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PREGNANCY AFTER PRIMARY INFERTILITY INVESTIGATION

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In the 21-year period 1937-57 inclusive, 1,182 cases of primary infertility were admitted to the Aberdeen Royal Infirmary for investigation. This, at the minimum, involved a pelvic examination under anaesthesia in the premenstrual phase, with tubal insufflation, dilatation of the cervix, and endometrial biopsy. In the event of apparent tubal blockage or unsatisfactory endometrium, repeat examinations were carried out on one or more occasions before a final conclusion was formed. Where possible, the husband was examined and his semen analysed. The sperm count, regarded by Jeffcoate (1954) as the most significant single feature, has been taken as the measure of the husband's fertility. Sperm activity, now generally regarded as at least equally important, was found difficult to evaluate objectively from the data available and therefore has not been taken into account.

A follow-up inquiry of the 1,182 cases investigated has been carried out by me personally at intervals of three to four years, the most recent being September, 1960. The number of cases successfully traced over the years is 1,004—that is, 85% of the total—and these form the basis of this paper. Where pregnancy occurred accurate details are available in almost every case, as, with few exceptions, the patients were under the surveillance of the Aberdeen Maternity Hospital staff and I had ready access to the hospital records.

Pregnancy occurred in 355 cases, a conception rate of 35.5%, almost identical to that obtained by Grant (1951) and by Southam and Buxton (1957), who each reported a rate of 36% in 2,359 and 899 infertile women respectively. On the other hand, Bender (1952) and Jeffcoate (1954) both reported a conception rate of 46.3%, and Wilson *et al.* (1959) one of 49% from the Mayo Clinic. But there have been comparatively low rates, such as 23% in 707 cases reported by Barns *et al.* (1953).

The outcome of the first pregnancy is summarized in Table I. The prematurity rate (8%) is no greater than that for all births. The abortion rate (14%) is probably not much greater than that for spontaneous abortion

TABLE I.—*Outcome of First Pregnancy in 1,004 Cases Investigated for Primary Infertility (1937-57 Inclusive)*

Mature births	..	268 (75.5%), including 5 perinatal deaths
Premature	..	28 (8%), " 11 " "
Abortions	..	50 (14%), " 11 " "
Ectopic	..	9 (2.5%)
		355

in Britain generally (Royal Commission on Population, 1950). Most other investigators have found rates of between 19% and 21% (Bender, 1952; Southam and Buxton, 1957; Swyer, 1959).

The frequency of ectopic gestation (2.5%) is about eight times that estimated for the total population. Bender (1952), Grant (1951), and Southam and Buxton (1957) found incidences of 1.7%, 2%, and 4.3% respectively.

Type of Delivery in Mature Births

Table II shows that 207 (77.3%) were spontaneous deliveries, 40 (14.9%) were deliveries by forceps, and 21 (7.8%) by caesarean section. Comparing these results

TABLE II.—*Type of Delivery in 268 Mature Births by Age of Patient Previously Investigated for Primary Infertility*

	Under 30 Years	30 Years and Over	All Ages
Spontaneous	142 (83.5%) 84.5%	65 (66.3%) 67.9%	207 (77.3%) 82.3%
Forceps	21 (12.4%) 12.9%	19 (19.4%) 21.3%	40 (14.9%) 14%
Caesarean section	7 (4.1%) 2.6%	14 (14.3%) 10.8%	21 (7.8%) 3.7%
Total	170	98	268

For comparison, the rates for booked Aberdeen primigravidae over the 10-year period 1950-9 are given in italics.

with those of booked primigravidae generally, it will be seen that if allowance is made for age the only real difference in the mode of delivery is that more caesarean sections were performed in the infertility group, especially in those under 30 years of age. Some of the caesarean sections were elective and were performed to ensure a live baby in patients with pre-eclampsia, suspected disproportion, or other unfavourable feature. In short, the course of labour in the previously infertile patient is not significantly different from that of primigravidae in general. Swyer (1959), on the other hand, found a very much higher incidence of forceps and caesarean section delivery in his infertile cases.

The causes of perinatal death in mature babies were gross deformity in two, birth trauma in one, severe pre-eclampsia in one, and placental insufficiency due to post-maturity (18 days past the calculated date) in one. In premature babies one death was due to gross deformity. In the others prematurity was the basic cause of death resulting from severe pre-eclampsia in four but unexplained in the other six. It is noteworthy that the overall incidence of gross deformity (1%) is no greater than for all births. A similar low incidence was found by Bender (1952) and by Swyer (1959).

When the perinatal deaths, abortions, and ectopic pregnancies are deducted from the total of 355 conceptions, the number of successful first pregnancies, with a surviving child, is reduced to 280—that is, a first pregnancy success rate of 28%, agreeing almost exactly with Southam and Buxton (1957) in their follow-up of 899 primary infertility cases. A further follow-up of the

75 cases of unsuccessful first pregnancy yielded the results shown in Table III. There were 24 successes in the second pregnancy, five in the third, and a further four in the fourth, making a total of 33. When these

TABLE III.—Further Follow-up of the 75 Cases of Unsuccessful First Pregnancy

Unsuccessful 1st Pregnancy	Outcome in 2nd Pregnancy	Outcome in 3rd Pregnancy	Outcome in 4th Pregnancy	No. of Ultimately Successful Pregnancies
Mature perinatal deaths 5	2 mature alive	—	—	2
Premature perinatal deaths 11	5 mature alive 1 premature alive	—	—	6
Abortions 50	16 mature alive	—	—	25
	2 premature S.B.	1 mature alive 1 premature S.B.	1 mature alive	
	14 abortions	4 mature alive 6 abortions	3 mature alive 1 abortion	
Ectopic 9	1 ectopic	—	—	0
Surviving children 0	24	5	4	33

are added to those from the first, the ultimate success rate is 31.3%. A striking feature is the high incidence of recurrent abortion in the 50 women whose first pregnancy ended in abortion. This is in marked contrast to an incidence of only 10 (9.3%) abortions in 107 second pregnancies in the case of the 280 women who had successful first pregnancies. Of these patients, 173 had no further pregnancy—that is, just under two-thirds—thus indicating that they were still subfertile. A similar proportion was obtained by Jeffcoate (1954).

Aetiological Factors and Outcome of Pregnancies Achieved

Some of the more important factors are considered individually.

Dyspareunia.—In the cases where this was believed to be the principal reason the conception rate (58.5%) was the highest achieved (Table IV). The relatively high success is scarcely surprising since the majority of cases could be successfully treated by stretching or episiotomy in the case of rigid hymen or narrow introitus, or by appropriate advice in the cases of functional origin.

Gross Uterine Underdevelopment.—There were 69 cases in this group, and in the great majority the diagnosis was based on the fact that the uterus on bimanual palpation seemed very small and the endometrium was poorly developed. Despite this, pregnancy occurred in 20 cases (29%). Oestrogen therapy, which was often used in such cases, may have been beneficial. Table V summarizes the outcome of the pregnancy. Foetal growth was very satisfactory and uterine dysfunction in labour was not as frequent as might

TABLE IV.—Pregnancy Outcome in 65 Cases of Primary Infertility Associated with Moderate or Severe Dyspareunia

	No. of Cases	No. of Pregnancies
Mechanical factor (narrow introitus, rigid hymen, vaginal hypoplasia)	44	27 (61%) { 23 mature 1 premature 3 abortions
No apparent mechanical factor (functional)	21	11 (52%) { 10 mature 1 abortion
Total	65	38 (58.5%)

have been expected. In only one case was caesarean section necessary for this reason.

Abnormal Premenstrual Endometrial Development in the Normal-sized Uterus.—This was found in 107 cases. (In a few cases "timing" of the endometrial biopsy was difficult because of marked irregularity of the menstrual cycle.) The outcome of pregnancy in these cases of presumed hormone imbalance is given in Table VI. Hormone therapy was prescribed in many

TABLE V.—Pregnancy Outcome in 69 Cases of Primary Infertility Associated with Gross Uterine Hypoplasia

20 (29%) pregnancies occurred as follows:
 *14 mature births—average birth-weight 7½ lb. (3,290 g.)
 1 premature birth
 3 abortions
 2 ectopic
 *10 were spontaneous, 3 were low forceps deliveries on account of minor dysfunction; only 1 required caesarean section on account of major uterine dysfunction.

TABLE VI.—Pregnancy Outcome in 115 Cases of Primary Infertility Associated with Gross Premenstrual Endometrial Abnormality in Normal-sized Uterus

No secretory activity in 57 cases, of which 19 (33%) became pregnant as follows:
 10 mature births
 4 premature births
 4 abortions
 1 ectopic
 No curettings in 41 cases, of which 8 (19%) became pregnant as follows:
 7 mature births
 1 abortion
 Cystic glandular hyperplasia in 17 cases, of which only 1 became pregnant and progressed normally to full term

cases, but to what extent it contributed to the result is difficult to assess as in not a few cases conception occurred an appreciable time after treatment had been discontinued. It will be observed that even in cases where no curettings had been obtained pregnancy can occur and progress to full term. The outlook in cases with cystic glandular hyperplasia is particularly poor, only one pregnancy occurring in 17 cases.

Fibroid Uterus.—This diagnosis was made in 29 cases. In 24 the fibroids were small and myomectomy was performed in only three. In the other five the fibroids were relatively large and myomectomy was performed in each case. Only seven (24%) pregnancies occurred—three mature births (one after myomectomy) with surviving babies, and four abortions (one after myomectomy).

Retroversion of Uterus.—In 99 cases this appeared to be the only significant factor. In 69 of them mobility of the uterus was demonstrated, while in the remaining 30 the uterus appeared to be "fixed." The incidence of pregnancy in "mobile" retroversion of a normal-sized uterus (41%) was almost twice as great as that in apparently "fixed" retroversion of a normal-sized uterus (23%). The overall pregnancy incidence in retroversion was 35%, with an abortion rate of 11.5%—not significantly different from the general abortion rate.

Endometriosis.—In 13 patients the diagnosis of endometriosis was made on good evidence, and the only pregnancy in this group occurred in a Fallopian tube.

Pelvic Tuberculosis.—There were 25 cases, all diagnosed on evidence of tuberculous endometritis. One pregnancy (an ectopic) occurred.

TABLE VII.—Pregnancy Incidence in 1,004 Cases of Primary Infertility by Age at Time of Investigation

Age:	20-24	25-29	30-34	35-39	40-44
No. followed up	183	377	309	124	11
No. becoming pregnant ..	101 (55%)	139 (37%)	93 (30%)	21 (17%)	1 (9%)

Influence of Age upon Conception Rate.—The importance of age at the time of investigation is shown in Table VII. There is a steady fall from a 55% conception rate in the 20–24 age-group to only 9% in the 40–44 age-group. The average duration of marriage at the time of investigation was not significantly different in the various age-groups.

The Husband as a Factor

Firstly, an attempt has been made to assess the influence of diminished fertility of the husband on the outcome of pregnancy where no lesion would be detected in the wife. The results are given in Table VIII. It will be seen that there is little difference in the pregnancy rate with different sperm counts when the semen

TABLE VIII.—*Pregnancy Outcome in 352 Cases of Primary Infertility with Normal Findings in Wife by Sperm Count of Husband*

Sperm Count (millions/ml.)	No. of Cases	No. of Pregnancies	
50 and over ..	162	83 (51%)	<div> <div>Mature births .. 65</div> <div>Premature .. 8</div> <div>Abortions .. 8</div> <div>Ectopic .. 2</div> </div>
20 " " ..	62	30 (48%)	<div> <div>Mature births .. 25</div> <div>Premature .. 2</div> <div>Abortions .. 2</div> <div>Ectopic .. 1</div> </div>
10 " " ..	24	9 (37.5%)	<div> <div>Mature births .. 19</div> <div>Premature .. 1</div> </div>
1 " " ..	30	9 (33%)	<div> <div>Premature .. 1</div> <div>Abortions .. 2</div> </div>
Under 1 " " ..	24	4 (16.5%)	<div> <div>Ectopic .. 1</div> </div>
Azoospermia ..	50	0	

contains 20 millions or more per ml. The same conclusion was reached by Macleod and Gold (1958) in studying the quality of semen on a very large scale. Below this level there is a progressive fall in the success rate, but even when the count is extremely low the outlook is far from hopeless, as was also found by Bender (1952). Pregnancy did not occur in any of the cases with azoospermia. When pregnancy was achieved the incidence of premature labour and abortion did not increase with decreasing sperm count and accompanying higher rate of malformed sperm.

Secondly, for comparison, the effect of reduced fertility of the husband on the pregnancy incidence where adverse factors are present in the wife has been determined as shown in Table IX. It is evident not only that there is a reduction in the conception rate at all sperm-count levels, as might be expected, but that, more significantly, this reduction does not remain propor-

TABLE IX.—*Pregnancy Incidence in 385 Cases of Primary Infertility with Adverse Factors in Wife by Sperm Count of Husband*

Sperm Count (millions/ml.)	No. of Cases	No. of Pregnancies
50 and over ..	232	95 (41%)
20 " " ..	78	25 (32%)
10 " " ..	24	5 (21%)
1 " " ..	21	3 (14%)
Under 1 " " ..	14	0
Azoospermia ..	16	0

tionate as the counts fall. Thus at the 50 million/ml. level the pregnancy incidence in the wives with causal factors is only one-fifth less, whereas where the count has fallen to between 1 and 10 million/ml. it is more than half less. Furthermore, whereas a count of 20 million/ml. might be regarded as the critical level where the wife is normal, it would certainly have to be raised

where the wife is subfertile. In other words, the results indicate that a high-quality semen is especially important in cases of lowered fertility in the wife.

Therapeutic Value of Infertility Investigations

It is difficult to assess the therapeutic value of infertility investigations, but a study of Tables X and XI would seem to indicate that it is much higher than might have been anticipated from taking into account the

TABLE X.—*Distribution by Age at Marriage and Duration of Marriage at Time of Hospital Investigation in 1,004 Cases of Primary Infertility*

Years Married	Age at Marriage						All Ages	
	<20	20–24	25–29	30–34	35–39	40–44	No.	%
Up to 1½ ..	4	19	13	4	3	2	45	4.5
1½–3 ..	25	65	49	23	8	2	172	17
3–5 ..	75	193	131	46	6	0	451	45
6–10 ..	54	117	96	23	0	0	290	29
10+ ..	3	17	25	1	0	0	46	4.5
Total ..	161	411	314	97	17	4	1,004	100

TABLE XI.—*Interval from Completion of Investigation to Conception in 355 Cases*

Up to 6 months ..	120 (34%)
6 months to 1 year ..	85 (24%)
1 to 1½ years ..	43 (12%)
1½ to 2 years ..	36 (10%)
2 to 3 " ..	38 (11%)
Over 3 " ..	33 (9%)

infrequency with which lesions are found for which a specific or effective treatment is known. Table X shows that four-fifths of the subjects have been married for at least three years before investigation, yet of those who conceived (Table XI) one-third did so within six months of investigation, three-fifths within one year, and four-fifths within two years. This strongly suggests that the investigations themselves, followed in some cases by specific treatment, were of real therapeutic value. Bender (1952) thought that perhaps half of the successes in his series could be attributed to the investigation or treatment. Sharman (1958), in a follow-up of 2,390 patients with primary infertility, variously investigated and treated, for one year during a 15-year period 1940–55, obtained a minimum pregnancy rate of 10.8% where merely a bimanual examination had been carried out, but more than double this rate (22.3%) when full hospital in-patient investigation and therapy had been done. On the other hand, Barns *et al.* (1953) believe that the therapeutic value of infertility investigation and treatment is slight, basing this on finding a pregnancy rate of only 23% in 707 treated patients as against 18.4% in 501 untreated patients.

Contraception

Since infertility increases with age, it seemed desirable to determine what part contraception played in voluntary postponement of the effort to conceive. Information on this score was available in 944 of the 1,004 cases (94%). Only 6% practised contraception up to a year and still fewer (3.5%) over a longer period. The limited use made of contraceptives makes it clear that in this series voluntary postponement of child-bearing played little part in predisposing to infertility, particularly as the great majority of patients had been married three or more years.

Summary

Of 1,004 women investigated for primary infertility and successfully kept under observation for between 3 and 23 years, rather less than one-third (31%) eventually gave birth to a child which survived.

The prematurity rate was similar to the general rate. The abortion rate was not much greater than that estimated for spontaneous abortion. The ectopic rate was very high, being no less than eight times the general incidence.

An attempt has been made to relate possible causal factors of the infertility to the outcome of the pregnancy. There is inevitably a lack of precision in assessing causal factors, especially when factors in both husband and wife have to be considered together. Generally speaking, however, the outcome is surprisingly good once pregnancy has been achieved, and labour is no more difficult in these cases. There is no increased risk of a deformed child.

The results suggest that routine hospital investigation of primary infertility, followed in some cases by treat-

ment of specific abnormalities, increases the chance of pregnancy quite considerably.

I should like to thank Professor Sir Dugald Baird for his helpful advice and criticism.

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METRONIDAZOLE TREATMENT OF TRICHOMONIASIS IN THE FEMALE

REPORT OF AN EXTENDED TRIAL

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The cautious initial claims (Durel *et al.*, 1959) of the efficacy of metronidazole (1- β -hydroxyethyl-2-methyl-5-nitroimidazole) in the treatment of trichomoniasis in both sexes have been confirmed. In France, Durel *et al.* (1960) still favour combined local and oral metronidazole in the treatment of females, but in Britain it has been stressed that coincident local application is unnecessary (Nicol *et al.*, 1960; Rodin *et al.*, 1960; Watt and Jennison, 1960a; Willcox, 1960). Table I combines the results obtained by these British workers in the treatment of females and shows that 219 (84.9%) of 258 patients were cured and 39 (15.1%) showed post-treatment recurrence.

TABLE I.—Results of Treatment (Various Workers)

Reports	No. of Cases	Successful Treatment		Treatment Failure					
		No.	%	Primary		Late		Total	
Nicol <i>et al.</i> (1960)	122	105	86	5	4.1	12	9.8	17	13.9
Rodin <i>et al.</i> (1960)	52	43	83	3	5.8	6	11.5	9	17.3
Watt and Jennison (1960a)	50	44	88	2	4	4	8	6	12
Willcox (1960)	34	27	79.5	2	5.8	5	14.7	7	20.5
Total ..	258	219	84.9	12	4.6	27	10.5	39	15.1

Primary failure of response to the drug occurred in 12 (4.6%) of these and 27 (10.5%) showed recurrence after initial apparent cure. In males with trichomoniasis 100% response to treatment is reported in 11 patients (Nicol *et al.*, 1960), 20 patients (Rodin *et al.*, 1960), and 32 patients (Sylvestre *et al.*, 1960).

Only minor side-effects have so far been reported and no evidence of any haemopoietic or hepatic damage has been noted (Jennison *et al.*, 1961).

Present Investigation

The present study was undertaken in St. Mary's Hospital for Women, Manchester, to gain further experience of the treatment of trichomonal vaginitis with metronidazole and to investigate some possible causes of

treatment failure and recurrence. During the investigation no restriction was placed on coitus, and the possibility of sexual reinfection (Watt and Jennison, 1960b) received particular attention.

The clinical material, methods of examination, and criteria of cure were as described previously (Watt and Jennison, 1960a). The ages of the patients varied widely, the extremes being a virgin of 15 and a woman of 74 with coincident diabetic vulvitis. All were given a standard course of 600 mg. of metronidazole daily for one week and were regarded as cured if clinically and bacteriologically free from infection for three months. Some who showed recurrence were re-treated with 1,200 mg. daily for seven days or 600 mg. daily for 14 days. Patients discharged cured were instructed to return if symptoms recurred.

Efforts were made to examine the male consorts of all women who suffered late recurrence after initial apparent cure. The methods of examination of males were as described previously (Watt and Jennison, 1960b), reliance being placed on cultural examination of specimens obtained from the urethra, prostate, and post-massage urine. If *Trichomonas vaginalis* was found in the male both partners were treated simultaneously with a standard course. If *T. vaginalis* was not found in the male the female alone was re-treated. In each case a further three months' observation for the female was instituted. Because of the difficulty in persuading males to attend, absence of further signs of infection in the female was taken as presumptive evidence of cure of the male.

Results

Including the 50 reported previously (Watt and Jennison, 1960a) 200 consecutive female patients with trichomonal vaginitis have been treated, and 8 (4%) of these defaulted without post-treatment observation and 1 (0.5%) was unable to tolerate the drug in the standard dosage. Of the 191 followed, 142 (74.3%) remained free from clinical or laboratory evidence of infection during