



## COUNTERCURRENT

# Ovulation induction in anovulatory infertility is obsolete

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## ABSTRACT

Women with polycystic ovary syndrome make up the vast majority of patients with anovulatory infertility. The commonly accepted treatment guidelines recommend ovulation induction for timed intercourse as the first-line treatment. After a 2-year treatment period, the cumulative pregnancy rates with a singleton live-born baby reached 71% and 78% in two prospective studies. Despite aiming for monofollicular growth, multifollicular responses with subsequent multiple/higher order multiple pregnancies are a dreaded risk associated with ovarian induction. However, the lengthy treatment, the increase of maternal age and the psychological effects of 'obligatory intercourse' are also factors challenging the concept of ovarian induction as the first treatment approach in anovulatory infertility. Nowadays, individualized IVF treatment with cycle segmentation, freeze-all strategies and single-embryo transfers in frozen embryo transfer cycles dramatically reduces the risk of multiple pregnancies, and a cumulative pregnancy rate of 83% can be achieved over three complete cycles, thereby reducing exposure to fertility medication and time to pregnancy. Although on first sight ovarian induction might present the easier and less costly approach, efficient and individualized IVF treatments with low complication rates and the chance of preventing multiple pregnancies challenge this concept, and it seems that the time has come to abandon ovarian induction in anovulatory infertility.

## INTRODUCTION

At first sight, anovulatory infertility might present an 'easy' cause of infertility, which can be overcome by ovulation induction with subsequent timed intercourse, thereby seemingly presenting a quite natural way of achieving a pregnancy. However, in times of highly sophisticated assisted reproductive technology (ART) programmes the question arises of whether ovulation induction in anovulatory infertility should remain the first choice of treatment or whether it should be abandoned.

Anovulation is a condition in which the complex process of oocyte release from the follicle is disrupted. Clinically, anovulation manifests as a bleeding disorder, ranging from irregular cycles to amenorrhoea and infertility. For practical reasons, the World Health Organization proposed three groups of anovulation. Group II is characterized by a normogonadotrophic, normo-oestrogenic hormonal profile and constitutes the largest and most inhomogeneous group of patients. Within group II, approximately 80% of women are affected by polycystic ovary syndrome (PCOS). They represent the target group of patients to undergo ovarian induction

for timed intercourse, when a male factor is ruled out. Several papers have focused on treatment recommendations in this specific group; however, acknowledging all publications would be beyond the scope of this work. Hence, the following recommendations are based on the publications of Balen and colleagues and Teede and co-workers, the latter also reflecting international guidelines (*Balen et al., 2016; Teede et al., 2018*):

- Lifestyle intervention is recommended first in women who are obese.
- First-line treatment is clomiphene citrate or letrozole (treatment duration 6–9 cycles if ovulation is detected).

## KEYWORDS

Anovulation  
Multiple pregnancy  
Ovulation induction  
PCOS  
Preimplantation genetic testing for aneuploidies  
Single embryo transfer

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- Second-line treatment involves gonadotrophins and laparoscopic ovarian drilling (treatment duration six cycles if ovulation is detected).
- Third-line treatment is IVF for women with PCOS who do not become pregnant with ovarian induction therapy or have additional infertility factors.

A graph with an algorithm in the paper of Balen and colleagues ([Balen et al., 2016](#)) depicts the treatment sequence.

## CHALLENGING THE DOGMA OF OVULATION INDUCTION IN ANOVULATORY INFERTILITY

### Lifestyle intervention in real-life scenarios

The two basic elements of lifestyle management are weight loss by improving diet and introducing exercise ([Balen et al., 2016](#)), thereby aiming for a weight loss of 5 to 10%, as this has been shown to improve the metabolic situation and ovulation rate in women with PCOS. Under study conditions, participants are subjected to intensive coaching, guidance and follow-up appointments, helping them to achieve their goals. Unfortunately, patients outside study settings seem to struggle to achieve an improvement of their metabolic and reproductive function.

### Efficacy and risks of ovulation induction and timed intercourse

After a treatment duration of up to 24 months, cumulative singleton pregnancy rates with a live-born baby of 71% and 78%, respectively, were reported after ovarian induction treatment according to the guidelines (clomiphene citrate, followed by gonadotrophins) in two prospective studies ([Eijkemans, 2003](#); [Veltman-Verhulst et al., 2012](#)). It is important to acknowledge that the participants included in these studies had a 'good prognosis' due to their young age (<29 years) and their relatively short history of infertility (2 years).

In contrast to the study settings, however, women in 'real-life scenarios' are commonly older – which questions not only the accuracy of the reported pregnancy rates for these patients outside study populations, but also whether couples are willing to endure a 2-year treatment journey. Also, even in study populations, approximately 20–30% of couples remain childless after an intensive

2-year treatment period. Failure to achieve a pregnancy might leave a trail of disappointment and frustration for these couples, and it has been clearly demonstrated that the incidence of depression and anxiety increases in parallel with the treatment length. Furthermore, no study to date has evaluated from the patient perspective the time and expense invested in an extended cycle monitoring process, taking into account the time consumed for clinic visits (travel times, waiting times, times for monitoring procedures), the time off work needed to travel to and attend appointments and, last but not least, the costs of the stimulation medication as well as the travel, as many patients will not have a fertility clinic in close proximity to their home.

Ovarian induction aims to induce monofollicular growth, but the risk of multiple pregnancy should not be neglected as data suggest a multiple pregnancy rate of approximately 10% after clomiphene citrate ([Balen et al., 2016](#); [Fauser et al., 2005](#)) and up to 32% after the use of gonadotrophins, meaning that higher order multiple pregnancies result almost exclusively from ovarian induction treatments. In 2022, this multiple pregnancy rate is unacceptably high, especially as the implementation of single frozen embryo transfer (FET) cycles in ART treatments has led to a drastic decline in twin and triplet rates over recent years ([Chambers et al., 2021](#)).

From the financial perspective, ovarian induction is undoubtedly cheaper for the couple or the health insurance system, compared with IVF treatment. However, twin or higher multiple pregnancies and deliveries create, compared with singleton pregnancies, 5 times/20 times higher costs as a consequence of a higher incidence of pregnancy complications and the need for neonatal intensive care for the neonates due to prematurity. These calculations do not even include expenses for the further medical care of children born preterm beyond the costs of early hospitalization when there is disability as a result of prematurity. In addition, the financial considerations completely neglect the enormous burden for the couple or family that has to care for a child with disabilities.

### Psychological treatment burden and sexual function

Studies evaluating the efficacy of ovarian induction in anovulatory infertility

commonly focus on the female partner and treatment outcome, often neglecting the other half of the couple: the man. Infertility can cause psychological distress for both partners, and a negative correlation between psychological stress/anxiety and sexual function is well described in women. Although data on the impact of impending intercourse on specific, medically indicated dates on men are scarce, available data point to the fact that men might experience erectile dysfunction as a consequence of the stress incurred by the thought of 'obligatory intercourse'.

### Infertility and cancer risk

Female infertility has been related to health problems beyond reproduction. In general, reproductive cancers (ovarian, breast and endometrial cancer) seem to be associated with nulliparity. The risk of cancer development in later life stages is a matter of controversial debate regarding the link between cause and consequence. Previous publications suggested an increase in ovarian cancer risk when clomiphene citrate is taken for more than 12 months; however, newer data have not found a conclusive link. For breast cancer, data are controversial and some suggest a slightly increased risk of endometrial cancer through ovarian induction medication. Due to the long time intervals between the intake of fertility medication and the diagnosis of cancer, the possible induction of cancer through fertility medication is difficult to verify, and cancer risk and development are also influenced by a variety of other factors outside fertility treatment. Despite the as yet reassuring data, treatment should be as effective and as short as possible to reduce the exposure time to fertility medication.

### Age and embryo ploidy

Over recent decades, women have tended to postpone childbearing due to several reasons. The crucial impact of female age on the chance of conceiving represents a further factor, calling for the most effective and least time-consuming treatment approach due to the well-described increase in the risk of aneuploidy with advanced maternal age. The lowest risk of embryonic aneuploidy was found between the ages of 26 and 30 years, with a steady rise in the prevalence from age 31 years onwards ([Fransiak et al., 2014](#)). Whereas abnormal conceptions commonly do not implant at all, a small risk of implantation

and consecutive miscarriage will remain, possibly further complicating fertility treatment.

### Effective ART programmes to replace ovulation induction

Taking the chances and challenges of the PCOS treatment algorithm into account while acknowledging the progress of ART in recent decades, the question arises of whether the commonly accepted treatment algorithm for anovulatory infertility is still appropriate in 2022. Gonadotrophin-releasing hormone (GnRH) antagonist/progestin-primed ovarian stimulation protocols with the administration of a GnRH agonist for final oocyte maturation and the freeze-all strategy (Devroey and Adriaensen, 2011) are highly effective in preventing the development of ovarian hyperstimulation syndrome (OHSS) in high-responder women. Improved culture conditions in IVF laboratories allow the extension of embryo culture until the blastocyst stage, identification of embryos with the highest implantation potential according to the development pattern and morphokinetic/morphological criteria, exclusion of embryo aneuploidy as a cause of implantation failure through pre-implantation genetic testing for aneuploidies (PGT-A) and effective cryopreservation of surplus embryos. Cycle segmentation with the embryo transfer being performed as an FET is not only a further step to eliminate early-onset OHSS after ovarian stimulation, but, performed as single-embryo transfer, it also dramatically reduces the risk of multiple pregnancies.

In stark contrast to the chance of a live birth of 71–78% after a 2-year period of ovarian induction treatment, prediction models for the cumulative chance of live birth over multiple complete cycles of IVF give a probability for good-prognosis patients (age 30 years, 10 oocytes retrieved and cryopreserved embryos) of 0.49 in the first intracytoplasmic sperm injection (ICSI) cycle, increasing to 0.83 over three complete cycles (Leijdekkers et al., 2018), which could be performed in a far shorter time period than 2 years. Through the addition of PGT-A, the cumulative live birth rate can even reach 92.6% after three consecutive single FET cycles (Pirtea et al., 2021). Moreover, the use of cryopreserved surplus embryos should allow couples to fulfil their dream of having more than one child without again going through the tedious and

lengthy process of ovarian induction treatments.

### Decision-making in fertility treatment

Undoubtedly, infertility and its treatment come at a high emotional, physical and financial cost for the couple involved, and couples need to be counselled thoroughly before embarking on fertility treatment. In the 'pre-internet' era, information related to infertility and ART treatment was provided mainly through physicians and nurses. Nowadays, a massive amount of information on ART is available on the internet and can be accessed 24/7 from almost every place on earth.

Then and now, decisions related to fertility treatment are influenced by multiple and interacting factors. In 1990, and therefore in the early years of ART, the anticipated length and nature of the treatment were among the most important factors considered for treatment decisions, and patients preferred treatments of a more routine and less intrusive nature, being sceptical of IVF. Over recent decades, it seems that the taboo on infertility has declined and the attitude towards sophisticated ART treatments has become more liberal. A survey (Fauser et al., 2019) published in 2019 with 8700 participants (although it should be noted that the panel did not include only patients with infertility) demonstrated a high acceptance of IVF as a tool to overcome infertility.

### CONCLUSIONS

With the availability of highly sophisticated, individualized IVF treatments with low complication rates, high success rates and a reduced time to pregnancy, patients nowadays might not be willing to accept time-consuming ovarian induction treatments and risk higher multiple pregnancies. It seems that the time has come to replace ovarian induction in anovulatory infertility with IVF treatment including cycle segmentation and single-embryo transfer in an FET cycle.

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