

# NICE CG156: fertility update. What it means for general practitioners

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## BACKGROUND

Infertility affects one in seven couples during their lifetime and has an annual incidence of one couple per 1000 total population, which means that each general practitioner (GP) will see on average one to two couples with infertility each year.<sup>1</sup> Over 80% of couples in the general population will conceive within 1 year of regular unprotected sexual intercourse (UPSI) if the woman is less than 40 years of age.<sup>2</sup> Thereafter, clinical investigation should be offered. The main causes of infertility are male factor problems (30%), disorders of ovulation (25%), tubal problems (20%), unexplained infertility (25%) and uterine or peritoneal disorders (10%).

## WHAT'S NEW IN CG156? KEY MESSAGES

A woman's age should be used as an initial predictor of her overall chance of success through natural conception or with *in vitro* fertilisation (IVF). In women considering IVF treatment, ovarian reserve testing is useful to predict the likely ovarian response to stimulation. This can be performed by an antral follicle count by scan, serum anti-Müllerian hormone or early follicular phase serum follicle-stimulating hormone.

The updated guideline clearly states that investigation should be offered after 1 year of regular UPSI. Early referral to an infertility specialist is recommended for any woman aged  $\geq 36$  years and for any couple where a clinical cause has been identified or there is a history of predisposing factors for infertility.

Where a cause is not identified, the threshold for access to IVF treatment for women with unexplained infertility has been reduced from 3 years to 2 years of regular UPSI, and a clear statement that clomifene citrate does not increase the chance of pregnancy or a live birth in this cohort. Moreover, intrauterine insemination with

or without ovarian stimulation is not routinely recommended.

For women with World Health Organization (WHO) Group II anovulatory infertility, clomifene, metformin or a combination of these agents can be offered. Women who receive ovulation induction with clomifene should have the first cycle monitored with ultrasound to minimise the risk of multiple pregnancy and treatment should not continue beyond six cycles.

Perhaps the most significant change is raising the age threshold for National Health Service (NHS)-funded IVF treatment. Women aged 40–42 years, who have neither conceived after 2 years of regular UPSI, nor have previously had IVF treatment, who do not have low ovarian reserve and who have discussed the relative risks of IVF and pregnancy at this age, can be offered one full cycle of IVF. In order to reduce the incidence of multiple pregnancy there is a move towards single embryo transfer. Double embryo transfer is only offered in NHS treatment cycles if there are poor quality embryos, the woman is aged  $\geq 40$  years or there have been more than two previous unsuccessful treatment cycles. A full cycle of IVF, with or without intracytoplasmic sperm injection (ICSI), has also been clarified as one episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s). Offering three IVF cycles to women aged  $< 40$  years remains unchanged. For those women aged  $< 40$  years who qualify for IVF, three full treatment cycles are recommended, however this still remains variable throughout the country as Primary Care Trusts (PCTs) and now Clinical Commissioning Groups (CCGs) use clinical and social criteria to restrict access in an attempt to 'balance the books'.

The updated guideline contains more detail on HIV infection. For couples

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where the man is HIV-positive, the couple's decision should be informed by discussion with a fertility and HIV specialist. HIV transmission to the woman is negligible through UPSI when treatment compliance is good, the plasma viral load is <50 copies/ml, there

are no other inter-current infections and UPSI is limited to the time of ovulation. If the man is HIV-positive, non-compliant with highly active anti-retroviral therapy or the plasma viral load is >50 copies/ml then seminal viral load estimation should be

### Box 1 NICE Clinical Guideline 156: summary of the main points applicable to general practice

#### Defining infertility

- ▶ Couples should be informed that over 80% of couples in the general population will conceive within 1 year.
- ▶ People who have not conceived after 1 year of unprotected sexual intercourse (UPSI) should be offered further investigation.
- ▶ If there is a history of predisposing factors for infertility [such as pelvic inflammatory disease (PID), oligomenorrhoea, amenorrhoea, undescended testes] investigation should begin immediately and early referral offered.

#### Principles of care

- ▶ The management of infertility should involve the couple. The care should be sensitive, informed and backed by patient information literature, and couples should be informed of a patient support group.
- ▶ A specialist team should treat couples. An expert not directly involved with the infertility management should offer counselling before, during and after treatment.

#### General advice

- ▶ Couples should be advised to have regular UPSI every 2–3 days.
- ▶ Couples should be advised to limit the use of alcohol.
- ▶ Couples should be advised to stop smoking.
- ▶ Couples should be offered specific advice in relation to recreational drug use where appropriate.
- ▶ Men should be advised to avoid tight fitting underwear and avoid testicular hyperthermia.
- ▶ Women should be advised to lose weight if their body mass index is greater than 29 kg/m<sup>2</sup>.

#### Preconceptual advice

- ▶ Women should be advised to take 400 µg folic acid before conception and up to 12 weeks' gestation. Women on anticonvulsants, or with diabetes, or a history of a child with a neural tube defect should be offered 5 mg folic acid per day.
- ▶ Rubella status should be determined and if seronegative, they should be offered immunisation and should avoid pregnancy for 1 month.

#### Initial assessment

- ▶ Semen analysis should be performed on behalf of all couples presenting with infertility. If the first sample is abnormal, a second sample should be taken 3 months later.
- ▶ For the assessment of ovulation, a menstrual history should be taken. If women have regular menses, they should be informed that they are ovulating. Confirm ovulation with mid-luteal (Day 21 of a 28-day cycle) progesterone. Depending upon the timing of menstrual periods, this test may need to be conducted later in the cycle (e.g. Day 28 of a 35-day cycle).
- ▶ Temperature charting is not recommended.
- ▶ Follicle-stimulating hormone (FSH), anti-Müllerian hormone and antral follicle count can be used to predict the likely ovarian response to gonadotrophin stimulation.
- ▶ Women with irregular cycles should have serum FSH and luteinising hormone measured. High levels may indicate ovarian failure.
- ▶ Women who have symptoms of thyroid disease or oligo/amenorrhoea should have their thyroid function checked.
- ▶ Women who have galactorrhoea, a pituitary tumour or oligo/amenorrhoea should have their serum prolactin measured.
- ▶ Before undergoing uterine instrumentation, women should be offered chlamydia trachomatis screening and treatment where necessary.
- ▶ For the assessment of tubal damage, women who are not known to have co-morbidities (such as PID, previous ectopic pregnancy or endometriosis) should be offered hysterosalpingography or hysterosalpingo-contrast-sonography (HyCoSy). Women with co-morbidities should be offered laparoscopy and dye as other pelvic pathology can be assessed at the same time.

#### Referral

- ▶ Early specialist referral should be offered where the woman is aged ≥36 years, or there is a known cause or history of predisposing factors for infertility.

offered. If the seminal viral load is undetectable the risk of HIV transmission to the woman is negligible. If the seminal viral load is detectable, sperm washing can be used to minimise, but not completely eliminate, the risk of HIV transmission.

Final noteworthy points include the recommendation of a higher dose of 5 mg folic acid where a woman has previously had an infant with a neural tube defect or who is receiving anti-epileptic medication or who has diabetes. For women in same-sex relationships up to 12 cycles of unstimulated intra-uterine insemination are recommended before considering IVF treatment.

For interested readers there are additional new recommendations in NICE CG156 that are more applicable to fertility specialists.

### CG156 RECOMMENDATIONS APPLICABLE TO GPs

Box 1 is a distillate of the 2013 fertility guideline summarising the points that can be translated into the GP consultation. Initial investigation in primary care should evaluate the main causes of infertility.

### WHAT INVESTIGATIONS SHOULD/CAN GPs PERFORM?

An initial assessment of the infertile couple in general practice includes semen analysis, serum mid-luteal progesterone, serum gonadotrophins (for women with irregular menstrual cycles), rubella status, chlamydia trachomatis screening and open access hysterosalpingography (HSG) where available. During these investigations, a couple may be found to have an abnormal HSG or semen analysis, which will prompt onward referral for IVF or ICSI. If an ovulatory disorder is discovered, this will require further detailed

investigation. Following evaluation of anovulation, some GPs with a special interest in fertility management will initiate ovulation induction therapy with clomifene and/or metformin.

### IN SUMMARY

For GPs the key messages in NICE CG156 include starting infertility investigations at or after 1 year, informing women that their fertility does decline with age and providing appropriate preconception counselling, including advising women to lose weight if their body mass index is over 29 kg/m<sup>2</sup> as this will significantly increase their chances of success with natural or assisted conception. A couple with normal endocrine blood tests, semen analysis and HSG essentially have unexplained infertility and should be offered IVF treatment after 2 years of regular UPSI. Couples should be offered early referral for specialist consultation where the woman is aged  $\geq 36$  years or if there is a known cause or history of predisposing factors for infertility. Finally, GPs should check the NHS funding criteria applied by their local CCG.

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### REFERENCES

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