

North Staffs and Stoke on Trent CCGs' CPAG

Prioritisation scorecard

Intervention/service: **fertility services**

key question: what is the relative clinical value of specialist fertility services and ART in particular?

This topic is being re-assessed in the light of the updated NICE guidance in line with the protocol for reviewing the scoring of a topic.

The NICE guideline (1) gives this context:

It is estimated that infertility affects 1 in 7 heterosexual couples in the UK. Since the original NICE guideline on fertility published in 2004 there has been a small increase in the prevalence of fertility problems, and a greater proportion of people now seeking help for such problems.

The main causes of infertility in the UK are (per cent figures indicate approximate prevalence):

- unexplained infertility (no identified male or female cause) (25%)
- ovulatory disorders (25%)
- tubal damage (20%)
- factors in the male causing infertility (30%)
- uterine or peritoneal disorders (10%).

In about 40% of cases disorders are found in both the man and the woman. Uterine or endometrial factors, gamete or embryo defects, and pelvic conditions such as endometriosis may also play a role.

Given the range of causes of fertility problems, the provision of appropriate investigations is critical. These investigations include semen analysis; assessment of ovulation, tubal damage and uterine abnormalities; and screening for infections such as *Chlamydia trachomatis* and susceptibility to rubella.

Once a diagnosis has been established, treatment falls into 3 main types:

- i. medical treatment to restore fertility (for example, the use of drugs for ovulation induction)
- ii. surgical treatment to restore fertility (for example, laparoscopy for ablation of endometriosis)
- iii. assisted reproduction techniques (ART) – any treatment that deals with means of conception other than vaginal intercourse. It frequently involves the handling of gametes or embryos.

This assessment by CPAG is concerned with the provision of ART.

The NICE overview and care pathway is attached.

NICE National Institute for Health and Care Excellence



Fertility overview

NICE Pathways bring together all NICE guidance, quality standards and other NICE information on a specific topic.

NICE Pathways are interactive and designed to be used online. They are updated regularly as new NICE guidance is published. To view the latest version of this pathway visit:

<https://www.nice.org.uk/guidance/ta257/Pathways>

This document contains a single pathway diagram and uses numbering to link the boxes to the associated recommendations.

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What is the evidence of clinical effectiveness?

This section will look at two aspects of the management of fertility problems.

i. Psychological problems are recognised to require management The NICE quality standard on fertility (QS73) states: People who are having problems conceiving are offered counselling before, during and after investigation and treatment for their fertility problems. The rationale is that fertility problems themselves, and the investigation and treatment for fertility problems, can cause emotional stress.

This is consistent with a review from Denmark (2) which found that medical/sociological analyses (in various studies) showed that the variables of psychosocial consequences of infertility and treatment are interwoven with each other in a complex pattern, a pattern that both differed and was similar when comparing women and men.

However there is no evidence on the impact of ART in terms of mitigating the stress of having fertility problems, rather research studies have looked at the impact of distress on the outcomes of ART. A meta-analysis (3) found that small but significant associations were found between stress and distress and reduced pregnancy chances with ART. However, there were a limited number of studies and considerable between-study heterogeneity. Taken together, the authors concluded the influence of stress and distress on ART outcome may be somewhat limited.

However there is interest in the effectiveness of psychological therapies for people with fertility problems. The Danish study (2) reported some interesting results and the author's review of the literature brings out some important points. The study used data from surveys, a cohort study, qualitative studies with couples engaged in the fertility clinic, and from the Communication and Stress Management Training Programme, an intervention study among couples engaged in fertility treatment at The Fertility Clinic.

Fertility problems are a stressor and how individuals or couples cope is dependent on skills such as communication and coping strategies. Among both men and women difficulties in partner communication predicted high fertility problem stress. This finding concurs with past research referenced by the author showing that the marital relationship is an important predictor of negative outcomes. Among both men and women high use of active-avoidance coping (e.g., avoiding being with pregnant women or children; turning to work or substitute activity to take mind off things) predicted high fertility problem stress.

One dimension in this study was the concept of marital benefit, defined as the perception that infertility has brought the partners closer together and strengthened their relationship. Therefore, marital benefit is a beneficial gain, a positive effect of infertility. 25.9% of the women and 21.1% of the men reported high marital benefit at baseline in the infertility cohort. Only few women (2.5% and 2.6%) and few men (5.1% and 5.4%) disagreed strongly.

These findings suggest that effective interventions for stress-related disorders associated with fertility problems will be psychological therapies and that ART per se are not going to influence the psychological outcomes, i.e. mental well-being. Interventions addressing resilience (4) and the use of emotionally-focused therapy for couples (5) are reported to have positive impacts on infertility associated

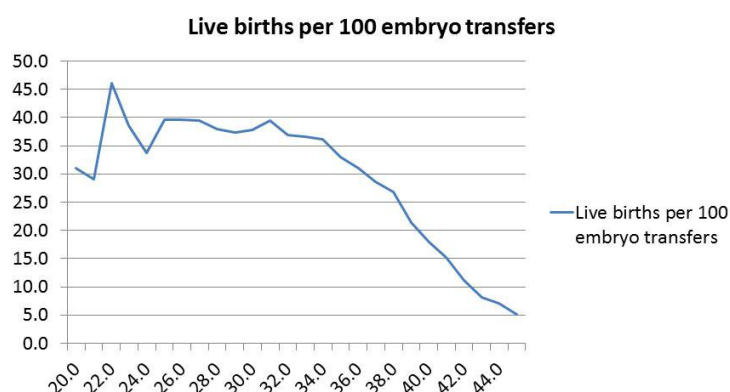
ii. Birth rates

The NICE guideline states in the section headed *Prediction of IVF success*:

- Inform women that the chance of a live birth following IVF treatment falls with rising female age (see figure 1).
- Inform people that the overall chance of a live birth following IVF treatment falls as the number of unsuccessful cycles increases.

Figure 1

Live birth rates per transfer by age (HFEA post-October 2007 data)



An overview of Cochrane reviews (6) on assisted reproduction technologies used these outcomes: the primary outcome of was live birth. Secondary outcomes were clinical pregnancy, multiple pregnancy, miscarriage, and ovarian hyperstimulation syndrome.

The latest published data from the Human Fertility and Embryology Authority (HFEA) is for 2014. The HFEA collates all the data for registered clinics in the UK. The tables below are from the report. (7)

Table 1: Pregnancy rate (per embryo transfer) for patients receiving IVF treatment using their own fresh eggs, 2013 and 2014

age	2013	2014
18-34	41.7%	43.7%
35-37	38.3%	38.7%
38-39	30.2%	30.3%
40-42	23.0%	21/3%
43-44	12.3%	11.3%
45+	7.0%	2.2%
All ages	35.5%	36.3%

Table 2: Live birth rate, per cycle started, fresh own eggs, 2012 and 2013

Age	2012	2013
18-34	32.9%	32.8%
35-37	27.3%	29.5%
38-39	20.7%	21.8%
40-42	13.2%	13.7%
43-44	5.4%	4.9%
45+	1.1%	2.0%
All ages	25.9%	26.5%

Table 3: Live birth rate per cycle started, after frozen embryo transfer using woman's own eggs, 2012 and 2013

age	2012	2013
18-34 25.1% 28.3%	25.1%	28.3%
35-37 22.8% 24.8%	22.8%	24.8%
38-39 18.8% 23.2%	18.8%	23.2%
40-42 16.1% 16.7%	16.1%	16.7%
43+ 9.2% 10.4%	9.2%	10.4%
All ages 22.0% 24.8%	22.0%	24.8%

The multiple birth rate in 2013 as a proportion of live births for fresh own eggs was 15.3%.

The likelihood of success:

Most women typically see success rates of 20-35% per cycle, but the likelihood of getting pregnant decreases with each successive round, while the cost increases. The cumulative effect of three full cycles of IVF increases the chances of a successful pregnancy to 45-53%. This is why NICE has recommended 3 IVF cycles as they considered it to be the most cost effective and clinically effective number for women under the age of 40.

The study (8) on which NICE based their recommendation estimated cumulative live-birth rates among patients undergoing their first fresh embryo, nondonor IVF cycle between 2000 and 2005 at one large centre. Couples were followed until either discontinuation of treatment or delivery of a live-born infant. Analyses were stratified according to maternal age and performed with the use of both optimistic and conservative methods. Optimistic methods assumed that patients who did not return for subsequent IVF cycles would have the same chance of a pregnancy resulting in a live birth as patients who continued treatment; conservative methods assumed no live births among patients who did not return.

The Kaplan-Meier curves showed these values for probability of live births (%) per cycle.

Table 4.

cycle	1	2	3	4	5	6
optimistic	25	40	53	62	68	72
conservative	25	37	45	49	50	51

The assumption is that the clinical pathway and guidance published by NICE provide the best practice and therefore the best chance of achieving the optimum live birth rates. The NICE evidence update in March 2015 (9) found very few key points which would have an impact on the guidance. NICE quote the Cochrane overview (2): the authors summarised 58 published Cochrane reviews on assisted reproduction procedures. Of these, 19 reviews identified interventions that were effective, and 13 identified interventions that were promising. A total of 14 reviews found interventions that were ineffective or possibly ineffective, and 12 reviews were unable to reach conclusions because of lack of evidence.

There was no new key evidence on prediction of success.

what is the evidence on cost-effectiveness?

NICE created a new economic model as the studies they reviewed did not meet all the criteria set by the GDG. This section from the full guideline (1) is important:

The QALY is the preferred measure of health outcome using NICE methods, primarily because it allows a comparison of the value for money of interventions which will be intended to improve many different dimensions of health-related quality of life. However, assisted reproductive treatments present difficulties for the QALY approach. For example, it has been stated that:

“QALYs are intended to capture improvements in health among patients. They are not appropriate for placing a value on additional lives. Additional lives are not improvements in health; preventing someone’s death is not the same as creating their life and it is not possible to improve the quality of life of someone who has not been conceived by conceiving them.”
10)

Or, in a similar vein: “Cost-utility analysis has little relevance to the management of infertility where lives are produced and not saved.” (11)

This reasoning was accepted for the HE model and therefore any QALY gain in the analysis had to relate to the couple seeking treatment and not to a ‘not yet conceived life’. A health state utility decrement of 0.07 from being infertile has been reported recently in a UK economic evaluation of eSET versus DET (Scotland et al., 2011). Correspondence with the authors of this study provided the following explanation of how this utility decrement of 0.07 was identified. It came from a US study where the state of being infertile was assigned a profile – on the Health state Utilities Index Mark II (HUI2) – with a utility value of 0.82. This 0.82 was then subtracted from US population norms for the HUI2 (which is 0.89 for women of reproductive age) to give an estimated decrement of 0.07.

The NICE economic model produced these results (Table 5):

Table 5. Incremental cost-effectiveness ratios for women aged 34

Strategy	Cost	QALY	Incremental cost	Incremental QALY	ICER
EM £0 0.00 - - -	£0	0.00			
IVF1	£4103	0.49	£4103	0.49	£8395
IVF2	£7050	0.75	£2948	0.26	£11122
IVF3	£9288	0.9	£2238	0.14	£15519

EM expectant management, ICER incremental cost effectiveness ratio, IVF in vitro fertilisation, QALY quality adjusted life year

References:

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factor	comments	score
Strength and quality of evidence	Rates are derived from registers, and cohort studies.	20
Magnitude of health improvement benefit	20-35% per cycle. Cumulative live birth rates estimated 45-53% at 3 rd cycle	10
Prevention of future illness	NO	0
Supports people with existing health problems	yes	10
Cost effectiveness ratio	ICER £15,519 for 3 cycles	10
<i>“Opportunity Costs“ total cost of service”</i>	£4200 (NICE 2010/11 costs adjusted) for cycle with fresh eggs (2 cycles)	15
Addresses health inequality or health Inequity	Association between infertility and obesity.	0
Delivers national &/or local requirements/targets	NICE CG 156	10
TOTAL		75