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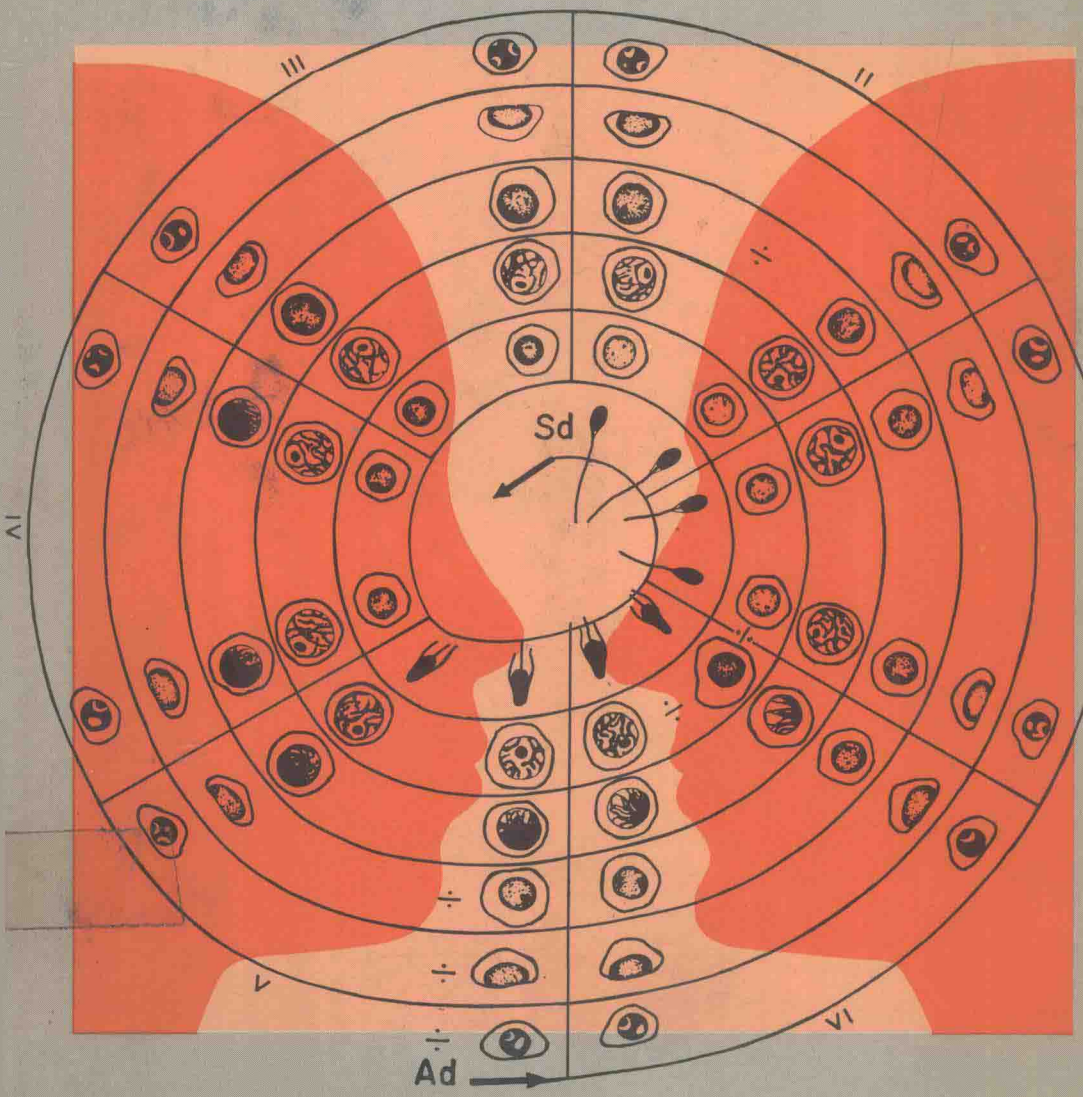
The Infertile Couple

Edited by
R. J. Pepperell
Bryan Hudson
Carl Wood



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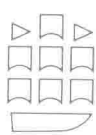

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The Infertile Couple

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Preface

In writing this book we have been conscious of the high standards set by Behrman and Kistner in their *Progress in Infertility*. Our aim has been to match these standards and to provide a problem-orientated approach to the investigation and treatment of the infertile couple as they present to the general practitioner, gynaecologist or physician.

Melbourne, 1980

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Contents

The problem of infertility

The management of the infertile couple presents a challenging problem always, a disappointing one often and a rewarding one sometimes. Several medical specialties may be involved in the management of the couple: the family physician who must decide that the couple are infertile and that further investigation is warranted; the gynaecologist or endocrinologist who must decide on and supervise the plan of investigation and treatment—should this be possible—and the urologist who may be called upon to intervene surgically. Paraclinical specialists may also be associated with the investigation of the couple. These include radiologists, and those with training and skills in semen analysis, in histopathology, in immunology or microbiology. Continued infertility can place psychological stresses on the marriage so that psychiatric intervention is sometimes required. If the couple's infertility cannot be corrected and adoption becomes the only possible means to provide them with a child, the social worker is likely to become directly involved. This book, to which a number of authors have contributed, has been written not only to help those who may be directly involved in the management of couples with infertility, but also for students and those physicians who wish to know more about recent trends in the management of infertility.

How should infertility be defined? Without contraceptive practices pregnancy can be achieved within 12 months by 75 per cent of couples (Southam, 1960). For this reason we believe that if a couple has not conceived after 12 months of normal sexual practice without contraception, they should be regarded as potentially infertile and be investigated. We would stress that this is a problem of two people and the physician who decides that the couple are potentially infertile should interview them together and explain the likely plan and scope of the investigations and, so far as it is possible, the reasons for the studies. All too often in the past and regrettably even today, the investigation and particularly the treatment of infertility are obscure and sometimes apparently mystical to the couple who have become desperate, sick at heart and disillusioned by being subjected to procedures of which they have little understanding or insight.

We regard it as axiomatic that the couple should be investigated simultaneously and the minimum investigations required are a semen analysis for the husband and an assessment of ovulation and tubal patency in his wife.

Accurate statistics on the aetiology of infertility are not available as all infertile couples do not present for treatment and many infertility clinics are referred patients with 'special' problems because of their known interest or expertise in this area.

During the 1970s the number of babies available for adoption in most Western countries has decreased significantly and this has led to an increase in the number of couples referred for consideration of artificial insemination, especially where the male has been shown to have mild or moderate oligospermia (Newton, Craig and Joyce, 1974).

Geographic and socio-economic factors must also be considered before broad statements are made regarding the causes of infertility. Genital tuberculosis is common in Scotland, the Mediterranean countries and South-East Asia, but is very uncommon in Australia, except in the immigrant population. Tubal obstruction due to gonococcal infection is common in parts of Africa and New Guinea, whereas obstruction due to post-abortal sepsis is the more usual cause in Western countries, particularly where legalized abortion is not freely available. In Western communities, socio-economic class may also account for differences in the incidence of disorders that may lead to infertility. Thus endometriosis and irregularities of ovulation are more common in patients in higher socio-economic classes, while the reverse is true for patients with tubal obstruction resulting from pelvic infection.

Table 1.1 Diagnosis of the causes of human infertility

	London* n = 440	Adelaide† n = 900	World‡ n = unknown
Disorders of ovulation	24·9%	43·3%	15%
Tubal obstruction	18·6%	11·0%	30–35%
Oligo- or azoospermia	21·6%	19·7%	30–35%
Mixed gynaecological problems	7·0%	26·0%	15–25%
Others	27·9%		

*Newton, Craig & Joyce (1974)
†Cox (1975)
‡Behrman & Kistner (1975)

Notwithstanding any differences that may be attributable to geographic or socio-economic factors, the identifiable causes of infertility and their approximate incidence are listed in Table 1.1. We would stress that there are many couples, perhaps 15 per cent of those whom we see, in whom appropriate investigations show abnormalities in both partners, especially mild to moderate oligospermia in the male associated with infrequent ovulation in the female.

The criteria by which a semen sample should be evaluated are discussed in Chapter 4 in which it is pointed out that it is not always easy to be absolutely certain whether a semen sample is abnormal. If the sample is abnormal, however, the test should be repeated on at least two more occasions and the husband investigated further along the lines described in that chapter.

The initial studies in the female require the demonstration that she ovulates regularly and has patent tubes. The assessment of ovulation can be done by instructing her about the symptoms of ovulation, making a basal body temperature record and by measurement of urinary pregnanediol or plasma progesterone in the mid-luteal phase of the cycle. It is crucial that an ovulatory disorder be recognized, since most are amenable to treatment. For about 65 per cent of women with ovulatory failure the treatment is relatively simple. Although induction of ovulation with gonadotrophins is a more complex and expensive regime of treatment, the success rate is sufficiently acceptable to warrant the use of this approach for women whose

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ovulatory failure has not responded to more simple therapies such as clomiphene citrate or bromocriptine. An extensive account of the diagnostic procedures used for the detection of disorders of ovulation and for their treatment is outlined in Chapter 2. At the risk of being repetitious, we would stress that these are potentially curable causes of infertility and should not be overlooked.

The union between sperm and egg is the very core of the reproductive process, another essential feature of which is the transport of the egg to the outer third of the Fallopian tube where this union takes place. Hence the investigation of tubal structure and function is an essential procedure in women who have ovulatory cycles and whose partners have been shown to have normal, potentially fertile semen samples. Abnormalities of tubal function account for approximately 30 per cent of women with infertility. The most satisfactory procedure for the investigation of tubal structure and function is laparoscopy. Fibre optics have made this procedure a safe one with a high pay off but, we would stress, only in the hands of the gynaecologist trained in this technique. In addition to the assessment of tubal patency, laparoscopy can delineate tubal anatomy and may reveal kinks and tortuosities in the Fallopian tubes that would not be shown by an hysterosalpingogram. This is now a 'second best' method for the demonstration of tubal patency, but a necessary one when laparoscopy may be deemed unsafe, for example in patients with a history of major lower abdominal surgery or sepsis. An added advantage of laparoscopy is that it will demonstrate abnormalities other than those of the Fallopian tubes, which often cannot be diagnosed on routine clinical examination. It is particularly useful in the diagnosis of endometriosis, the treatment of which is discussed in detail in Chapter 7.

If tubal obstruction is shown by laparoscopy, can this be corrected? Sometimes, yes. Advances in microsurgical techniques over the past two decades or more have enabled successful plastic microsurgery for tubal disorders that would not have been possible for a preceding generation. The different types of tubal lesions encountered and the surgical approaches used to correct these are described in Chapter 3. Although this is a moderately technical account, it highlights nonetheless advances which have taken place in this particular field, and will provide the reader with a better insight into these problems. There remains, of course, a substantial number of women with irreparable tubal disease or persistent tubal obstruction after tubal surgery.

Are these couples forever destined to remain childless? In most Western communities today this will certainly be the case because of the very limited number of children available for adoption. It is for the couple with irremediable tubal disease particularly, that a union between basic and applied medical science has been consummated. For many years our colleagues in veterinary science have been able to transfer ova fertilized *in vitro* to surrogate mothers. Stimulated by these successes, gynaecologists and reproductive biologists have worked together and dedicated themselves to the *in vitro* fertilization of the human ovum and the transfer of the fertilized ovum into the uterus of the mother. Although success in these endeavours has been very limited, the concept and reality of the 'test tube' baby is now widely appreciated by virtue of spectacular media publicity. The indications for and the extraordinary difficulties of this procedure are described in Chapter 10. It has been argued that this procedure is not an acceptable one on moral grounds. We believe that the new knowledge gained from these studies about early human embryogenesis is important. For the couple with a disorder for which this procedure is indicated and

has a chance of success, we do not believe that the issue is either one of ethics or morality. It is clear, however, that in the foreseeable future *in vitro* fertilization and embryo transfer will be a therapeutic approach to overcome infertility in very few centres.

While the causes of infertility in many women are well understood and rational treatments are now feasible, the same cannot be said for men with infertility. The management of the infertile male provides little satisfaction to the physician who enjoys recognizing causes, understanding pathology and applying logical treatment with a good prospect of success. We have already indicated that the criteria by which a male should be judged infertile are not clearly defined. It is possible to understand why men with a history of bilateral cryptorchidism are infertile and why men with chromosomal abnormalities such as Klinefelter's syndrome have no germ cells. It is also possible to appreciate that men who have germinal cell aplasia or arrest cannot make sperm, even though the cause of their condition may not be understood.

The difficulties arise in those men who have a slight reduction in their sperm count, but only minor changes in their seminiferous epithelium, no abnormalities in hormone secretion and often adequate numbers of morphologically normal sperm. The assessment of these men is frequently made more difficult by the substantial changes in semen quality that may occur from week to week. This applies not only to absolute numbers but also to motility, which is certainly the most important quality of sperm but which is still a subjective measurement in nearly all laboratories which undertake semen analysis. More sophisticated equipment for the measurement of motility is being introduced which, while it may enable more objective measurements to be made, does not identify the cause of the problem nor assist with a cure. A common association is between varicocoele and low sperm motility. Although we know that improvements in semen quality occur after varicocoele ligation we do not know the reason for this, nor do we know why the operation is apparently successful in some patients and a failure in others. Despite the many theories advanced, it is not known why defects in spermatogenesis are found in patients with varicocoele.

The finding of low motility in otherwise normal men with normal sperm counts is a cause of further uncertainty and quandary. In some of these men there may be an immunological cause, such as immobilizing antibodies, that can be demonstrated in the patient's serum or seminal plasma. In the past studies of this type usually have not been undertaken as part of the conventional investigation of the man thought to be infertile. The potential of immune disorders as a cause of infertility is discussed in Chapter 6, which also outlines the many diagnostic approaches that have been used to demonstrate immunological abnormalities in the infertile couple. Particular reference is made to the importance of using donor sperm and cervical mucus. The techniques and possible outcomes of these tests are described in further detail in Chapter 5. Both of these chapters illustrate the meticulous care that must be taken in the conduct of tests in which both the husband and wife are involved. For many, busy in the practice of gynaecology or internal medicine, the logistics of tests which have to be carefully timed and demand skills in interpretation, become almost insurmountable unless they have access to trained staff in large hospital departments.

In the face of these difficulties it is germane to ask: what is the outcome if an immunological incompatibility between the couple can be demonstrated or if it can be shown that the male has antibodies that immobilize sperm? The various

treatments that have been described are not outstandingly successful; the use of high dose corticosteroids as immunosuppressive agents carry potential risks in a clinical situation that does not threaten life. While these tests may provide an explanation for the infertility, this discovery may be of little comfort to the couple other than the knowledge that a cause has been found. In this chapter, Jones acknowledges his attitude of therapeutic nihilism for these couples.

In the treatment of men with infertility one may also be understood for having a similar attitude. The success of varicocele ligation is not remarkable, and some remain unconvinced that this procedure is warranted, although we would always recommend it when a varicocele is discovered in a man with oligospermia or low motility. Is there any evidence that any treatment is useful for the large group of men with idiopathic oligospermia? Probably not: many have been tried and not one has been shown to be singularly successful. When success has been claimed this has rarely been supported by a properly controlled trial. Although infection of the genital tract is known to be associated with defects in sperm morphology and motility, it is not possible to know how important this is; indeed there is no general agreement as to the diagnostic criteria for infection. This ignorance only compounds our difficulties in investigating and treating the infertile man. Unfortunately (in the therapeutic sense) men with endocrine abnormalities as a cause of their infertility are few in number. Hyperprolactinaemia, a relatively common cause of anovulatory infertility in the female, is found only infrequently in men. Treatment of men with idiopathic oligospermia and normal prolactin levels with dopamine receptor agonists has not been successful. Gonadotrophin deficiency can be treated and is the only indication for the use of gonadotrophins in men.

What can be offered those couples in whom the male partner has a defect in sperm production which is not amenable to treatment? For those who are prepared to accept it, artificial insemination by donor sperm (AID) is the treatment of choice. Although this approach is not new, it has become increasingly common, partly because of an increased demand resulting from the unavailability of children for adoption. The methods and indications for the use of AID are described in Chapter 9. This is a most comprehensive account of an excellent facility developed in association with an academic department of Obstetrics and Gynaecology. This service also poses substantial logistic problems for those who conduct it. Matthews gives an excellent account of these; the availability and selection of donors, the cryopreservation of sperm, the advantages of fresh versus preserved sperm and the overall success rate of their programme. He also discusses the potential ethical and legal problems of this procedure, for which legislation has been enacted in very few countries or states. More and more couples in whom the male is the infertile partner are now accepting this procedure to overcome their childlessness, but there are some who cannot accept it either on personal or moral grounds.

Even in a well organized and carefully monitored AID service there is still a residual number of women who do not become pregnant. In the majority of these women there is no obvious reason for their failure to conceive. There is known to be a group of apparently normal couples who by the most stringent criteria are normal, and constitute a small proportion of all infertile couples. We felt it was important to describe our experience with this group since they are the cause of concern, quandary and frustration. This problem is outlined in Chapter 8 and the methods used to

investigate and treat these couples are described. It is encouraging to note that with attention to detail and what might be called 'tender loving care' more than 60 per cent of these couples successfully conceive. Could this be called a placebo response? Such a response may occur during the initial investigations of women with presumed anovulatory infertility. If this is indeed a placebo response, what role has the psyche as a cause or contributing factor to a couple's infertility?

The final chapter attempts to define the possible role of psychological factors in infertility and the way in which couples may be helped to overcome these. While it is extremely difficult, or even impossible, to prove an association between psychological factors and infertility, there is good evidence of the influence of these factors at the extremes of disordered behaviour. One is the ovulatory failure that occurs in patients with anorexia nervosa, in whom ovulation may be re-established with successful treatment of the disorder. Sperm quality has been shown to become impaired in medical students under the stress of examinations. Failure of ovulation is not uncommon in young, otherwise healthy girls who take up nursing and are subject to the rigours of training in the early days of their vocation. We do not believe that psychiatric intervention is warranted for the vast majority of infertile couples. What is required, however, is empathy and understanding between the physician and the couple, an essential ingredient of which is frankness and honesty about what must be done by way of investigation and what may be offered by way of treatment.

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Disorders of ovulation

CLASSIFICATION OF DISORDERS OF OVULATION

Disorders of ovulation are best subdivided into the clinical conditions of:

1. Primary amenorrhoea—no spontaneous bleeding by the age of 18 years,
2. Secondary amenorrhoea—no spontaneous bleeding for periods of six months or more. These patients are often further subdivided into (a) amenorrhoea for 6–12 months, and (b) amenorrhoea for more than 12 months,
3. Oligomenorrhoea where cycles are occurring at intervals varying between six weeks and six months; these may be further subdivided into ovulatory and anovulatory function,
4. Anovulatory cycles—where cycles are of three to six weeks' duration but are anovulatory, and
5. Ovulation occurs as judged by the usual criteria but follicular development or corpus luteum function is deficient and the patient remains infertile.

When the presenting symptom is amenorrhoea, a uterine cause for the amenorrhoea (viz. uterine absence, Asherman's syndrome) must be excluded before failure of ovulation can be assumed.

In order to understand the investigations and treatment required in patients with disorders of ovulation, an appreciation of the endocrinology of the normal menstrual cycle and of the physiological basis of the tests applied is essential.

ENDOCRINE RELATIONSHIPS DURING THE NORMAL MENSTRUAL CYCLE

The present discussion of the normal menstrual cycle deals mainly with pituitary and ovarian function although many other endocrine organs and neural connections can influence the pituitary-ovarian axis. The timings given are for an average 28-day cycle. The cycle is initiated by an early follicular phase rise of FSH and peaks of FSH and LH occur at mid-cycle in association with ovulation (Jacobson *et al.*, 1968; Midgley and Jaffe, 1968; Ross *et al.*, 1970). Both gonadotrophic hormones are present in significant amounts at all stages of the cycle, their levels being generally higher in the follicular phase than in the luteal phase (Fig. 2.1). The early follicular phase rise of FSH commences just prior to the menses ending the previous cycle and probably occurs in response to the fall in progesterone and oestrogen secretion which results from regression of the corpus luteum. This pre-menstrual rise continues for

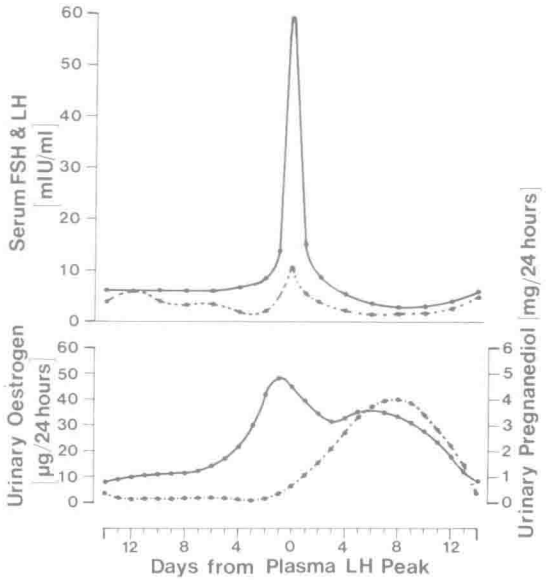

Fig. 2.1 Changes in plasma FSH (-------) and LH (———) and in urinary oestrogens (———) and pregnanediol (....) through the normal menstrual cycle centred on the day of the plasma LH peak.

the first four to five days of the follicular phase and is responsible for stimulating a group of follicles into their rapid growth phase. Although FSH alone, in pharmacological amounts, can achieve adequate follicular maturation, the presence of a small amount of LH greatly enhances this effect and seems to be necessary for steroidogenesis (Jones et al, 1969; Midgley et al, 1971; Bertrand et al, 1972; Araki et al, 1972). As the follicles are activated oestrogen secretion begins to increase and during the second week of the follicular phase this increase becomes exponential, being derived mainly from the rapid growth of the follicle which is to ovulate. Increasing oestrogen secretion operates a negative feedback mechanism and FSH levels fall; LH levels tend to rise gradually at this time. When a critical level of oestrogen secretion is reached this operates a positive feedback mechanism which results in a conspicuous surge of LH secretion, together with a smaller but significant peak of FSH secretion. The surge in LH lasts for approximately three days, with the peak value occurring on the second day; the LH initiates ovulation and luteinization of the ruptured follicle by a mechanism not completely understood.

The secretion of oestrogen declines markedly during the 24 hours before ovulation, then rises again in parallel with the secretion of progesterone by the corpus luteum and falls before onset of menstruation. The pre-ovulatory fall in oestrogen secretion coincides with an increase in sensitivity of the follicle to LH at mid-cycle (Zeleznik et al, 1974; Brown, 1978). The high levels of steroids synthesized by the corpus luteum suppress secretion of both FSH and LH during the luteal phase and, in the absence of pregnancy, the decline in steroid secretion at luteal involution is followed by a rise in FSH secretion which initiates the next cycle of follicular development. Luteinizing hormone has been shown to be necessary for the maintenance of the corpus luteum (Van de Wiele *et al.*, 1970), and Lee *et al.* (1973) have demonstrated specific receptors for LH in human corpora luteal tissue.

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