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OPINION ARTICLE

# Good oocytes for successful IVF cycles



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## KEYWORDS

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*Abstract:* Human fertility is mainly related to the egg quality both in spontaneous and IVF induced cycles.

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## 1. Ex ovo omnia

The human oocyte is the rarest and most rapidly ageing cell in the body, and yet one that is essential for fertility (20). In fact “everything comes from the egg”. William Harvey published this visionary statement in the 16th century (8). We now have compelling evidence that also origins of birth defects and perhaps other childhood and adult diseases can arise during the earliest stages of gonad development and gamete differentiation and are almost exclusive to the egg. Unexpectedly also common lifestyle choices may be the frequent cause of such specific oocyte defects. Advances in contemporary biomedical research and reproductive medicine are now offering relevant insights showing the direct correlation between these lifestyle choices of the parents and both the short- and long-term health of future generations (7).

## 2. The ageing egg

### 2.1. Late reproduction

Postponing childbirth is a frequent choice (5). However, since fecundity in the woman is decreasing with age, delaying conception is accompanied by an increased age in the subfertile population and by an increased demand for medical care (4). In fact, in developed countries, the prominent reason for reduced fertility is the age related decline in the number and quality of eggs (12). Not surprisingly, though the possibilities for the treatment of infertility have been improved, not every couple ultimately obtains the desired child. Nowadays, in subfertile couples, crude overall pregnancy rates of 50–65% per patient can be achieved, irrespective of the type of fertility treatment applied first. IVF only accounts for about 20% of the initiated pregnancies in subfertile couples. Noteworthy, even after failed IVF, spontaneous pregnancies may occur. Dropout is an important reason for not reaching the estimated pregnancy rate. Long-term cumulative live birth rates of 80% may be expected if dropout can be limited (6).

Another harmful consequence of postponed childbearing is the actual higher frequency of spontaneous dizygotic twins. The increased mean maternal age is associated with elevations in circulating FSH due to the decline in ovarian feedback capacity. Therefore, in older women, there is a tendency toward multiple follicular development and an increased prevalence of twins and an additional 5–8 twins per 1000 births will

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**Table 1** The contribution of IVF to compensate for the fertility lost with postponed childbearing. It is assumed that all eligible women will use IVF (10).

	Mean age at first attempt		
	25	27.5	31
Years of postponement	–	2.50	6.00
No. of naturally conceived children	2.00*	1.90**	1.77***
IVF contribution	0.04****	0.05****	0.05****
Total No. of children	2.04	1.95	1.82

\* CF, Cohort fertility.

\*\* Minus 5% of CF.

\*\*\* Minus 11% of CF.

\*\*\*\* Plus 2.5% of CF.

be born every year (1). Elevated maternal age is the more frequent cause of dizygotic twinning.

### 2.2. Role of IVF and the frequent decision to stop treatments

The impact of IVF on fertility rates can be estimated by setting the parameters to the current situation in a country like France, where cohort fertility is close to 2.0 children per woman and the mean age at first pregnancy attempt is around 25 years (Table 1).

Overall IVF adds about 0.05 points to the total fertility rate (TFR). In Denmark, where IVF utilization is high, IVF fertility was estimated to contribute an absolute net effect on the cohort of 1975 of only 0.049–0.079 (18).

Since IVF success declines with female age, IVF contribution to TFR also reduces with age.

Despite the fact that chances of eventually achieving a pregnancy are usually high for couples undergoing infertility treatment, many couples do not commence these potentially effective therapies, or alternatively discontinue treatment prematurely (2).

Discontinuation is usually defined as the decision of the couple to refrain from further treatment; the reasons for discontinuation may not be treatment related and the couple may have a favorable prognosis. Cumulative success rates of any repetitive intervention are reduced under those circumstances due to less exposure to the benefit of subsequent treatment cycles. Improved access to treatment along with more couples undergoing repetitive treatment cycles by reducing drop-outs is fundamental in augmenting overall success rates of infertility treatments.

### 2.3. Attempts to avoid the age related decline in egg quality

The following are the available approaches:

- 1) Preimplantation screening of embryo quality in older women or
- 2) Freezing young eggs to preserve their quality.

For preimplantation screening in IVF cycles there exist only few high quality studies. A recent randomized trial (15) showed a significant increase in live birth rates after the screening of chromosome abnormalities in single-cell day 3 biopsies for advanced maternal age: 32.3% vs 15.5% (OR 2.6 95%CI 1.3–5.3). Similarly, an improved performance was observed

in young women (mean age 32 years) in an RCT with chromosome screening on blastocyst biopsies (16), where the incidence of sustained implantation rates was significantly higher in the screened group (66.4%) compared with the controls (47.9%). The authors prudently conclude that “future studies and broad based clinical application will be required to fully define the role of aneuploidy screening” (16).

On the contrary the increasing use of egg vitrification improved substantially the resulting pregnancy rate obtained in IVF cycles carried out with cryopreserved oocytes. However “the financial costs and limited success rate likely to the restricted number of oocytes obtained from a single stimulation cycle mean that this approach will appeal and be available to only very few” (13).

### 3. Other life style related egg defects

#### 3.1. Overweight and obesity also negatively influence fertility

Several studies in the past have reported an increased risk of infertility, lower conception rates and raised miscarriage rates in obese women. It has been suggested “that compromised oocyte and early embryo mitochondrial metabolism, resulting from excessive nutrient exposure may underlie poor reproductive outcomes frequently reported in obese women” (9).

Also large IVF programs confirmed the negative effect of obesity in IVF cycles. In particular, the US IVF national program in the year 2007 showed that obesity impacts negatively for treatments using autologous oocytes. This detrimental effect does not apply to egg donation cycles and is more pronounced in women with younger age and with higher BMI (11).

A reduced pregnancy rate in younger overweight IVF users was already shown by Sneed et al. (17) in a smaller study.

This year, the Danish nationwide study found that overweight of either women or men may lower IVF success rate. In the 25191 cycles observed, the IVF-treated couples showed a reduced probability of a live birth when both female and male BMI were higher, both independently and, to a greater extent, in combination (14).

Nevertheless, in overweight women lifestyle changes can promote in a few months spontaneous fertility, in particular when overweight is associated with the PCOS. In a small study, physical exercise and diet in overweight PCOS patients quickly normalized ovarian morphology and improved fecundity (3).

#### 3.2. Smoking and infertility

- The literature strongly supports an association between cigarette smoking and infertility (19).
- Two systematic reviews have analyzed the evidence and results are suggestive for a suboptimal egg quality.
- However, both concluded that causality cannot be excluded but would require more rigorous empiric evidence.

Specific points for women. There is good evidence that:

- smoking may advance the time of menopause by 1–4 years;
- smokers require nearly twice the number of IVF attempts to conceive as nonsmokers;
- nonsmokers with exposure to tobacco smoke may have reproductive consequences.

Discouraging smoking and in general eliminating the exposure to tobacco in women and men are both evidence-supported preventive approaches to infertility.

#### 4. Conclusion

Oocyte quality plays a key role in the success of both spontaneous and assisted reproduction programs.

#### Conflict of interest

None declared.

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