

In My Own Time

Infertility

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A crutch in the crotch. That this was the main role of the gynaecologist in dealing with infertility was the first of two conclusions omitted from my paper "The end-results in primary sterility" in the *BMJ* in 1952. The second was that not all women referred to the infertility clinic really wanted a baby. Indeed, it was the last thing a few of them wanted: they had seen their GP and been referred, impelled not by maternal instinct but by external pressures—from a husband with a greater procreative urge, a mother-in-law demanding a grandchild, friends asking bluntly, as friends do, why she had not yet become pregnant. Most of these reluctant patients were of one of two types—baby doll or career woman. I was intrigued to read some time later a paper by a Canadian psychiatrist claiming that such women had a high rate of spontaneous abortion. And some women sought a pregnancy as a solution to a problem—for instance, as a tether for a wandering husband or as a means to better housing.

Initiation

I was initiated into infertility work in the late 1940s in the department in Liverpool of Professor T N A (now Sir Norman) Jeffcoate, a human cornucopia of original ideas throughout his specialty. He encouraged us to have an optimistic attitude to the infertile couple and a critical attitude to our own ideas and practices. Among other things he measured the false-negative and false-positive rates of tubal patency tests and showed how kymographic tracings could be affected by bowel impinging on tube. We used to say that we never got as good tracings after trams stopped running past the hospital. I recall that impotence in returning prisoners-of-war, whose wives were anxious to catch up with others by starting a family, was treated by instructing the wives in self-AIH (artificial insemination by husband) with an eyedropper. As soon as pregnancy was confirmed, potency returned. My first contribution was a paper in 1949 on "Peritoneal pockets and sterility" in the first number of the proceedings of the Society for the Study of Fertility, the predecessor of the British Fertility Society.

To revert to the first conclusion; this was based on our limitations. In most cases we could not *treat* infertility, we investigated it. And our cheerful optimism was rewarded by some of the women arriving at the clinic already weeks or even days pregnant, and by others becoming pregnant between initial interview and first special tests. Our Canadian psychiatrist and others might claim that seeking medical help had transferred

the burden of infertility from the couple to us and released mental and, thereby, physical inhibitions. If to the two stated groups of early successes were added those who became pregnant more than a year after dismissal from the clinic with an optimistic rating of their chances of conception sooner or later, then nearly half of all those who became pregnant did so not directly due to our treatment. The corollary is that pursuing an infertile couple with a well-spaced programme of successive tests and treatments is rewarding for the doctors as well as for the patients, if only because most women do get pregnant. And if a woman conceives soon after a tubal patency or other test, as often happens, it is not necessarily because of it. One of my most grateful patients was a woman on whom I did a tubal insufflation and an endometrial biopsy on the 17th day of her normally 28-day cycle. The biopsy showed a secretory phase. She had no further period until after the birth of a mature baby 38 weeks later. I disclaimed credit for the success but she said I was being overmodest. I did not tell her that, on the contrary, I could have blown her fertilised ovum back out of the fimbriated end of the tube.

Perspective

That we should be critical of our successes is further evidenced in a wide-ranging review of male infertility by Hendry in the July 1979 number of the *British Journal of Hospital Medicine*. Thirty years ago we thought that seminal standards were generally set too high and that a gloomy prognosis was too often given. Of 57 men in our report with counts repeatedly below 10 million sperm per ml (but not nil), 19 of the wives became pregnant within a limited follow-up period. Hendry's figures for 1971-7 are similar. But what is the point of demanding three or four days' abstinence from coitus before providing a seminal sample for testing if the husband normally performs much more often?

In Liverpool 30 years ago Donald Young, an energetic expatriate Canadian and a congenial member of the Jeffcoate team, pioneered the surgical cure of obstructive azoospermia. Since then, advances in skill have brought increasing success, and the popularity of vasectomy an increasing demand for its reversal. A husband nowadays rarely refuses to provide a seminal specimen for analysis. It is less rare for him to refuse to attend the clinic. If two seminal specimens from a man who has not been seen show no sperm, then he must be examined. He may have Klinefelter's syndrome, which is untreatable. But if he is cryptorchid, while you may not be able to improve his fertility you may be able to save him from the risk of testicular malignancy. Operations for varicocele are now followed by pregnancy in the fertile wife in about half the patients treated, but post hoc is again not propter hoc. Three years ago a patient's husband with counts repeatedly below 5 million sperm per ml successfully impregnated her three months after his operation for a large left varicocele. A further sample when she was 16 weeks pregnant showed a count of 4 million sperm per ml.

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In the medical treatment of low-sperm count, arginine has been discredited, but good results have been reported with clomiphene, tamoxifen, and testosterone. Has anyone tried all three consecutively at spaced intervals to ascertain whether they are all equally effective in the same man? Similarly, when sperm antibodies were indicted as the cause of infertility, Hendry reported three pregnancies in 30 couples when the treatment was sperm-washing, and three in 20 and three in 17 with two regimens of steroid therapy. Is it relevant that, at the BMA meeting in Nottingham in April 1979, Miss Jequier cast serious doubts on the importance of sperm antibodies as a cause of infertility? Further, if Hendry's "non-specific" treatment in male subfertility is worth while for 3-4 months, because some pregnancies occur during that time, how do we know that success after specific treatment is always because of it?

In other words, is support in the scrotum as effective in a man as the crutch in the crotch in a woman? Has anyone recently reported a follow-up of couples whose treatment had been discontinued by patients or doctors to find out how many later achieved a pregnancy? In our 1952 series, 115 of the 324 women who conceived did so more than 12 months after all investigations and treatments had been discontinued.

Advances

All these doubts and questions do not minimise the considerable incontrovertible advances in knowledge and their application over the past 30 years. There was no satisfactory treatment for anovulation before Gemzell and his colleagues reported in 1958 the value of extracts of human pituitary glands. The recovery of gonadotrophins from menopausal urine and their use in tandem with human chorionic gonadotrophin from pregnancy urine made it easier and cheaper to induce ovulation. In Zagreb last autumn, Dr Asim Kurjac demonstrated to me at ultrasound scanning ripe ovarian follicles produced in response to menopausal gonadotrophins. If these number more than one, then withholding human chorionic gonadotrophin can prevent multiple ovulation and the possibility of multiple pregnancy. This is an easier and more direct alternative to measuring urinary or plasma oestrogens. While I was there he also, by chance, scanned a corpus luteum of pregnancy 21 days after ovulation. But I was particularly interested in his finding that serial scans sometimes showed a twin pregnancy at 7-10 weeks, but only one normal sac at 12-14 weeks. It seemed to me that the early death and absorption of one sac account for most episodes of so-called decidual bleeding, hitherto never convincingly explained, as well as probably many of threatened abortion which continue normally. This makes it wise to defer until after the first trimester telling a woman that a scan has shown a multiple pregnancy.

Whatever the value of ultrasound scanning in later pregnancy, it is going to teach us more about early pregnancy, normal or abnormal. The knowledge gained in a scientific advance may be more important than the advance itself—as became apparent most recently in the brilliant work of Steptoe and Edwards. Louise Brown was the manifest success of their tenacity of purpose, but in reaching this happy conclusion to extracorporeal fertilisation they illuminated many other facets of normal and abnormal conception and implantation. Incidentally, does not their work refute the belief that spermatozoa have to be capacitated in a woman's genital tract before they are capable of fertilising an ovum?

Soon after Gemzell's first publications came the introduction by Greenblatt in 1961 of clomiphene, a drug which could induce ovulation by a different pathway, either alone or with supplemental human chorionic gonadotrophin. In 1971 the isolation of the hypothalamic release factor or hormone LH-RH (or LH-FSH-RH) was a further step, though at present its main use is as a diagnostic and research tool. Next came the

discovery of hyperprolactinaemia, with or without thyroid disorder, discernible pituitary tumour, galactorrhoea, and even amenorrhoea, as a cause of anovulation. Treatment with bromocriptine in such cases has been so successful that the drug has been tried extravagantly for more tenuous indications—in women with subnormal luteal function, and even in unexplained infertility. Not surprisingly the results are unconvincing. The question remains whether, if the prolactin concentration is high after the puerperium, the drug should be withheld so long as the couple do not want another pregnancy; even so, it is still advisable to examine the woman periodically to exclude development of a pituitary tumour. And if medical advances seem to have outstripped the surgical, the popularisation of the laparoscope by Steptoe and the advertisement by Winston of techniques in microsurgical tubal reconstruction have been major developments.

In 1952 I wrote that the spontaneous abortion rate in women previously infertile was above average, but that the congenital malformation rate in their *viable* babies was not raised. I suggested that it was possible that it was an increased incidence of developmental abnormalities that accounted for the high abortion rate. Chromosomal analyses were not then available to us, but today the chromosomes of both partners should be checked in cases of unexplained infertility and of repeated abortion—especially if early.

Outlook

Investigations into infertility are naturally restricted to factors known to us to be relevant, so there is scope for the future—including research into the role of prostaglandins in fertility. Meanwhile, the specialist may combine a critical attitude with enthusiasm and the knowledge that about half the couples who will achieve a pregnancy will do so within six months of referral, investigation, or treatment. Regrettably, some general practitioners still insist that a couple have a minimum of two years' fruitless uncontracepted intercourse before being referred to a specialist clinic. This is illogical. If the woman is younger she should have become pregnant within one year, and if she is older she has no time to waste.

A final thought relates to artificial insemination by donor, now becoming more available in Britain as part of the normal free service. A woman who has an irretrievably sterile husband is now offered a reasonable chance of becoming a mother. But what about the fertile man with an untreatably sterile wife? There were at least 15 such among the 700 couples in our 1952 report. Will the time come when surrogate mothers will be made available to such men, to have and to hold the pregnancy until birth do them part from the fruit of their incubation?

What is the effect of phenytoin sodium (Epanutin) on potency and fertility?

Anticonvulsants diminish sexual potency and fertility in young male epileptics.¹ Abnormal sperm morphology and reduced sperm motility were prominent features in semen analysis in 45 out of 47 patients. In other studies with animals² phenytoin caused sterility in female rats—resorption of embryos and chromosome aberrations (abnormal metaphases) in the bone-marrow cells of the treated rats. Teratogenicity of phenytoin in man has never been established convincingly from case reports, and it is impossible to identify the extent to which either drug treatment or epilepsy cause teratogenic effects in epileptic patients. Phenytoin is excreted in human semen in small quantities,³ and this may possibly affect sperm morphology and motility.

¹ Christiansen, P, Deigaard, S, and Lund, M, *Ugeskrift for Laeger*, 1975, **137**, 2402.

² Roman, I C, and Caratzali, A, *British Medical Journal*, 1971, **4**, 234.

³ Swanson, B N, et al, *Drug Metabolism and Distribution*, 1978, **6**, 70.