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ANALYSIS

Are we overusing IVF?

The indications for IVF have expanded from tubal disorders to many causes of subfertility, including unexplained. But with limited evidence underpinning its extended remit **Esme Kamphuis and colleagues** explain how the risks could outweigh the benefits

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Since the birth of the first baby by in vitro fertilisation (IVF) in 1978, the technique has earned its reputation as a major medical breakthrough of the 20th century. IVF was developed for women with tubal disease,[1] but its indications soon began to grow. In the 1990s intracytoplasmic sperm injection was developed to treat couples in which the man has poor semen quality,[2] which like tubal infertility prevents sperm from coming into close proximity with an egg. In recent years, however, IVF has been applied to other types of subfertility such as mild male subfertility, endometriosis, and unexplained subfertility. The birth of many healthy children has enhanced provider and patient confidence in the safety of IVF. But does applying IVF to wider forms of infertility result in overtreatment of couples who had a reasonable chance of conceiving naturally? Is it equally effective in these conditions? And, as more is understood about the adverse health outcomes in IVF children can the risks of IVF be justified for these more liberal applications?

Rising rates of IVF

One million babies were born in the first 25 years of IVF between 1978 and 2003. It took only two more years for the tally to reach two million in 2005, with over five million estimated to have been born by the end of 2013.[3] In developed countries with public health systems 2-3% of the births each year are through IVF, rising as high as 5% in Denmark and Belgium.[4] This is despite the fact that an observational study showed that 95% of 350 couples planning a first pregnancy conceive within 24 months.[5]

The reasons for the rise in IVF are complex. Women may plan to have children later and some are choosing to freeze their eggs.[6] A lack of confidence, among both subfertile couples and their doctors, that conception will eventually occur naturally can lead to access to IVF within two to three years of trying to conceive, and the lure of new technology and access to more patient friendly IVF programmes make it more appealing.[7]

Evidence has also undermined alternatives to IVF such as clomifene citrate.[8] Another factor is that procedures are increasingly performed in private health systems, where the focus on commercial returns has resulted in less academic oversight of who receives treatment and when.[9] Amid this the indications for IVF have been expanded to include mild male subfertility, the effect of ageing on ovarian function, and unexplained subfertility where no absolute barrier to conception can be proved (table 1⇓). And it is in these groups, that use of IVF is expanding the most.

In the United States, the number of IVF cycles offered annually increased from 90 000 in 2000 to 150 000 in 2010, but the proportion with tubal problems as an indication fell from 25% to 16%.[10] In the UK the proportion of IVF cycles for tubal problems fell from 19% to 12% between 2000 and 2011, although the number of cycles remained at around 7000 (table 1⇓).[11] The figures for unexplained subfertility tripled from 6204 to 19 552 cycles. Similar shifts have been reported in the Netherlands.[12]

IVF and unexplained infertility

The value of IVF for tubal blockage and severe male factor infertility, where a live birth rate of 20-30% per cycle offers the only chance of conception, is not in dispute. However, the evidence for newer indications such as unexplained subfertility is less clear. Unexplained subfertility accounts for 25% to 30% of all couples presenting for IVF, many of whom will conceive before treatment.[12 13 14] In a cohort of 500 Dutch subfertile couples with on average almost two years of unexplained subfertility, 60% conceived naturally after the initial assessment in the fertility clinic.[15] Other observational studies have confirmed natural conceptions in couples with subfertility for two to three years.[16 17]

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A Cochrane review comparing IVF with expectant management in women without tubal problems identified one trial of 51 women with unexplained infertility who had been trying to conceive for an average of four years.[18 19] The trial reported live birth rates of 29% in women randomised to one cycle of IVF versus 1% in the expectant management group. Although this may seem like a success for IVF, the women in this trial had been trying to conceive for four years, which is much longer than is current practice in many countries. A randomised clinical trial comparing intrauterine insemination and ovarian hyperstimulation with expectant management in couples who had an average of two years' unexplained subfertility found a pregnancy rate of 25% after six months and 75% after three years in both groups.[17] It seems that a short delay in treatment does not affect ovarian reserve in such a way that more couples will end up childless.

Another randomised trial (FASTT) in the US of alternative strategies in unexplained infertility showed that limiting the number of cycles of intrauterine insemination with ovarian hyperstimulation treatment in favour of early access to IVF reduced the time to pregnancy as well as costs, but it did not alter the 75% pregnancy rates in both randomised arms at 24 months.[20] Evidence from the Netherlands suggests that couples with a clinical profile similar to those in the FASTT trial would be expected to have natural conception rates of over 50%.[17]

It is not just a question of whether to intervene in unexplained subfertility, but when. Economic modelling studies indicate that, in younger women with no obvious cause of infertility, IVF is not cost effective within three years of trying to conceive.[21] However, experimental and observational IVF research often does not mention how long couples have been trying to conceive. Forty five of the 71 (63%) randomised trials of IVF in 2009 and 2010 did not state length of infertility. National fertility registries in Sweden, Australia, Belgium, New Zealand, Canada, and the United States also do not collect data on duration of infertility.

In the UK the National Institute for Health and Care Excellence changed its recommendation regarding the timing of access to IVF in couples with unexplained infertility where the woman is younger than 40 from three to two years.[22] However, it did not provide any references to justify the threshold.

Emerging risks of IVF

Extended use of IVF also increases the risk of harm. Multiple pregnancies are associated with maternal and perinatal complications such as gestational diabetes, fetal growth restriction, and pre-eclampsia as well as premature birth.[23 24] And even singletons born through IVF have been shown to have worse outcomes than those conceived naturally (table 2⇓).[25-28] Although some countries have mitigated the risk of multiple births by requiring single embryo transfer, multiple transfer is still common in many parts of the world, including the United States and Asia, where multiple birth rates are 20% to 30%.[29] Furthermore, studies suggest that single embryo transfer, which involves extended embryo culture and transfer of a blastocyst, is associated with a 50-70% additional risk of preterm birth and congenital malformations.[30-32]

Concern has also been raised about the long term health of children born through IVF**.** Otherwise healthy children conceived by IVF may have higher blood pressure, adiposity, glucose levels, and more generalised vascular dysfunction than children conceived naturally (table 2⇓). These effects seem to be related to the IVF procedure itself rather than to underlying subfertility.[33-36] Animal studies have shown epigenetic and developmental abnormalities after assisted reproduction, which give further cause for reflection.[37] Until these concerns are resolved, there should be caution about using IVF in couples when the benefit is uncertain or the chances of natural conception are still reasonable.

Need to question IVF

A lack of will to question the perceived success of IVF is preventing progress. Currently funding bodies seem to have limited interest in funding long term studies on safety**.** IVF has evolved in many parts of the world as a profit generating industry that values the money brought in by immediate gains of pregnancy and live birth over long term considerations about the health of the mothers and children. This is true not only for private clinics but also for academic institutions, which also benefit economically from the number of couples they recruit for fertility treatment. Neither the American Society for Reproductive Medicine nor the European Society of Human Reproduction and Embryology has guidelines on use of IVF. Given the rapid increase in uptake of IVF across the world, it is time to reconnect the drive to "regulate practice" with a drive to generate knowledge on best practice and long term safety.

IVF has allowed many infertile couples to have a family. Its early pioneers persevered in opposition to scientific, societal, and religious dogma. Similar determination is needed in attempts to evaluate the extension of IVF to new indications. Patients and researchers are understandably reluctant to include a "no intervention" arm in randomised clinical trials of IVF, but without these there is a risk that the balance of benefit and harm may be disrupted. The paucity of high quality evidence on who should have IVF and when should be addressed. Trials on effectiveness of new indications and long term follow-up to determine the safety of IVF are needed to inform couples.

As a society we face a choice. We can continue to offer early, non-evidence based access to IVF to couples with fertility problems or follow a more challenging path to prove interventions are effective and safe and to optimise the IVF procedure. We owe it to all subfertile couples and their potential children to use IVF judiciously and to ensure that we are first doing no harm.

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Key messages

- The scope of IVF has expanded in the last two decades to embrace a wider range of indications, including unexplained subfertility
- The evidence underpinning the use of IVF for some of these newer indications is weak
- Outcomes in children conceived through IVF seem to be poorer than in those conceived naturally
- We need to evaluate which couples have a reasonable chance of natural conception
- For those needing help, the effectiveness and safety of IVF should be investigated afresh

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Tables

Table 1| Table 1 Evidence of effectiveness of IVF treatment for different types of infertility and change in indications between 2000 and 2011 in the United Kingdom[11]

		No (%) of IVF cycles	
Reason for fertility problem	Evidence of effectiveness	2000 (n=35 450)	2011 (n=60 473)
Two sided tubal pathology	Effective: no chance of conception without medical assistance[1 2]	6771 (19)*	7 470 (12%)*
Severe male infertility		9777 (28)†	19 643 (33%)†
Obstructive male infertility		†	†
Anovulation		7%	6%
Unexplained subfertility	IVF treatment effective in subfertility>4 years; no more effective than less invasive alternatives in subfertility <2.5 years; effectiveness unknown for subfertility 2.5-4 years[18]	6204 (18)	19 552 (32)
One sided tubal pathology		*	*
Mild male subfertility		†	†
Endometriosis		886 (3)	2 550 (4)
Poor ovarian reserve	No comparative effectiveness data available	NA	NA
Advanced maternal age		NA	NA
Other or mixed factors		12 691 (25)	11 252 (12)

* One sided and double sided tubal pathology were reported together.

† Severe male infertility, obstructive male infertility, and mild male subfertility reported together.

Table 2| **Potential harms of IVF in singleton pregnancies compared with natural conception**

	Odds ratio (95% CI)
Perinatal outcomes	
Preterm birth (<37 weeks)[26 35]	1.5 (1.5 to 1.6)
Very preterm birth (<32 weeks)[26 35]	1.7 (1.5 to 1.9)
Low birth weight (<2500 g)[26 35]	1.7 (1.6 to 1.8)
Very low birth weight (<1500g)[26]	1.9 (1.7 to 2.2)
Perinatal mortality[26]	1.9 (1.5 to 2.4)
Small gestational age[26]	1.4 (1.3 to 1.5)
Congenital malformations[26 36]	1.7 (1.3 to 2.1)
Long term outcomes	
Cerebral palsy[36]	2.8 (1.3 to 16)
Generalised vascular dysfunction[33]	Increase
Diastolic/systolic blood pressure (mm Hg)[34]	61/109 *v* 59/105
Fat deposition[35]	Increase or no change
Fasting glucose[35]	Increase or no change