The Practitioner

Optimising the management of patients with infertility

Child T. Optimising the management of patients with infertility. *Practitioner* 2013; 257 (1759):19-22

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Medical Publishing Ltd

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A normal female pelvis at laparoscopy

What are the main causes of infertility?

INFERTILITY AFFECTS AROUND ONE IN SEVEN COUPLES OF REPRODUCTIVE AGE.[1]

In February 2013, NICE published a revised guideline on the assessment and treatment of fertility problems[2] which updated the recommendations in the 2004 guideline.

The aim of the updated guideline is to enable healthcare professionals to help people affected by infertility access the most appropriate NHS investigations and treatments at the right time and in the right setting. A number of treatments have been found to be ineffective and not to warrant NHS funding.

The main causes of infertility are shown in table 1, right.

How should patients be investigated?

ASSESSMENT

The woman and her partner should be seen together as both will be affected by decisions about investigations and treatment. The environment in which investigation of fertility problems takes place should enable people to discuss sensitive issues such as sexual abuse.

It is important to reassure patients that more than 80% of couples will conceive within one year if the woman is under 40 and they have regular sexual intercourse. Of those who fail to conceive in the first year, around half will do so in the second year giving a cumulative pregnancy rate > 90%.

Where there are concerns about delays in conception patients should be offered an initial assessment which is likely to be in primary care. It is important to enquire about »

Table 1

Main causes of infertility
Female factor
● Anovulation
● Tubal damage
● Endometriosis
● Ovarian failure
Male factor
● Absent or low numbers of motile sperm in the ejaculate
● Erectile dysfunction
Unexplained infertility

What are the evidence-based treatment options?

Table 2

Primary care investigations

Women
● Ovulation test — mid-luteal progesterone
● If irregular/absent cycles do FSH & LH (day 2-5 if cycling), prolactin and TSH, and transvaginal ultrasound scan (look for PCO)
● Tubal patency — HSG or HyCoSy after confirmation of normal semen analysis (tubal tests may need to be requested from secondary care)
Men
● Semen analysis

lifestyle and sexual history to identify those who are less likely to conceive.

A woman of reproductive age who has not conceived after a year of regular sexual intercourse, and has no known cause of infertility, should be offered referral for further clinical assessment and investigation with her partner.

However, if the woman is 36 years or older, has a known clinical cause of infertility or a history of predisposing factors, she should be referred sooner.

In cases where patients are planning to undergo treatment that may result in infertility, such as treatment for cancer, early fertility specialist referral should be offered. Patients who have chronic viral infections such as hepatitis or HIV should be referred to centres that have appropriate expertise and facilities to provide safe risk-reduction investigation and treatment.

LIFESTYLE FACTORS AFFECTING FERTILITY

Women who are trying to conceive should be told that limiting drinking to no more than one or two units of alcohol once or twice per week reduces the risk of harming a developing fetus. For men, alcohol consumption within the recommended limits of three to four units per day is unlikely to affect the quality of their semen.

Smoking in women, including passive smoking, is likely to reduce the chance of conception. For men, an association between smoking and reduced semen quality has been found, although the effect of this on fertility is unknown.

Dietary supplementation with folic acid 0.4 mg/day, before conception and up to 12 weeks gestation, reduces the risk of neural tube defects. For women who have previously had an infant with a neural tube defect; who are being treated with antiepileptic drugs; or have diabetes a dose of 5 mg/day is recommended.

Obese women (BMI $\geq$ 30) are likely to take longer to conceive. If they are not ovulating then losing weight is likely to increase their chance of conception. Men with a BMI $\geq$ 30 are also likely to have reduced fertility. Women with a BMI < 19 who have irregular or absent menstruation should be advised that putting on weight is likely to improve their chance of conception.

Some prescription, over the counter, and recreational drugs interfere with fertility so it is important to ask the woman and her partner about any drugs they are taking.

Intercourse every two to three days optimises the chance of pregnancy. Those who are using artificial insemination to conceive should have insemination timed around ovulation.

INVESTIGATIONS

Investigations that can be carried out or ordered in primary care are listed in table 2, above.

Suspected ovarian disorder

The majority of women with regular menstrual cycles are ovulating. The best test is an appropriately timed mid-luteal serum progesterone level. The blood should be taken seven days before the subsequent period (e.g. day 25 of a regular 32 day cycle). If the cycles are irregular then tests may need to be repeated weekly until menstruation occurs.

Women with irregular or absent menstrual cycles should be offered a blood test to measure serum gonadotrophin levels (FSH and LH).

Suspected tubal and uterine abnormalities

Women with no known comorbidities, such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis, should be offered hysterosalpingography (HSG) or hysterosalpingo-contrast-ultrasonography (HyCoSy) to screen for tubal occlusion.

Those with comorbidities should be offered laparoscopy and dye so that tubal and other pelvic pathology can be assessed.

Semen analysis

The semen analysis results should be compared against current WHO reference values. If the first semen analysis is abnormal, the test should be repeated, ideally three months after the initial analysis, to allow the first cycle of spermatozoa formation to be completed. However, if a gross abnormality such as azoospermia or severe oligospermia has been found, the test should be repeated as soon as possible.

TREATMENT

Unexplained infertility, mild endometriosis and mild male factor infertility

If the pelvis is normal, the woman is ovulating and the semen analysis normal then the diagnosis is unexplained infertility. The appropriate treatments are also similar for women with mild endometriosis and men with mild male factor infertility.

'Oral ovarian stimulation agents such as clomifene citrate should not be offered [for unexplained infertility]'

Oral ovarian stimulation agents such as clomifene citrate should not be offered as they do not increase the chances of a pregnancy or a live birth. Expectant management is appropriate. Furthermore, do not routinely offer intrauterine insemination (IUI), either with or without ovarian stimulation. This is a major change from the 2004 guideline. Couples should be advised to try to conceive for a total of two years (including up to one year before their fertility investigations) before in vitro fertilisation (IVF) should be considered.

Unstimulated IUI can be considered as a treatment option in the following groups as an alternative to sexual intercourse:

- Patients unable to have vaginal intercourse because of a physical disability or psychosexual problem who are using partner or donor sperm
- Patients with conditions that require specific consideration in relation to methods of conception (e.g. after sperm washing where the man is HIV positive)
- Same sex couples

When conception has not occurred after six cycles of donor or partner insemination, despite evidence of normal ovulation, tubal patency and semen analysis, a further six cycles of IUI should be offered before IVF is considered.

Suspected tubal and uterine disorders
If the tubes are patent, but endometriosis is present in the pelvis, then surgery should be offered. Surgical laparoscopic ablation or resection of minimal or mild endometriosis plus adhesiolysis has been shown to increase the chance of pregnancy, and may also result in a reduction of any co-existing pelvic pain. Women with moderate or severe endometriosis should be offered surgical treatment. If ovarian endometriomas are present then laparoscopic cystectomy (rather than drainage and attempted ablation of the cyst) is appropriate since this leads to a higher rate of natural conception, and a lower rate of cyst recurrence.

If tubal damage or intra-uterine adhesions are diagnosed on HSG, or laparoscopy and dye then treatment options will depend on the disease severity and type.

For mild tubal disease surgery to open the tube may be more effective than no treatment. If the tubal obstruction is proximal then either selective salpingography plus tubal catheterisation (under radiological guidance) or hysteroscopic tubal cannulation may be options to improve the chance of natural conception.

In women with amenorrhoea, who have intrauterine adhesions, hysteroscopic adhesiolysis is more likely to restore menstruation and improve the chance of pregnancy.

These radiological and surgical techniques may not be available in all centres.

The presence of a hydrosalpinx visible on ultrasound is associated with a significant reduction in the likelihood of live birth following IVF. Salpingectomy of the affected tube(s), ideally laparoscopically, restores the IVF success rate. The same effect (of preventing fluid from the hydrosalpinx leaking into the uterine cavity and affecting implantation) can be achieved by laparoscopically clipping or dividing the proximal part of the affected tube.

Suspected ovarian disorders
Anovulatory infertility may be caused by four types of ovulation disorders, as classified by the WHO (see table 3, below).

WHO Group I: Advise women with hypogonadotropic hypogonadism causing anovulatory infertility that they can improve their chance of regular ovulation, conception, and an uncomplicated pregnancy by putting on weight if they have a BMI < 19 and/or moderating their exercise levels if they undertake high levels of exercise. Gonadotrophin ovulation induction, or pulsatile administration of gonadotrophin releasing hormone (not commonly used) should be offered. The second-line treatment is IVF.

WHO Group II: Women with PCOS who have a BMI ≥ 30 should be advised to lose weight as this may restore ovulation, improve their response to ovulation induction agents, and have a positive impact on pregnancy outcomes. One of the following can be used as a first-line therapy:

- Clomifene citrate
- Metformin
- A combination of the two

Metformin may be relatively more effective in women with a BMI < 30. Ultrasound follicular monitoring is required, during at least the first cycle, for women receiving clomifene. This is likely to limit its use in primary care. Metformin, if successful, generally results in mono-ovulation so ultrasound monitoring is not required. Up to six cycles of clomifene should be used, and women prescribed metformin should be warned about the gastrointestinal side effects.

If women with PCOS fail to ovulate in reponse to clomifene i.e. are clomifene resistant then second-line options include:

- Combined clomifene and metformin treatment
- Laparoscopic ovarian drilling. This is a day case procedure in which a mono-polar diathermy needle is used to cauterise the outer surface of each ovary at a few points. Regular and ongoing spontaneous ovulations often occur. Laparoscopic drilling has replaced the now obsolete wedge resection procedure
- Injected gonadotrophins (ovarian ultrasound monitoring required)

The third-line treatment is IVF.

Table 3

WHO Classification of ovulation disorders

- **Group I** — hypogonadotropic hypogonadism
- **Group II** — PCOS
- **Group III** — ovarian failure disorders
- **Group IV** — hyperprolactinaemia

WHO Group III: Ovarian failure is indicated by amenorrhoea and raised levels of FSH and LH. The most appropriate fertility treatment is oocyte donation.

WHO Group IV: Patients with hyperprolactinaemic amenorrhoea should be offered treatment with dopamine agonists such as bromocriptine.

‘In women aged 40-42 offer one full cycle of IVF (+/- ICSI) if there is no evidence of low ovarian reserve’

IN VITRO FERTILISATION

A full IVF cycle is now defined as one episode of ovarian stimulation followed by the transfer of any resultant fresh and frozen embryos. Women aged under 40, who have not conceived after two (previously three) years of regular intercourse or 12 cycles of artificial insemination (where six or more are by IUI) should be offered three full cycles of IVF, with or without intracytoplasmic sperm injection (ICSI).

In women aged 40-42 years offer one full cycle of IVF (+/- ICSI) provided the following three criteria are met:

- No previous IVF treatment has been given
- There is no evidence of low ovarian reserve
- There has been a discussion of the additional implications of IVF and pregnancy at this age.

One of the following tests are used to assess ovarian reserve to predict »

key points

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The main causes of infertility are female factor (anovulation, tubal damage, endometriosis and ovarian failure), male factor (low or absent numbers of motile sperm in the ejaculate, and erectile dysfunction), or unexplained infertility. More than 80% of couples will conceive within one year if the woman is aged under 40 and they have regular sexual intercourse. Of those who fail to conceive in the first year, around half will do so in the second year, giving a cumulative pregnancy rate > 90%.

A woman of reproductive age who has not conceived after a year of regular sexual intercourse, and has no known cause of infertility, should be offered referral for further clinical assessment and investigation with her partner. Women intending to become pregnant should be informed that dietary supplementation with folic acid 0.4 mg/day before conception and up to 12 weeks gestation reduces the risk of neural tube defects.

Women who have a BMI ≥ 30 are likely to take longer to conceive. Those with a BMI < 19 who have irregular or absent menstruation should be advised that putting on weight is likely to improve their chance of conception. The best test of ovulation is an appropriately timed mid-luteal serum progesterone level. Women with irregular or absent menstrual cycles should be offered a blood test to measure serum gonadotrophin levels (FSH and LH). Women with no known comorbidities should be screened for tubal occlusion. Those who are thought to have comorbidities should be offered laparoscopy and dye testing.

Unstimulated intrauterine insemination can be considered as a treatment option where people are unable, or would find it very difficult, to have vaginal intercourse. If the tubes are patent, but endometriosis is present in the pelvis, then surgical laparoscopic ablation or resection should be offered. If tubal damage or intra-uterine adhesions are diagnosed surgery to open the tube may be effective for mild tubal disease. Women with PCOS who have a BMI > 30 should be advised to lose weight since this alone may restore ovulation. Clomifene citrate or metformin can be used as first-line therapy, second-line treatments include combined treatment, laparoscopic ovarian drilling, or injected gonadotrophins. Women under 40, who have not conceived after two years of regular intercourse or 12 cycles of artificial insemination, where six or more are by IUI, should be offered three full cycles of IVF.

Sperm cryopreservation should be offered to men and adolescent boys who are preparing for medical treatment for cancer which is likely to make them infertile. Similarly, oocyte or embryo cryopreservation as appropriate during IVF should be offered to affected women or adolescent girls.

the likely response to gonadotrophin stimulation before IVF treatment:
- Baseline FSH
- Anti-Mullerian hormone (AMH)
- Ultrasound total antral follicle count (AFC).

All women under 37, who are undergoing their first IVF cycle should have elective single embryo transfer (eSET) in order to reduce the chance of a multiple pregnancy. Older women and/or those in their second or third full cycle may have single or double embryo transfer recommended depending on the quality of the embryos.

CRYOPRESERVATION FOR CANCER PATIENTS

This area has now been brought within the NICE fertility guideline. For cancer-related fertility preservation the eligibility criteria used for conventional infertility treatment do not apply.

Sperm cryopreservation should be offered to men and adolescent boys who are preparing for medical treatment for cancer which is likely to make them infertile. Similarly, oocyte or embryo cryopreservation as appropriate during IVF should be offered to affected women or adolescent girls.

VIRAL TRANSMISSION

Women concerned about their fertility should be offered testing for their rubella status. If the woman is susceptible, then offer vaccination and advise her not to try to conceive for the following month. Before undergoing uterine instrumentation women should be offered screening, and if necessary, treatment for *Chlamydia trachomatis*.

Couples where the man is HIV positive should be advised, in association with an HIV specialist, that the risk of HIV transmission to the female partner is negligible (and not lowered further by sperm washing) through unprotected sexual intercourse when all of the following criteria are met:
- The man is compliant with HAART
- The man has a viral load below a certain threshold
- There are no other infections present
- Unprotected intercourse is limited to the time of ovulation

For partners of men with hepatitis B offer vaccination before starting fertility treatment; do not offer sperm washing. The risk of transmission of hepatitis C to a female partner through unprotected sexual intercourse is thought to be low. However, men with hepatitis C should first discuss treatment options to eradicate the virus before conception is considered.

CONCLUSIONS

The 2013 NICE fertility guideline is an up-to-date and evidence-based review of the clinical and cost effectiveness of infertility investigations and treatments.

The guideline lays out clear pathways for healthcare professionals to help those affected by infertility to access effective interventions in a timely manner.

REFERENCES

1 Human Fertilisation and Embryology Authority. Facts and figures. 2006. www.hfea.gov.uk.
2 National Institute for Health and Clinical Excellence. CG156. Fertility: Assessment and treatment for people with fertility problems. NICE. London. 2013

Useful information

For healthcare professionals
British Fertility Society
Multidisciplinary organisation representing professionals practising within the field of reproductive medicine
www.britishfertilitysociety.org.uk

For patients
Infertility Network UK
National infertility charity
www.infertilitynetworkuk.com

British Infertility Counselling Association
www.bica.net

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