending with various combinations of oligomenorrhoea, hirsuties, and infertility.

Data from 85 gynaecographies suggest the existence of two ovarian populations, one with enlarged polycystic ovaries and the other a more normal group.

Analysis of the data relating to cycle length, growth of body hair, ovulatory behaviour, ovarian size, and fertility suggests that disease entities in this group of patients cannot be distinguished on clinical grounds alone.

Relative infertility occurs more often than absolute infertility in this group of patients, and the management of threatened abortion is as important as the initiation of pregnancy.

Corticosteroids seemed more effective in the treatment of infertility in the hirsute patients than in the remainder, and possibly less effective in the treatment of patients with enlarged polycystic ovaries than of those with normal-sized ovaries.

The effect of wedge-resection in this series was disappointing.

Progress in this field is hampered by a lack of information regarding the normal range for various parameters involved, by a lack of methods for distinguishing between physiological and pathological departures from average findings, and by deficiency in precise information about the natural history of untreated patients.

A plea is made for an aetiological approach to problems presented by this group of patients.

We wish to thank all those who have referred cases, and in particular Mr. J. C. Brace, Miss M. Moore-White, and Mr. R. M. Millen. We are also grateful to many members of the medical and nursing staff for their assistance, notably Dr. T. E. Broadbent and Dr. B. C. Hale, radiologists to the hospital, and Sister M. Gallagher; to Miss F. Makloof for statistical studies; to Dr. J. F. Heggie and Dr. W. G. Dangerfield for laboratory facilities; to Dr. V. H. T. James for assistance over steroid aspects; to Miss Sylvia Vaughan for steroid assays; and to the North-east Metropolitan Regional Hospital Board and Organon Laboratories for generous grants towards expenses.

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