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The role of Natural Cycle IVF in assisted reproduction

Michael von Wolff, MD, Professor *

University Women's Hospital, Division of Gynaecological Endocrinology and Reproductive Medicine, Inselspital, University Hospital, Berne, Switzerland

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Natural Cycle IVF (NC-IVF) with and without modifications is being increasingly performed. NC-IVF and conventional gonadotropin-stimulated IVF (cIVF) should not be understood as competing treatments, but as complementary treatments with different target groups and to some extent other indications. NC-IVF is particularly interesting for couples who wish to save money, wish a treatment with as few risks as possible and for women who would like to avoid selection and cryopreservation of embryos. NC-IVF therefore contributes to the concept of individualized and patient-oriented therapy. The time to pregnancy is slightly longer than with conventional IVF. NC-IVF is particularly suitable for younger women and for women with a very low ovarian reserve. In this article, the principles of NC-IVF, i.e. monofollicular IVF without gonadotropin stimulation, are described and the technical differences to cIVF, advantages and disadvantages, perinatal outcome and indications for NC-IVF are highlightened.

Introduction

The world's first successful IVF pregnancy occurred after natural-cycle IVF (Natural Cycle IVF, NC-IVF), i.e. after IVF without the use of exogenous hormones and with natural folliculogenesis. Not

* Universitäts-Frauenklinik Bern, Abteilung für gynäkologische Endokrinologie und Reproduktionsmedizin, Freidbühlstrasse 19, 3010, Bern, Switzerland. Fax: +41 31 63211305.
E-mail address: Michael.vonWolff@insel.ch.

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much later, gonadotropin treatments were used to increase the pregnancy rate through polyfollicular stimulation and the associated transfer of multiple embryos (conventional IVF, cIVF).

The wish that many women express to undergo as little hormonal treatment as possible, progress was made in the implementation of NC-IVF and new insights into the benefits of this treatment are now leading to couples expressing increasing interest in this therapy, which is becoming ever more common in some countries [1]. In contrast, among physicians NC-IVF is often discussed controversially, as it is considered to be a therapy which competes with conventional IVF therapy. However, NC-IVF and cIVF are completely different forms of treatment which can only be compared to a limited extent. NC-IVF and cIVF should therefore be understood as complementary IVF treatments that expand the treatment spectrum in terms of individualized, patient-oriented treatment.

In this article, the principles of NC-IVF, i.e. monofollicular IVF without gonadotropin stimulation are described and the technical differences to cIVF, advantages and disadvantages, perinatal outcome and indications for NC-IVF are highlighted.

Principle and definition

The principle of NC-IVF is based on the concept of natural follicle recruitment and selection and an unsupported luteal phase. This avoids gonadotropin injections and luteal phase support. The implantation rate per fertilized oocyte seems to be higher, possibly due to better oocyte quality and unaffected endometrial function. However, it needs to be stressed that the high number of oocytes collected in most cIVF cycles can overcompensate these disadvantages resulting in shorter time to pregnancies in cIVF. Furthermore, the term “natural” is only related to the menstrual cycle, whereas the process of oocyte fertilization requires the same laboratory techniques as in cIVF such as insemination or intracytoplasmic sperm injection (ICSI).

According to the definition by the International Society for Mild Approaches in Assisted Reproduction, ISMAAR [2] published in 2007, Natural Cycle IVF is defined as IVF without any medication. The term “modified NC-IVF” includes some medication to reduce the likelihood of cycle cancellation, such as human chorionic gonadotropins (hCG), to induce final oocyte maturation and/or gonadotropin releasing hormone (GnRH) antagonists (GnRHant) with or without follicle stimulation hormone (FSH) or human menopausal gonadotropin (hMG) as addback therapy. According to Nargund et al., 2007 [2], luteal phase should be given if GnRHant are applied.

These definitions are currently under review by ISMAAR and it can be expected that they will be slightly modified. The reasons are obvious. Firstly, NC-IVF almost always requires ovulation triggering with HCG as otherwise the technique is inefficient, secondly, single injections of GnRHant do not require gonadotropin add-back, thirdly, the likelihood of cycle cancellation can also be reduced by other medication such as non-steroidal anti-inflammatory drugs (NSAIDs) and fourthly, luteal phase support is not required using these treatment strategies.

Therefore, in this manuscript NC-IVF will be defined as any IVF without gonadotropins or any other stimulation of follicular growth, allowing natural follicle recruitment and selection and as IVF without any luteal phase support. However, medications such as single GnRHant injections, NSAIDs and very low dosages of clomifene citrate (CC) to avoid premature LH surge as well as hCG to trigger ovulation can be applied (Fig. 1). Clinically this kind of NC-IVF leads in most cases in the development of only one follicle and can therefore also be defined as “monofollicular IVF”.

Conventional IVF (cIVF) is defined in this article as any IVF with gonadotropin stimulation and GnRHant or GnRH agonists to prevent LH surge in order to generate many follicles, without preimplantation genetic testing. cIVF can also be defined as “polyfollicular IVF”.

Minimal stimulation IVF is defined as any IVF therapy with some stimulation of follicular growth and can also be described as “oligofollicular IVF”.

All calculations and comparisons in this article, which only focuses on NC-IVF compared to cIVF, are based on these definitions.

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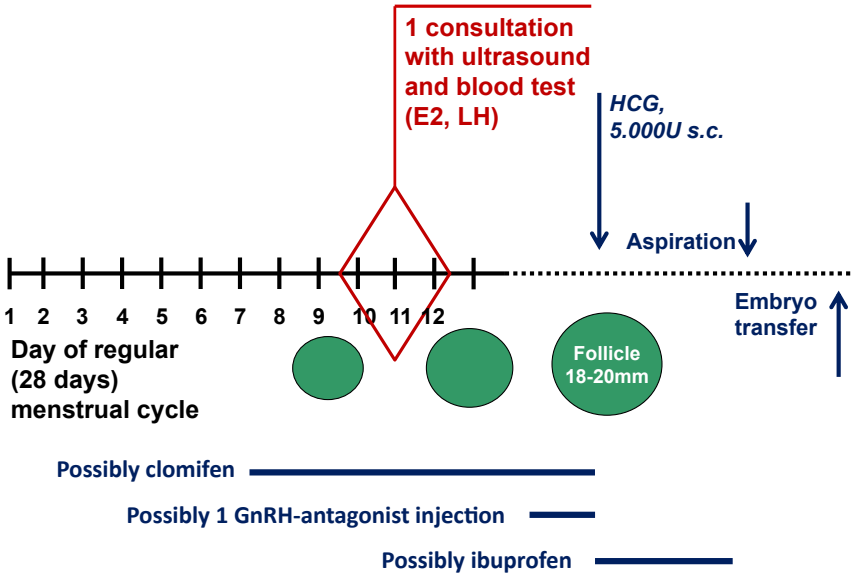

Fig. 1. NC-IVF treatment protocol.

NC-IVF specific technical aspects

Follicle monitoring

NC-IVF can only be an alternative to cIVF if treatment is kept to a minimum, i.e. with the least possible effort for the patient (Fig. 1). Essential here are the number of follicular growth monitoring. An exact evaluation of the follicular growth monitoring performed has so far only been done in the studies by von Wolff et al., 2014a [3] and Hämmerli et al., 2017 [4]. The first follicular growth monitoring was performed during a 28-day cycle between the 10th and 12th cycle day. When the follicular diameter was expected to reach at least 16 mm and estradiol (E2) concentration was expected to be $\geq$ 700 pmol/L, 5000 IU human chorionic gonadotropin (HCG) was administered subcutaneously 36 h before oocyte retrieval. This procedure required 1.2 follicular monitoring sessions per cycle. It was comparatively determined that arithmetically, 7.8 consultations would be required for 3 NC-IVF cycles compared to 5 consultations for a cIVF with a fresh transfer [5]. Hämmerli et al., 2017 [4] compared the psychological burden of NC-IVF therapy (up to 3 NC-IVF cycles) with cIVF therapy (1 therapy cycle) and also analysed the number of consequent consultations. There were 5.5 consultations for c-IVF and 6.2 for NC-IVF with the same pregnancy rate in both study arms. Thus, the number of consultations required for one cIVF cycle is equivalent to 2–3 NC-IVF cycles.

Control of premature ovulation

The transfer rate is crucial for the effectiveness of the NC-IVF. This depends essentially on the egg cell collection rate and thus on the number of available follicles. Since the oocyte must be harvested as late as possible to minimize the risk of collecting immature oocytes, there is a risk that ovulation has already taken place at the time of scheduled oocyte collection. Various techniques have been described to reduce this risk.

Injection of a GnRH antagonist (GnRHant)

GnRHant can be used if the LH surge has not yet started and ovulation should be postponed by one day. If more than one injection is administered, gonadotropins must be added in addition [6] as not

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only LH, but also FSH is down-regulated. However, according to the definition used in this publication, this no longer corresponds to NC-IVF. An injection of GnRHant can be used if the follicular puncture is to be delayed by one day, e.g. for logistical reasons, or if the follicular size is still <15 mm, but the E2 concentration is already so high that an LH surge is expected.

Administration of non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs, e.g. indomethacin or ibuprofen, may be used to postpone ovulation by several hours both before and at the onset of LH surge [7–9]. NSAIDs inhibit cyclooxygenase (COX) which catalyses the synthesis of PGE2, a key prostaglandin in the inflammatory cascade of ovulation. According to Bienz et al., 2018 [10], orally administered ibuprofen penetrates the follicle, where it leads to similar concentrations as in the blood serum. In the follicular fluid, ibuprofen leads to a (non-significant) reduction in the concentration of PGE2 and a reduction of inflammatory cytokines such as interleukin 8 [10]. This seems to inhibit the LH surge-induced inflammatory process and thus the break-down of the follicular wall. Indomethacin [8] ibuprofen [10] and other NSAIDs are used. Ibuprofen at a dose of 3 × 400 mg does not cause any gastrointestinal side-effects [11]. Although NSAIDs are used in each cycle in some studies [8], this approach results in unnecessary drug administration in most cases. The administration of NSAIDs can be minimized if they are only used if a commencing LH surge is detected. Kohl et al. [9], showed that when ibuprofen at a dose of 3 × 400 mg was given at an incipient LH surge (LH = 10–20 U/l) and oocyte collection took place 2 days and thus about 48 h later, the rate of premature ovulation was only 20.6%. Transfer rate per initiated cycle was 46%, pregnancy rate per transfer was 27.6% and per initiated cycle 12.7%.

These numbers were similar to a control group without premature LH surge and without ibuprofen, demonstrating that oocyte competence does not seem to be negatively affected by ibuprofen.

Preovulatory administration of low-dose clomifene citrate (CC)

Low dose CC can be used prophylactically to delay the LH surge. Clomiphene contains a mixture of two isomers, about 1/3 in the zuclomifene (cis) form and 2/3 in the enclomifene (trans) form. Enclomifene probably has estrogen antagonist effects and inhibits the positive feedback at the level of the hypothalamus [12]. As enclomifene is eliminated rapidly within around 24 h [13], clomifene tablets need to be given once a day until the day of ovulation triggering. In contrast, clomifene which probably has estrogen agonist actions at the pituitary level [12], is eliminated at a much slower rate [13], which can clinically result in cyst formation in consecutive stimulation cycles, especially when higher doses were applied.

In a clinical study, CC reduced the rate of premature ovulation from 27.8% without CC to 6.8% and increased the transfer rate from 39.8% to 54.4% respectively [3]. Pregnancy rates per transfer were 25.0% with and 27.9% without CC and per initiated cycle 13.6% and 11.1%, respectively. Use of CC resulted in mild flushes and headache in 5% of patients. Persisting ovarian cyst formation was not observed.

Follicle aspiration

The transfer rate depends crucially on the egg cell collection rate. To increase the oocyte collection rate, follicular flushing is carried out in NC-IVF by several working groups.

For cIVF with a multifollicular response [14] and a low response [15], follicular flushing has no additional benefit. However, in monofollicular NC-IVF, follicular flushing appears to increase the IVF success rate.

Von Wolff et al., 2013 [16], used a monoluminal 19G aspiration needle and flushed the follicles three times. By flushing, the total oocyte yield increased by 80.9% from 44.5% to 80.5%. Oocyte yield per aspiration was 44.5% in the aspirate, 20.7% in the 1st flush, 10.4% in the 2nd flush and 4.3% in the 3rd flush. Flushing increased the transfer rate by 91.0% from 20.1% to 38.4%.

However, this is the only study to date on the effect of flushing in NC-IVF and it is a retrospective study. The results of a prospective randomized study by our research group, comparing aspiration followed by 5-fold follicular flushing compared to aspiration without flushing in NC-IVF, are expected in 2019(ClinicalTrials.gov Identifier: CT02641808).

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Luteal phase support

IVF requires luteal phase support until the pregnancy test results positive [17]. The supra-physiological E2 concentrations in particular lead to a suppression of LH release, resulting in a luteal body insufficiency [18].

Although these factors do not apply to NC-IVF, many physicians still perform luteal phase support, especially since it cannot be ruled out that the function of the corpus luteum is limited by the follicular aspiration and follicle flushing. However, von Wolff et al., 2017 [19] showed that the luteal phase is unaffected by follicular aspiration and repeated follicular flushings. They conducted a prospective cohort study and compared women aged 18–40 who underwent both a reference cycle with hCG-induced ovulation as well as a flushing cycle with hCG-induced ovulation, followed by follicular aspiration with follicle flushings. The length of the luteal phase and luteal concentrations of progesterone and estradiol were analysed. Duration of the luteal phase was (median [IQR]) 13 days [12; 14.5] in reference cycles, and in flushing cycles 14 days [12.5; 14.5]. Progesterone and estradiol concentrations were also not different, indicating that follicle aspiration and flushing of follicles does not have a negative effect on the luteal phase.

Thus, luteal phase support in NC-IVF therapy is not usually required. Because vaginal administration of micronized progesterone causes troublesome side effects in up to 50% of women [20,21], this is a relevant relief for many women. Whether women >40 y or women with a shortened luteal phase of <12 days could benefit from luteal phase support is still unclear.

Psychological stress induced by NC-IVF

cIVF imposes substantial distress [22] and many couples stop treatment prematurely because of psychological stress, thus reducing the likelihood of success [23]. In addition to the pressure to succeed, stress-inducing factors include daily injections, treatment risks and costs, but also factors such as embryo selection and cryopreservation of embryos [24].

In NC-IVF almost no injections are required, the cost per cycle is lower [5], and embryo selection and cryopreservation are not required. However, about 3 times as many treatment cycles are required per pregnancy achieved [25]. Since all these factors can influence the treatment stress, Hämmerli et al., 2018 [26] investigated psychological distress during and after cIVF and after up to three NC-IVF therapies. They showed that NC-IVF patients had a significantly lower level of depression and a higher satisfaction with the treatment after the treatment cycles than cIVF patients.

NC-IVF therefore appears to cause less treatment-induced stress than cIVF. It should be noted that this study was conducted in Switzerland, where IVF treatments are not reimbursed by the health insurance system. Therefore, it cannot be ruled out that in other countries with other reimbursement systems and in other cultures, the treatment stress of the various IVF therapies will be perceived differently.

Costs of NC-IVF

The costs of an NC-IVF cycle are significantly lower than those of a cIVF cycle due to the lack of gonadotropin stimulation, avoidance of anaesthesia and less effort in the IVF laboratory. A couple with good prognostic factors for successful therapy has a chance of becoming pregnant after only 1–2 NC-IVF cycles, therefore making considerable cost savings.

However, for a cost comparison, it is not the cost per cycle that should be calculated, but the cost per pregnancy achieved and, ideally, even per birth achieved. Thus, according to Sunkara et al., 2016 [25], about 3 NC-IVF therapy cycles are required to achieve the same pregnancy rate as with one cIVF therapy.

Von Wolff et al., 2014b [5] determined the cost per pregnancy achieved in NC-IVF and cIVF. The NC-IVF was based on own data from women aged 35.4 $\pm$ 4.7 y (21-42 y), 1.2 follicular controls per cycle, a transfer rate of 54.3% and a pregnancy rate of 13.6% per initiated cycle. For cIVF, 3 consultations per fresh cycle and 2 consultations per thawing cycle were calculated. The pregnancy rate was calculated for cIVF according to the ESHRE IVF registry [27] with 30% for a fresh cycle and 20% for a thawing cycle.

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Based on these guidelines, the cost per pregnancy achieved when performing NC-IVF is 15% lower than for cIVF.

Groen et al., 2013 [28], determined the cost per birth achieved for NC-IVF and cIVF. Based on the success data from two major Dutch centres and the cost of 6 NC-IVF cycles and a complete cIVF using a single embryo transfer, they compared two techniques that mainly produced no multiple births. The age of women was 18–36 y, the delivery rate per cycle was 6.0% for NC-IVF and 22.7% for cIVF. Based on these numbers, the cost per birth achieved when performing an NC-IVF was 12% higher than with cIVF.

In summary, the cost per cycle for the NC-IVF is much lower than for cIVF. However, the overall costs of NC-IVF and cIVF seem to be similar for each pregnancy and birth achieved.

Success rates of NC-IVF

A number of studies has shown that the implantation rate per oocyte collected during cIVF is lower than for NC-IVF. The reasons for this are unclear. A dysregulated endometrium due to supra-physiological estradiol concentrations [29] and an altered endocrine milieu due to reduced LH concentrations [30] are suspected to be responsible. Embryo quality also appears to be better in NC-IVF [31–33], although the aneuploidy rate of the embryos is not lower [34].

However, the success rates of NC-IVF can only be compared with cIVF to a limited extent, since these are completely different therapies. Accordingly, no study has been conducted with a head-to-head comparison of both therapies.

It should also be noted that one cycle of a cIVF, including timing and the often-used subsequent wash-out or recovery cycle takes 3 months, during which three NC-IVF cycles can be performed. It therefore makes more sense to calculate the success rate per unit of time or per cost (see below) and not per initiated cycle.

The data on the success rate are confusing, as the published studies are often small, various IVF therapy protocols were used, the success rates per transfer rather than per cycle are given [35] and IVF therapies were performed under unfavourable conditions such as in low responders [36], or only after the performance of several classical IVF treatments because of national reimbursement policies as in Germany [37].

According to registry data [38] and data from centres also offering NC-IVF as the primary IVF therapy in normal responders [39,3], the pregnancy rate per initiated cycle is on average between 10 and 15%. However, as with cIVF, the success rates are strongly age-dependent and are below 10% in women >38 years [40].

Several studies have calculated how many NC-IVF cycles are required to achieve the same success rate as cIVF. According to [25] Sunkara et al., 2.9–3.5 NC-IVF cycles are required. In a study by Hämmerli et al., 2018 [26], 2–3 NC-IVF cycles were required. These figures roughly correspond with the calculation by von Wolff et al., 2014b [5], who calculated that the time to pregnancy with NC-IVF is 30% longer than with cIVF because of the monthly but less effective cycles.

The success rate of cIVF naturally depends very much on the number of oocytes which can be collected. As a result, the success rate in low-responders undergoing NC-IVF is higher than for c-IVF [40], whereas women around 40 years of age with a high ovarian reserve should benefit from cIVF because of the age-related decline in chances of success (Fig. 2).

In summary, the success rate of NC-IVF per initiated cycle is significantly lower than for c-IVF. With consistent monthly NC-IVF treatment, which allows about 3 cycles in the same time period as one cIVF, the success rate per unit time is only slightly reduced. With low responders, the effectiveness of NC-IVF is higher than with cIVF. Older women with a high ovarian reserve benefit more from cIVF than from NC-IVF.

Perinatal outcome after NC-IVF

Pregnancies after IVF are at a risk of adverse perinatal outcomes compared with those conceiving naturally [41,42]. This might be due to the underlying infertility cause, but also to the IVF procedure itself, which includes ovarian stimulation, in-vitro gamete handling, embryo culture and cryopreservation of embryos [42]. Many of these factors apply to NC-IVF, NC-IVF but not ovarian stimulation and

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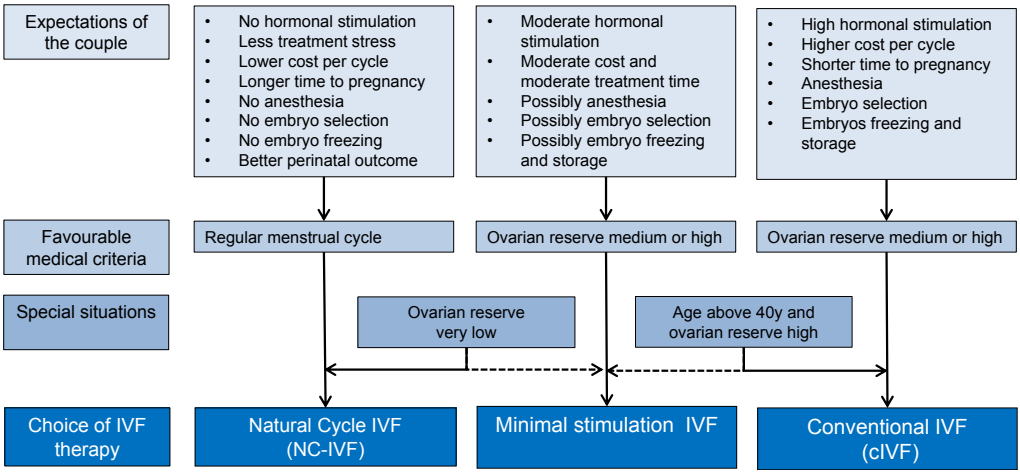

Fig. 2. Decision aid for patient orientated IVF therapy.

cryopreservation of embryos. The first factor, ovarian stimulation, leads to supraphysiological estrogen concentrations in the blood circulation, which lead to dysfunction of the endometrium and placenta. In animal models it has been shown that high serum estradiol levels have a negative effect on uterine spiral artery invasion into the placenta [43]. Furthermore, supraphysiological estradiol concentrations may result in an edematous endometrium, impairing trophoblast differentiation and abnormal placentation [44]. These effects might be causative for the increased risk of low birth weight, LBW (<2500 g) (RR 1.95, 95% CI 1.03 to 3.67) in cIVF versus NC-IVF therapies as shown in a meta-analysis [45]. Furthermore, the risk for small gestational weight for age, SGA (birth weight <10th percentile), is also increased in cIVF compared to NC-IVF therapies [46]. We confirmed an increased risk of SGA in cIVF versus NC-IVF and specified a supraphysiological E2 concentration of ≥10 000 pmol/l to be a risk factor (aOR 3.78, 95% CI 1.1–13.2, $p = 0.037$) [47].

The second factor, cryopreservation of embryos, when compared to a fresh transfer in stimulated IVF, leads to an increased risk (RR) of hypertensive disorders of pregnancy (1.29; 95% CI 1.07–1.56), large baby for gestational age (1.54; 95%). CI 1.48–1.61) and a high birth weight (1.85, 95% CI 1.46–2.33) [48]. Since the child's weight is also increased in comparison to natural conception (AOR = 1.31 95% CI 1.20–1.43 $p < 0.001$) [49], cryopreservation per se seems to have an effect. Whether this effect is due to epigenetic modifications due to the freezing process is not yet clear.

In summary, the perinatal outcome of NC-IVF is probably better due to the lack of stimulation and the associated physiological estradiol concentrations as well as the lack of cryopreservation of the embryos than in classical, stimulated IVF. However, whether this improved outcome is functionally and clinically relevant for the children in later years of life has yet to be shown in further studies.

Indications for and against NC-IVF

The indications for or against NC-IVF are based on the individual wishes of the couple as well as on the individual chances of success and therefore on the objective prognosis factors of IVF therapy.

The wishes of the couple, especially the woman, are often individual but also culturally very different and are shaped by previous experiences with IVF therapies, as well as religious reasons. Some women develop a variety of side effects during cIVF, so they refuse gonadotropin stimulation in further treatments. Some couples do not want embryo selection and cryopreservation of embryos for religious reasons. On the other hand, some couples seek the treatment with the shortest time to pregnancy and are willing to accept the risk of multiple births.

Irrespective of individual wishes, the success of the treatment is usually, if not always, at the centre of the decision-making process. Because of this, it may be useful to consider the individual needs as

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secondary and to put the medical prerequisites at the forefront. Thus, cIVF in low responders, in which only 1–2 follicles would form under gonadotropin stimulation, makes little sense. In contrast, for a woman in her forties with a well preserved ovarian reserve, treatment with the shortest time to pregnancy and therefore cIVF is preferable. A logarithm that considers the individual wishes as well as the medical prerequisites for the indication is shown in Fig. 2.

In contrast to the individual wishes, prognostic factors for the occurrence of a pregnancy can be objectified. For cIVF, a meta-analysis [50] revealed a negative association between pregnancy and female age (OR 0.95, 95% CI: 0.94–0.96), duration of subfertility (OR 0.99, 95% CI: 0.98–1.0) and basal FSH (OR 0.94, 95% CI: 0.88–1.0). It also described a positive association with the number of oocytes (OR 1.04, 95% CI: 1.02–1.07) and better embryo quality was also associated with higher pregnancy chances. The relevance of the cause of infertility seems to be limited as shown by an Australian registry study [51], which showed a success rate of 22.0% in couples with a male factor compared to 19.2% with a female factor (see Table 1.

The prognostic factors for NC-IVF have so far only been examined in two studies (Table 2). Gonzales-Foruria et al., 2016 [52], found age (OR 0.93, 95% CI: 0.88–0.98) but not infertility to be a prognostic factor in NC-IVF. This study investigated pregnancy but not live birth rates and included varying numbers of IVF cycles per patient and gonadotropin stimulated cycles. Von Wolff et al. [40] only included one cycle per patient and analysed both pregnancy and live birth rates. This study included only transfer but not initiated cycles. Multivariate logistic regression analysis revealed high female age (OR 0.87, 95%: CI 0.78–0.95) and long duration of infertility (OR 0.61, 95% CI: 0.42–0.86) as predictors for live birth rates but not AMH concentration and infertility factors.

Controversies of NC-IVF

The comparison of NC-IVF with cIVF is often based less on scientific evidence than on philosophical considerations such as “natural” versus “artificial” and how effective the two IVF treatments really are.

That such a comparison does not make sense, is obvious. Follicle recruitment and selection, as well as the luteal phase of NC-IVF are actually “natural”; however, the process of egg fertilization is just as “artificial” as in cIVF. Furthermore, “effectiveness” can also be considered from different angles. The advocate of cIVF will only consider the pregnancy rate per cycle and transfer under “effectiveness”. The advocate of NC-IVF, however, would point out that “effectiveness” can also be related to the costs, the treatment stress, the risks, etc. and emphasize that factors other than the pure pregnancy rate per cycle and transfer are also relevant.

The controversies regarding NC-IVF versus cIVF are consequently based on different perspectives and on different sets of values.

A blanket approval or rejection of NC-IVF or cIVF does not make sense, and the decision for or against one of the two therapies should be based on the biological and medical conditions and the wishes of the couple, taking into account the advantages and disadvantages of the treatments (Table 2). Such a patient-oriented approach is exemplified in Fig. 2.

Due to the diversity of NC-IVF and cIVF, a head to head comparison of NC-IVF versus cIVF, as required by many scientists, does not make sense. On the one hand, it will hardly be possible to recruit enough patients for such a prospective randomized study, and on the other hand the

Table 1
Positive prognostic factors for NC-IVF and cIVF for treatment success [40,50,52].

NC-IVF
Low female age
Short duration of infertility
cIVF
Young female age
Short duration of subfertility
Low basal FSH
High number of oocytes
High embryo quality

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Table 2
Advantages and disadvantages of NC-IVF compared to cIVF.

Advantages of NC-IVF compared to cIVF
NC-IVF treatment can be performed every month
Daily injections are not required
Luteal phase support is not required
The endometrium is not negatively affected by supraphysiological estradiol concentrations
Adjuncts to improve endometrial function are not required
Anaesthesia is not required for follicle aspiration
Cryopreservation of zygotes or embryos is not necessary; discarding of surplus embryos is not required
The average psychological treatment distress seems to be lower
Ovarian hyperstimulation syndromes cannot occur
Multiple pregnancies rarely occur
The perinatal outcome is better
The costs per cycle are much lower
Disadvantages of NC-IVF compared to cIVF
NC-IVF cycles require more flexibility for the IVF centre, for the women and - if sperm is not cryopreserved – also for the man
The average time to pregnancy is longer in NC-IVF
The average total treatment costs per achieved live birth are not lower than in cIVF

question arises as to what the main outcome criterion of such a study should be. The pregnancy rate per cycle, per transfer, or per unit of time are just a few of the possible criteria, along with a variety of other outcome criteria, such as complication rates, multiple treatment rate, stress of treatment, cost, and many more. It makes more sense to further optimize NC-IVF with the help of further studies and to further refine the range of indications since they are less about competing but complementary techniques.

Some reproductive physicians might argue that cIVF provides the opportunity to perform a thawing cycle a lower costs and with less patient's stress and risks which should be taken into account if both techniques are compared. However, this is a complicated issue as thawing cycles still cost quite a lot, as the patient's stress has never been compared in thawing cycles and NC-IVF cycles and as thawing cycles could impose a still poorly understood risk to the children due to the freezing procedure [48]. The putative risks of freezing embryos also need to be taken into account if the “freeze all” strategy is discussed to avoid ovarian hyperstimulation syndrome. Indeed, this strategy avoids this maternal risk which might be an argument for cIVF, but as long as the fetal risks of the freezing process are not sufficiently understood, this argument should be used with care.

Another controversy may be based on different expertise in NC-IVF treatment. Since NC-IVF represents a completely different form of treatment, it also requires completely different knowledge and experience in order to achieve a high success rate with minimum effort for the couple. cIVF is based on treatment protocols that can be widely used consistently in all women. NC-IVF, however, requires a deeper understanding of basic endocrinology and individualized treatment.

Conclusion

NC-IVF and cIVF are basically different forms of treatment with different costs, burdens and risks. They both require specific knowledge and experience as well as various logistical requirements on the part of the IVF Centre. The treatments should not compete with each other but should be seen as complementary. They can be offered based on the medical prerequisites and wishes of the couple and contribute to personalized and patient-oriented IVF treatment.

Conflicts of interest

The author of this manuscript have nothing to declare and no conflicts of interest. He is running a Natural Cycle IVF network.

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Practice points

- Natural cycle IVF (NC-IVF) and conventional, gonadotropin IVF (cIVF) are not competing treatments but complementary treatments with different indications, advantages and disadvantages.
- NC-IVF contributes to an individualized and patient orientated IVF therapy.
- NC-IVF tends to be cheaper than cIVF, but time to pregnancy is on average longer.
- NC-IVF seems to be more successful in low responders but less successful in older women with a high ovarian reserve.
- NC-IVF require specific knowledge and experience to achieve low treatment burden and high success rates.

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