

Update on infertility

Assessment and management in primary care

Wayne Gillet

Definitions and epidemiology

Infertility is defined as the inability to conceive after one year of trying for a pregnancy. With an estimated 25% of couples being likely to suffer from infertility at some time in their lives, the National Health Committee in New Zealand has recognised infertility as an important health disability.¹ Many causes of infertility are associated with a physical and/or emotional disability. The emotional and social disability involves a reduction in the quality of life, and anxiety and depression are similar to other chronic medical conditions. The physical disability may require health resources in their own right, apart from those required to treat the infertility. For example, about 10% of women with infertility suffer from moderate to severe endometriosis, and of these most have menstrual or chronic pain. For these women, effective health care involves both conventional treatments (e.g. surgery) and assisted reproduction (e.g. IVF).

Epidemiological studies have suggested that the prevalence of infertility has not changed over the last three decades although there has been a significant increase in the use of medical services in this time. This increase is for various reasons and relates to the tendency for delayed childbearing, ageing of the baby-boom generation, and increasing treatment options. In New Zealand approximately 3 500 new referrals are made each year to either a secondary or tertiary service.

Female problems account for 25% of causes, in 25% the problem is predominantly male, in 25% it is both

partners and the remainder have no clear-cut cause.

Primary care assessment

Although most of the effective care strategies that will help the infertile couple reside with secondary and tertiary level services, there is still a very important place in the primary sector to evaluate and help many cases. The primary aims in primary care are two-fold:

Firstly to assess the likely severity of a couple's infertility; the more severe cases require prompt referral. The less severe may be helped by simple measures that can be directed by primary care providers.

Secondly to provide simple management strategies that will assist all infertile couples.

Taking a history – what are the key questions?

Table 1 lists key questions that will guide the evaluation of the infertile couple. This Table is a guide only and is not intended to be exhaustive.

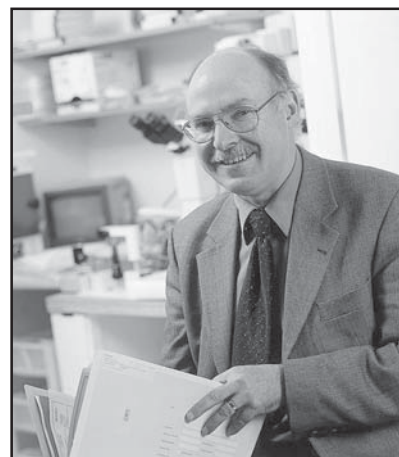
Management measures in primary care

Refer early if:

- A positive history is obtained.
- There is unexplained infertility of \geq 18 months.
- The female age is \geq 35.

Advice on smoking control

Stopping may improve fertility by as much as 40% for the woman and may improve male fertility.



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Assessment of rubella immunity

Vaccination for women who do not have immunity is strongly recommended.

Folic acid

Folic acid is known to diminish the risk of some fetal abnormalities, particularly spina bifida and other neural tube defects, 0.8 mg daily is recommended; 5mg should be prescribed if there are additional risk factors. This

is a Health Department recommendation for any woman planning a pregnancy starting four weeks before they might become pregnant through to 12 weeks of pregnancy. Diet alone does not provide sufficient folic acid. The use of multivitamins at the time of becoming pregnant is not advised.

Weight improvement programmes

Weight improvement programmes for the woman will improve the outcome of most treatments. The body mass index (BMI) is used to define women who are underweight or overweight (e.g. a woman who is 170 cms tall and weighs 92 kg will have BMI of 31.8). In women with a BMI under 18 or over 30 (32 for Māori and Polynesian women), the ovary is particularly affected and may affect the menstrual cycle. Responses to fertility treatments can be either poor or even excessive (thereby increasing the risk of complications). Even if a good outcome is obtained, these women are at risk of having health problems in their pregnancy. Most tertiary level services strongly encourage weight reduction before starting any treatment if a woman has a BMI over 32, and will not treat if the BMI is over 35. The added anxiety and stress that weight problems will produce adds to the burden of the infertility and makes it extremely difficult for many women.

Counselling

When concentrating on the medical issues there is a danger that the emotional impact of infertility is neglected. The GP is in an ideal position to recognise early problems and offer advice and direction early in the process. Infertility and its associated investigations and treatments is emotionally demanding for many couples. Infertility may affect people's self confidence, their communication with each other, their sexual relationship and their life plans. Responses to infertility involve a whole range of feelings that may include sadness, grief, anger, guilt and isolation. Treatment for infertility adds further stress, whether it be physical, emotional or financial.

Table 1. Key questions that will guide the evaluation of the infertile couple

| History | Significance |
|--|---|
| Female age | Fertility declines as women grow older. A general principle is that women aged 25–34 will have an average pregnancy rate of about 90% after one year. In the 35–39 year age group this will reduce to about 70% and to 60% if their partner is older. A 40- to 44-year-old women's fertility is about 40%, and over 45, about 10%. |
| Duration of infertility | Clearly many factors will influence the duration of infertility. Age, physical abnormalities, coital practices, to name the main contributors. The longer the duration the less likely there will be a spontaneous resolution. |
| Past history of pelvic surgery, pelvic inflammatory disease, STDs | All may cause tubal damage or pelvic adhesions. A past history of pelvic surgery is the single most common cause of ovarian adhesions. |
| Regular menstrual cycles | Is an excellent predictor of normal ovulation, conversely, irregular or infrequent menstruation is an excellent predictor of an ovulation disorder. About 20% of all women have polycystic ovaries that may be expressed as an irregular menstrual cycle. Weight gain and signs of androgen excess (hirsutism) are added features of the polycystic ovary syndrome that affects about a quarter of all women with polycystic ovaries. |
| Pelvic pain | For all specialists dealing with young women with pelvic pain there appears to be a significant increase in cases with severe endometriosis. Any woman with dysmenorrhoea persisting more than a day should have endometriosis as a primary diagnosis, since the consequences of the severe condition will make a life long disability. Does the woman experience painful defecation? If she does this warrants urgent assessment. |
| A male history of genital pathology, urogenital surgery, STDs | All of these conditions lead to impaired spermatogenesis or problems with sperm transport. There are vast arrays of environmental factors that may influence male infertility, from tight underwear to industrial chemicals, but a detailed assessment and knowledge of these is generally unhelpful in making a diagnosis. |
| Coital frequency and difficulties | Coital frequency does influence the rate of achieving a pregnancy. A Canadian study demonstrated that the probability of conceiving was at its highest when intercourse was a daily event (0.37); was still excellent with 3–4 times per week (0.33) and reduced to 0.15 if intercourse was on average once a week (see below for advice on timing). Psycho-sexual difficulties in either the male or the female partner are a less common cause of infertility, but should be sensitively sought early in the consultation to aid early intervention. In addition, many commonly used drugs may affect the sexual performance. |



Figure 1. A three-cell embryo (two days old).

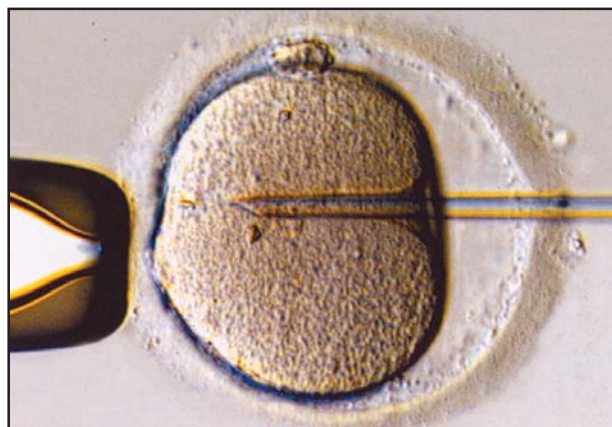


Figure 2. An oocyte being injected by a sperm. This process, ICSI, has revolutionised IVF to make it accessible for even very male factor problems.

All tertiary level services provide counselling for couples preparing, undergoing or recovering from assisted techniques.

Fertility awareness

The fertile phase is a five-day period preceding ovulation and ending on the last day of ovulation. For a woman with a menstrual cycle length of 28 days the fertile phase will begin on day 9–10 and finish on day 14–15. For a woman with an irregular cycle pattern this phase may be potentially quite variable and this adds to their frustration. In this circumstance ovulation defects should be actively sought.

There is no evidence that the use of temperature charts and LH detection kits to time intercourse improves outcome. They are useful aids to assist women with a knowledge about their cycle, but other than this they should be discouraged to time intercourse. Couples should be advised about the fertile phase and for them to use this to enhance their sexual relationship with a practice that suits them.

Investigations

Unfortunately there are few good investigations. Investigations that can act as a guide to therapy are of better value than those that only explain the cause of infertility. Not many can

achieve this without significant interpretation bias. The problem is of such concern that there is little uniformity in the diagnostic criteria used for classifying patients. The semen analysis is a good test when abnormalities are severe, but are poorly predictive when defects are borderline. Tests that are useful in primary care include:

Health screening tests for the female partner – rubella immunology, hepatitis B antigen, blood group antibodies. There is an increasing concern about HIV in pregnancy and this test should be offered.

Routine semen analysis, repeated in four to six weeks if abnormal.



Figure 3 (left): An embryologist working in a specially adapted incubator looking at embryos. Figure 4 (above): The embryologist injecting an egg.

Assessment of menstrual cycle including:

- A plasma progesterone timed for five to nine days before the next expected period. If the cycle is long, it should be repeated at weekly intervals until next period;
- A plasma FSH, LH and prolactin if the cycle is prolonged and/or irregular;
- An ultrasound of pelvis for women with suspected polycystic ovaries or who have an abnormal pelvic exam, or who have unexplained pelvic pain.

Ongoing support

Even though a couple may be referred to a secondary and tertiary level service the GP has a role in providing support for the couple as they go through (often) difficult management choices, decisions when to stop, and problems that may be encountered.

Overview of secondary and tertiary care

One of the striking changes in secondary and tertiary care management in the last decade has been the increasing and efficient use of the assisted reproductive techniques (ART). Gone are the days where years were taken in inefficient investigations and treatments, and today most couples are guided by the CPAC model (see next section) to plan their future with much more certainty than ever before. The resolution of uncertainty goes a long way in helping couples deal with the emotional distress of infertility.

Secondary and tertiary providers will complete appropriate investigations and hopefully enable couples to define their options quickly. The following treatments provide a summary of what options do exist for couples.

No specific treatment, waiting for the expectation of natural resolution

Waiting a period of time may result in a successful outcome. If the period of infertility is relatively short, or the infertility is unexplained, then waiting may be all that is necessary.

A criticism that is often levelled at IVF clinics is that IVF is undertaken too soon, where watchful expectancy may be all that is required.

Ovulation induction

Clomiphene citrate is the mainstay for ovulation induction. Treatment programmes may be monitored by the GP and, in general, the duration of treatment is limited to less than one year in duration. Should treatment not be successful in this time frame the move to more efficient therapy, including ART, is indicated.

For women with the polycystic ovary syndrome, if clomiphene is not successful, ovarian drilling may be used. This is a laparoscopic method of 'debulking' the ovary. Recently, metformin has been shown to help in cycle control for both obese and

non-obese individuals with polycystic ovaries.

Surgery

In New Zealand microsurgical expertise is available in all main centres. It is the mainstay of treatment for both men and women requesting reversal of sterilisation. More specific tubal abnormalities are also helped by microsurgery, but by and large IVF is replacing many of the older surgical treatments.

Endoscopic surgery is useful for less severe abnormalities, including adhesions, and is the primary form of treatment for women suffering from endometriosis.

In vitro fertilisation (IVF)

IVF is now the most effective and efficient treatment for almost all types of infertility. IVF involves:

- Hyperstimulation of the ovary using recombinant gonadotrophins; typically about 10 oocytes are obtained.
- Inseminating or injecting each oocyte with sperm. Intracytoplasmic sperm injection (ICSI, pronounced 'ick-see') is the process where each oocyte is injected with a single sperm. ICSI has revolutionised the management of male factor infertility. Prior to the mid-1990s the only real option for couples with a severe sperm defect was donor insemination (DI). Nowadays these couples have an excellent chance of having their own baby with ICSI.
- Typically one would expect about six normal embryos from the 10 oocytes. Two are transferred back into the uterus two to three days after fertilisation, and the remaining embryos are frozen and stored for subsequent use.

In the New Zealand context IVF has been shown to be cost effective.¹ Success is defined by the chance of a couple having a baby at the end of treatment (the live-birth rate). It is dependent on the age of the female recipient and for women less than 35 years a live-birth rate per commenced IVF treatment is expected to be about 20–30%. For women over 40–44 years this reduces to 5–10%. Thawing the frozen embryos for later use increases the chances of success by 15–20% per transfer. The number of embryos transferred is also a factor in the success of IVF. Most clinics report better success when more than one embryo is transferred, but this has to be balanced with the increased risk of multiple pregnancy. Few clinics offer a single embryo transfer because of the lower success.

Artificial insemination

Previously called AIH, it is now commonly described as IUI (intra-uter-

ine insemination). The majority of clinics in New Zealand advocate the use of IUI as a simpler and less harmful treatment than IVF.

Using donor gametes

Donor insemination (DI) with sperm has been used in New Zealand for over 20 years. Nowadays about a third of all donor treatments are used by single or lesbian women. Donor oocytes are becoming a common practice in all tertiary centres. In this situation the donor needs to go through with an IVF treatment. The recipients of the embryos include women with premature menopause, but an increasing number of older women (40–50) are using this facility.

The future in treatment options

As the understanding of the genetic link with many infertility conditions increases, new and effective treatments may become available. Already there are facilities that will enable the diagnosis and management of genetic conditions using IVF technology, or even being able to recognise the embryos that are likely to survive or not survive.

An area of development that will take place in the next few years is the introduction of legislation that will guide (and bind) infertility practices. For instance the current practice of donor anonymity in providing sperm or oocytes may well become a thing of the past as new legislation will identify what access (and how) a child may have to previously non-identifying information.

Public funding, the clinical priority access criteria (CPAC) model

In 1999 a significant increase in public funding for assisted reproduction occurred. As of 2002, approximately \$5.8 million is dedicated to assisted reproduction in six tertiary level

services. These funds provide about half of all ART services provided by the infertility clinics. Eligibility for publicly funded ART is directed by a priority point system that includes the age of the woman, the cause of the infertility, the duration of the infertility and the number of children a couple already has.² It is a system that directs treatment to those who are most in need of it and who are most likely to benefit from it.

The maximum 'score' a couple can reach is 100 points. In general, the lower the score the more likely a couple will achieve their own family by natural means. This certainly applies to scores less than 50 points. The current 'cut-off' for eligibility is 65 points. It is not a perfect system and eligibility for some needy couples may still take a few years to achieve.

Funded treatment will enable a couple to have one treatment using the IVF programme or four treatments using IUI or DI. The one IVF treatment includes the use of all frozen embryos obtained from that treatment. Despite this increase in funding, New Zealand infertile people are still a long way behind the access that Australian couples enjoy. There, IVF access is unlimited, being supported by the Medicare system. It is hoped that future New Zealand Governments will recognise the importance of fertility enhancing treatments and that they no longer are the expensive cost-inefficient services.

Further information

The NZ Fertility Society is a national organisation for those who are experiencing fertility difficulties. For further information contact: Robyn Scott, Executive Officer P O Box 34 151, Birkenhead, Auckland. Ph: 04-4795 952 or 0800 333 306 Fax: 04-4795 245 Email: nz.infertility@clear.net.nz

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