Natural Cycle IVF: Summary of the Current Literature

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Introduction

Since the first successful in vitro fertilization (IVF) by Steptoe and Edwards in 1978 [1] which was performed in a natural cycle, this way was abandoned in favour of controlled ovarian hyperstimulation to retrieve more oocytes and therefore to reach a better pregnancy rate and live birth rate.

In the last years, the natural cycle IVF received a renaissance and the in vivo-maturated oocyte without stimulation is assumed to have a better competence for fertilization and implantation. The most common problem in natural cycle IVF is still the spontaneous LH-surge as well as the premature ovulation. Furthermore, natural cycle IVF is the method of choice for women with low response in former controlled ovarian hyperstimulation cycles or with a low ovarian reserve, shown by a low antral follicle count and/or low anti-Muellerian hormone. Therefore, many studies deal with possibilities to enhance the success rates in natural cycle IVF.

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For this summary of the current literature dealing with natural cycle IVF/ICSI, a PubMed, Embase and Cochrane database search was performed with the key words "natural cycle IVF/ICSI", "fertilization rate" and "pregnancy rate". For the actuality, the search was limited to articles published in English in the period 2009 till 2014. This strategy yielded 144 articles, 28 of them were suitable for this summary (Table 5.1). The design of the studies was heterogeneous, most of them were retrospective studies, with study populations from 30 to 7244 patients undergoing 28–20,244 cycles with a mean age from 30.8 to 40.3 years.

Natural Cycle IVF

Many patients are asking for a "natural" IVF approach without any hormonal stimulation because of "fear of hormones", ethical or religious reasons or a history of hormone-dependent cancer in their own or family history [2]. A natural cycle IVF is emphasized to be more cost- and time-effective for the patients [3, 4]. Thus and for the scientific assumption that the unstimulated, in vivo maturated oocyte has a better competence for development, many IVF units established natural cycle IVF again.

However, difficulties such as premature LH-surge and ovulation, failure of retrieve an oocyte, and therefore lesser success rates still

Table 5.1 Overview on current studies on NC-IVF/ICSI

Study	Year	Method	Patients (n)	Age (years)	Cycles (n)	FR (%)	PR/ET (%)
Kedem et al. [8]	2014	Modified NC-IVF/ICSI in POR	111	39	111	0.67	0.9
Von Wolff et al. [21]	2014	NC-IVF	112	35.2	108	45.4	27.9
Von Wolff et al. [21]	2014	NC-IVF + Clomiphene	112	35.2	103	57.3	25.0
Bodri et al. [32]	2014	NC-IVF/ICSI + NSAID	365	40.3	1183	57.0	35.0
Roesner et al. [6]	2014	NC-IVF/ICSI	159	36.4	463	59.4	10.9
Rijken-Zijlstra et al. [20]	2013	Minimal stimulation-IVF + GnRH Antagonist + NSAID	60	30.9	250	67.1	Ongoing PR/Cycle 5.6
Rijken-Zijlstra et al. [20]	2013	Minimal stimulation-IVF + GnRH Antagonist	60	31.8	60	274	Ongoing PR/Cycle 8.4
Son et al. [29]	2013	NC-ICSI/IVM	28	33.3	28	73.4	20.8
Polyzos et al. [7]	2012	NC-IVF in POR	136	37.3	390	n.a.	LBR 7.4
Kawachiya et al. 19]	2012	NC-IVF/ICSI	n.a.	36.5	903	44.5	35.9
Kawachiya et al. [19]	2012	NC-IVF/ICSI + NSAID	n.a.	36.2	962	55.3	39.1
Kato et al. [26]	2012	Minimal NC-IVF	7244	39.4	20,244	77.0 IVF 83.2 ICSI	21.8
Gordon et al. [5]	2011	NC-IVF	n.a.	n.a.	795	n.a.	26.1
Papolu et al. [24]	2011	Mild stimulation IVF	150	n.a.	n.a.	n.a.	56.0
Lou and Huang [23]	2010	Modified NC-IVF	30	30.6	30	62.7	PR/Cycle 30.0
Xu et al. [28]	2010	NC-ICSI/IVM	323	31.5	364	86.3	35.9
Aanesen et al. [22]	2010	Modified NC-IVF	43	34.2	129	n.a.	26.7
Aanesen et al. [22]	2010	Mild NC-IVF	145	32.8	250	n.a.	27.2
Kim et al. [11]	2009	Minimal stimulation-IVF/ICSI in POR	90	n.a.	90	n.a.	LBR 13.5
Schimberni et al. [12]	2009	NC-ICSI	294	39.3	500	57.0	17.1
Lim et al. [27]	2009	NC-ICSI/IVM	140	31.4	153	81.9	40.4

FR Fertilization rate, *PR* Pregnancy rate, *ET* Embryo transfer, *LBR* Live birth rate, *n.a.* Not applicable

limit the use of natural cycle IVF. Gordon et al. [5] evaluated the SART Clinical Outcome Reporting System (CORS) database in the USA and found that unstimulated IVF cycles represent less than 1% of all IVF cycles. They could show that natural cycle IVF leads to significantly higher implantation rates in some age groups (35–37 years and 38–40 years) when compared to conventional IVF cycles (40.4% vs. 23.8% and 28.4% vs. 15.4%). In the authors' opinion, this may support the hypothesis that the endometrial receptivity is enhanced in natural cycles. A pregnancy rate of 35.9% in patients <35 years and live birth rate of 19.9% for all patients could be achieved. In conclusion, the authors would recommend natural cycle IVF especially to patients with good preconditions (e.g. <35 years, no poor ovarian response (POR)).

Another retrospective study by Roesner et al. [6] evaluated 463 cycles of natural cycle IVF and came to similar results. Because patients undergoing natural cycle IVF present often unfavourable preconditions (long duration of infertility, age >40 years, known history of low response in former conventional stimulated cycles), pregnancy rates still remain low. Further studies to optimize treatment strategies and to define patient groups suitable for natural cycle IVF were recommended.

Low Responders

In patients who are known to have a low ovarian reserve or who showed a low response in a former controlled ovarian hyperstimulation cycle, many teams prefer a natural cycle IVF instead of another controlled ovarian hyperstimulation attempt. The following studies focus on poor responder patients.

Only two studies [7, 8] followed the Bologna criteria of POR (at least two of the following): (1) advanced maternal age ($\geq$40 years) or any other risk factor for POR, (2) a previous POR ($\leq$3 oocytes with a conventional stimulation protocol) and (3) an abnormal ovarian reserve test [9]. Polyzos et al. [7] found a significant lower embryo transfer rate as well as live birth rate in the study group of low responders compared with the control group with normal responders. Acknowledging the limitations of their study—a retrospective design and a significant younger control group—they conclude that older patients with POR may be candidates for alternative therapies, e.g. such as oocyte donation programs.

Kedem et al. [8] support this thesis in their retrospective study with patients also fulfilling the Bologna criteria and undergoing a modified natural cycle with GnRH antagonist and human menopausal gonadotropin (hMG) stimulation after an IVF attempt with controlled ovarian hyperstimulation and poor response. The GnRH antagonist was started when the leading follicle had a diameter of 13 mm and two to three ampules of hMG were injected daily. Because of very poor pregnancy rates in this patient group, they conclude that genuine poor responders with a yield of only one oocyte in a previous conventional cycle did not benefit from a natural cycle program and should therefore not be offered a mild stimulation natural cycle IVF. The option of a controlled ovarian stimulation, egg donation or adoption should be discussed with these patients.

In contrast, Kadoch et al. [10] stated in a retrospective study that a modified natural cycle IVF with GnRH antagonists starting at a follicle diameter of 15 mm, mild human menopausal gonadotropin stimulation (150 IU/d) and 50 mg indomethacin three times a day to avoid a premature ovulation should be the first choice in young poor responders because it is a cheap and monthly repeatable option. They mentioned that a single oocyte of better quality as a consequence of natural selection and a better endometrial receptivity resulting in natural cycle IVF balances the low chance for an embryo transfer in these attempts.

In a prospective assessment, Kim et al. [11] reported a similar pregnancy rate and live birth rate in a minimal stimulation natural cycle IVF with FSH and GnRH antagonist compared with a conventional antagonist protocol in low responder patients. The GnRH antagonist was administered when the leading follicle reached 13–14 mm together with 150 IU/d FSH. The ovulation was triggered at a follicle diameter of 17–18 mm and the retrieval was performed 34–35 h later. Natural cycle IVF with minimal stimulation is considered to be a last chance for women who have failed to respond adequately to a conventional hyperstimulation IVF cycle before oocyte donation.

Another retrospective study by Schimberni et al. [12] reported about 500 consecutive cycles of natural cycle intracytoplasmic sperm injection (ICSI) in poor responders without any hormonal intervention. Similar rates of retrieved oocytes, embryo transfers and pregnancies per consecutive cycle but significantly different pregnancy rates in younger patients when analysing the date

depending on the patients age were found ($\leq$35 years PR = 29.2% vs. 36–39 years PR = 20.6%, vs. $\geq$40 years PR = 10.5%). In conclusion, natural cycle ICSI up to four attempts in younger patients ($\leq$40 years) was considered as a possible chance for patients with a low ovarian reserve.

Besides these studies, successful natural cycle IVF was also reported in case reports. Hyman et al. [13] described the live birth of twins after a modified natural cycle ICSI in a woman with decreased ovarian reserve. Despite of elevated FSH levels the patient present with regular monthly menstruation. After two IVF cycles with high dose controlled ovarian stimulation and poor response, it was decided to perform a natural cycle ICSI with early hCG administration. From three antral follicles with a maximal diameter of 12 mm at retrieval, three mature oocytes were collected. Two were fertilized, and a twin pregnancy was achieved.

Another team reported a successful pregnancy after a "double rescue" retrieval in a patient with low ovarian reserve following a natural cycle IVF [14]. The patient felt that she might have surged the previous evening when she attended the IVF unit. Because there was a leading follicle with good perifollicular blood flow as well as a triple-layer endometrium in the ultrasound present the decision for retrieval on the same day was made. No oocyte was identified. With the patients' consent, a second attempt after hCG injection for the following day was scheduled. A control on the next day showed a regular follicle with good ultrasound criteria (very good peri-follicular blood flow), so a further retrieval was attempted. At that time, a metaphase I oocyte was found which was matured after a few hours in in vitro maturation (IVM) medium. Fertilization could be achieved, and a pregnancy was induced.

Li et al. [15] described a series of three women with poor response in a former controlled ovarian stimulation cycle who got pregnant after a natural cycle IVF combined with IVM. In all three cases, immature and mature oocytes were collected. The immature oocytes were matured in IVM medium and fertilized by ICSI and transferred with the resulting embryos resulted after the fertilization of the mature oocytes.

In the last case, a pregnancy after modified natural cycle with GnRH antagonist started at a follicle diameter of 15 mm and 75 IU/d hMG began the same day in a poor follicular responding young (<35 years) patient with elevated FSH levels is reported [16].

All authors of the described case reports conclude that their attempt in a natural cycle IVF in low responders combined with new approaches such as early hCG administration, double retrieval, IVM or modified stimulation may be additional alternatives for poor responders as a last chance before, e.g. oocyte donation.

GnRH Antagonists

Of upmost importance in natural cycle IVF is the risk of spontaneous LH-surges and therefore premature ovulation. Many attempts are made to avoid this event. Meanwhile, the addition of GnRH antagonists became a standard in most natural cycle IVFs.

In a prospective randomized trial, Kim et al. [11] used a GnRH antagonist in combination with a low-dose FSH stimulation for natural cycle IVF in comparison with a conventional antagonist protocol. Monitored by ultrasound examinations the GnRH antagonist as well as the stimulation with 150 IU FSG daily were started in the natural cycle group when the leading follicle reached 13–14 mm. Ovulation was induced when the dominant follicle reached a diameter of 17–18 mm with 250 µg hCG. In this protocol, they achieved a similar cancellation rate, pregnancy rate and live birth rate as in the control group. Therefore, they conclude that a natural cycle protocol with the use of GnRH antagonists is a patient-friendly and cost-effective alternative especially in low responders.

Kadoch et al. [10] as well used GnRH antagonists for preventing the spontaneous LH-surge. When the dominant follicle reached 15 mm, the GnRH antagonist was started and indomethacin was also added to avoid a premature ovulation. At the same time, hMG was

administered to prevent a decrease in the estradiol concentration. hCG was given when the leading follicle had a diameter of 18 mm and the retrieval was performed 34 h later. Kadoch et al. consider better embryo quality and better endometrium receptivity as a result of the natural oocyte selection and thus a better chance for an embryo transfer.

NSAID

Another approach to prevent the premature ovulation is the administration of non-steroidal anti-inflammatory drugs (NSAID). They may delay the ovulation by inhibiting the production of cyclooxygenase-2 which is important for the ovulation process [17, 18].

Kawachiya et al. [19] proofed and confirmed this hypothesis in a large retrospective non-randomized study with 1865 natural cycles: 962 with NSAID use and 903 without. No other medication such as GnRH antagonists to prevent a spontaneous LH-surge nor other stimulation drugs (FSH, hMG) were used.

The NSAID (25 mg suppositories of diclofenac 8 and 14 h before oocyte retrieval) was added according to the level of serum LH: LH <10 IU/ml and progesterone <1.0 ng/ml no NSAID was given, triggering and oocyte retrieval as usual, LH 10–30 IU/ml, progesterone <1.0 ng/ml NSAID every 6 h, hCG immediately and oocyte retrieval the next morning, LH 30–110 IU/ml, progesterone <1.0 ng/ml, NSAID optional, hCG immediately, oocyte retrieval the next morning, LH 10–110 IU/ml, progesterone >1.0 ng/ml no NSAID, no triggering of ovulation, oocyte retrieval the same day.

A significant difference was found in the rate of premature ovulation in cycles using NSAID compared to cycles without administration of NSAID (3.6% vs. 6.8%). Therefore, the fertilization rate and the embryo transfer rate were also significantly lower in the group without NSAID (53.3% vs. 44.5% and 46.8% vs. 39.5%).

In contrast, a prospective randomized clinical trial by Rijken-Zijlstra et al. [20] analysing the effectiveness of indomethacin to prevent the ovulation in a natural cycle could not confirm these results. While monitoring the cycle per transvaginal ultrasound and serum estradiol measurements, the GnRH antagonist was started when the leading follicle reached a diameter of 14 mm, 150 IU gonadotrophins per day were also added. About 50 mg indomethacin or placebo capsules were administrated 3 times per day from the day of hCG injection till the morning of oocyte retrieval. No benefit could be shown in administration of NSAID to prevent premature ovulation in comparison with the placebo group (cancellation rate 6.4% vs. 10.6%).

Clomiphene Citrate

Another approach to prevent the premature ovulation is the administration of clomiphene citrate. Von Wolff et al. [21] demonstrated that the daily intake of 25 mg clomiphene citrate started at day 6 (in a 26–27 day menstrual cycle) or day 7 (28–30 days length of menstrual cycle) may reduce the premature ovulation rate significantly (6.8% vs. 27.8% without clomiphene citrate) and increases the embryo transfer rate significantly (54.4% vs. 39.8%) without enhancing side effects (e.g. hot flushes, headaches or ovarian cysts). The clinical pregnancy rate showed no significant difference. Just one or two consultations were necessary before the introduction of the ovulation. Clomiphene citrate consists of two isoforms: enclomiphene (trans form) with an estradiol antagonist effect and an elimination time of 24 h and zuclomiphen (cis form) with an estradiol agonist effect that may cause ovarian cysts and a much shorter elimination time. Therefore, clomiphene citrate must be administrated once a day until the introduction of ovulation. In the described low dose of 25 mg/d, just mild side effects such as mild headache and mild or moderate hot flushes were reported by the study patients. Because of fewer consultations, this protocol is considered as a patient-friendly approach. In addition, the authors conclude that the natural cycle protocol allows the oocyte to mature in vivo resulting in higher implantation rates.

Mild Stimulation

Despite the expected advantages of natural cycle IVF such as better competence for fertilization and implantation of in vivo-matured oocytes without any hormonal treatment, the disadvantages of low retrieval rates due to premature ovulation rates and only one retrieved oocyte leaded to the idea of mild stimulation for enhancing the outcome of natural cycle IVF.

Aanesen et al. [22] report on a ten-year experience with natural cycle IVF by a so-called modified natural cycle IVF or mild stimulation natural cycle IVF. Both varieties were offered to women with desire for low hormonal treatment as well as for women with former ovarian hyperstimulation syndrome, unexpected side effects in former controlled hyperstimulation IVF or women who are not allowed to get a hormonal treatment (e.g. history of breast cancer). For modified natural cycle, IVF monitoring includes ultrasound examinations and measurement of serum estradiol concentrations. When the dominant follicle reached 17 mm and the estradiol concentration was between 500 and 750 pmol/l, ovulation was induced with 5000 IE hCG and the retrieval was performed 37 h later. For minimal stimulation IVF, the patients were stimulated with 100 mg clomiphene citrate from day 3–7 of their menstrual cycle. The ovulation was triggered with hCG when the leading follicle reached a diameter of 18 mm and the retrieval was performed 37 h later. The cancellation rate was 13.6% in the modified natural cycles and 31% in the minimal stimulation cycles. The authors suppose a partial effect of clomiphene citrate in preventing a premature LH-surge because of its estradiol antagonist effect. No significant differences were found in implantation rates or pregnancy rates.

Lou and Huang [23] described in their study a mild stimulation natural cycle protocol where 150 IU/d hMG were administered beginning at day 2 or 3 of the menstrual cycle. When two or more follicles reached a diameter of 17 mm, hCG was given to introduce the ovulation. Oocyte retrieval was performed 32 h later. Results were compared to a group of patients undergoing a conventional-long agonist protocol. Except the number of retrieved oocytes (7.8 vs. 12.2), no significant differences were found nor in fertilization rates nor in pregnancy rates.

Papolu et al. [24] have used a protocol with 150 mg/d clomiphene citrate started between cycle days 5 and 7. Additionally, 300 IU hMG were injected on day 5 and 300 IU FSH on days 7 and 9 of the treatment cycle. At a diameter of the leading follicle of 17 mm, hCG was administered and oocyte retrieval was performed 30–35 h later. There were no significant differences shown between the study group and a control group undergoing a conventional long protocol.

Another mild/minimal stimulation protocol is described by Zarek and Muasher [25]. Patients started on day 3 of their menstrual cycle with 100 mg/d clomiphene citrate until day 7. One day after 150 IU/d, hMG were administered and from day 11 a GnRH antagonist was also added. When two follicles reached 17 mm, hCG for triggering the ovulation was injected. In this approach also, no differences were found in clinical pregnancy rates compared to the patients stimulated in a controlled ovarian hyperstimulation procedure.

In the largest study by Kato et al. [26], 7244 patients undergoing 20,244 natural cycles with minimal ovarian stimulation were included. In the majority of cycles (82%), 50–100 mg/d clomiphene citrate starting on day 3 until the day before oocyte retrieval were administered together with 50–150 IU/d of FSH or hMG. Ovulation was induced with a GnRH agonist. In 16.2% of the cycles, no hormonal interventions took place, and in 1.8% a letrozol stimulation was performed. When the leading follicle reached 18 mm and the estradiol level was more than 250 pg/ml, ovulation was triggered and the retrieval was scheduled 30–34 h later. A single embryo transfer to avoid multiple pregnancies was performed in all cases. If more than one embryo was obtained, the surplus embryos were vitrified and were transferred in a subsequent cycle if no pregnancy occurred. High fertilization rates were shown regardless the age of the

patients, but live birth rates showed a strong age-dependent decrease (>45 years <1% pregnancy rate). The authors registered also higher pregnancy rates in transfers with frozen-thawed embryos compared to fresh cycles and postulate also an anti-estrogenic effect of clomiphene citrate on the endometrium.

In Vitro Maturation

Besides the conventional ovarian hyperstimulation for IVF/ICSI, in vitro maturation was developed. This method was established especially for patients with a polycystic ovarian syndrome to avoid the risk of an ovarian hyperstimulation syndrome and for patients who have suffered for an ovarian hyperstimulation syndrome in a conventional stimulation protocol. In the attempts to enhance the success rates in natural cycle IVF, IVM was combined with the natural cycle. It is expected that besides the mature oocyte from the dominant follicle, immature oocytes could be collected and matured afterwards to yield more embryos for transfer. In cases where no oocyte could be obtained from the leading follicle, there could be also a chance to yield viable immature oocytes so that such cycles must not be cancelled.

In a large retrospective study, Lim et al. [27] combined natural cycle IVF with IVM. The first aim of this study was to identify the patients who would profit from this approach irrespectively their history of polycystic ovarian syndrome or not. The data from 410 cycles were analysed. In 63 cycles, an IVM protocol was used, in 196 cycles the patients were stimulated in a conventional ovarian hyperstimulation protocol. About 151 cycles were treated in a natural cycle protocol without any hormonal stimulation except triggering of the ovulation with hCG when the leading follicle reached a diameter of 12–14 mm. Oocyte retrieval was performed 36 h later. Mature oocytes were inseminated per ICSI the same day, and immature oocytes were cultured in a special IVM medium for 24 h. The oocytes which reached maturity were also inseminated per ICSI the next day. The resulting embryos of mature and immature oocytes were pooled and transferred together. Compared to the IVM and the conventionally stimulated group, there were no differences found neither in implantation rates nor in clinical pregnancy rates. Just the miscarriage rate was significant higher in the IVM group (38.5% vs. 27.9% in the NC-IVF/IVM group vs. 24.3% in the conventionally stimulated group). Therefore, the authors stated that more than the half of infertile women treated with IVF may profit from a natural cycle IVF combined with IVM.

Xu et al. [28] confirmed these findings in another large study with 323 cycles of natural cycle IVF combined with IVM. The patients in this trial were divided into five subgroups according to their infertility reasons (tubal factor, male factor, combined tubal and male factor, unexplained, other/mixed cases). IVM was carried out in the same way than in the study of Lim et al. [27]. They could also find no significant differences in pregnancy rates and live birth rates in the different subgroups they observed. Therefore, they consider the combination of natural cycle IVF with IVM as an efficient treatment for patients with various causes of infertility. It is patient friendly because of minimizing stress and costs for the patients.

In another study by Son et al. [29], natural cycle IVF in combination with IVM was analysed again. The induction of ovulation was also triggered when the leading follicle reached a diameter of 12 mm and oocyte retrieval was scheduled 36 h later. Acceptable pregnancy rates were found in total. However, the pregnancy rate was significantly better in cycles where at least one embryo obtained from an in vivo-maturated oocyte could be transferred (30.8% vs. 9.1% without in vivo-maturated oocytes). The authors conclude that further evaluations are needed to find out at which diameter of the leading follicle the ovulation should be induced to obtain viable immature oocytes also.

A case report by Yang et al. [30] described the first pregnancy after the transfer of vitrified blastocysts yielded from a natural cycle IVF combined with IVM. The patients' ovulation was induced when the leading follicle reached 13 mm and one mature oocyte from the dominant follicle

as well as five more mature oocytes and six immature oocytes were retrieved. All mature oocytes were fertilized, and four out of six immature oocytes matured after 24 h were also fertilized. Three of the embryos achieved from mature oocytes were transferred in the first embryo transfer, but no pregnancy could be achieved. The remaining embryos were cultivated and four reached the expanded blastocyst stage and were cryopreserved by vitrification. Six months later, two of them were transferred to the patient in a spontaneous cycle and a singleton pregnancy with the birth of a healthy girl was achieved.

Costs

In a clinical trial, Lou and Huang [23] described significant lower costs in natural cycle IVF compared with conventional stimulated IVF cycles with similar clinical pregnancy rates in both groups. Also Aanesen et al. [22] calculated the costs of modified and mild stimulated natural cycles. Modified natural cycle IVF would cost 2.5% and mild stimulated natural cycle IVF 3.7% of the costs for the least-expensive IVF cycle. Groen et al. [31] focussed on costs in a retrospective study with GnRH antagonists and 150 IU FSH started when the dominant follicle reached 14 mm. Ovulation was triggered with 10,000 IU hCG and follicle aspiration took place 34 h later. Despite the lower costs in each modified natural cycle IVF compared to a conventional IVF cycle, the cumulative costs to achieve a pregnancy were higher in modified natural cycles because of higher pregnancy rates in controlled hyperstimulation cycles and the need for multiple approaches in natural cycle IVF. On the other hand, multiple pregnancies and ovarian hyperstimulation syndromes were avoided and ensuing lower costs per live birth.

Additional Aspects

Some articles dealing with further interesting topics in natural cycle IVF were also found.

Timing of Oocyte Retrieval

Bodri et al. [32] described in a retrospective study the timing of the oocyte retrieval depending on the spontaneous LH-surge in a natural cycle IVF. The collective was divided into four groups: 1. LH <10 IU/l, 2. LH 10–30 IU/l, 3. LH 30–140 IU/l, 4. LH decreasing and progesterone >1.0 ng/ml. As in this department NSAIDs were routinely used, all patients belonging to the groups 1–3 achieved NSAIDs to prevent premature ovulation. The ovulation was induced immediately after the examination, and the oocyte retrieval was scheduled 1–2 days later. Patients of groups 3 and 4 did not get any triggering of the ovulation, and oocyte retrieval was performed in group 3 one day after the examination and in group 4 at the same day. The oocytes were fertilized with IVF or ICSI, and most of the achieved blastocysts were electively vitrified for a transfer in a subsequent cycle. No significant differences were found among the groups with regard to amount of retrieved oocytes, fertilized oocytes and live birth rate.

Analysis of Follicular Fluid

Since the beginning of hormonal stimulation for IVF, the impact of gonadotrophins is discussed to have an influence on the quality of the oocytes as well as on endometrial receptivity and therefore on the success rates of IVF.

Von Wolff et al. [33] analysed the concentrations of anti-Muellerian hormone, testosterone, androstenedione, DHEA, estradiol, FSH and LH in follicular fluid collected from patients undergoing natural cycle IVF and in comparison with conventional gonadotrophin-stimulated IVF cycles. Except DHEA concentrations, significant differences were found in all other hormonal analyses. However, no association between hormonal concentrations and implantation rates was found because the oocytes from stimulated cycles were cultured in groups in the IVF laboratory. The hypothesis was proposed that the endocrine follicular fluid profile could influence the outcome of an IVF attempt. Particularly the low Anti-Mullerian hormone in the follicular fluid of stimulated cycles, which is known as a marker for a high implantation potential of the

oocyte, may explain the unphysiological environment in conventional IVF cycles and therefore the difficulties to enhance the success rates in hormonal stimulated IVF cycles.

Immune cells are known to be increased during the growing of the follicle. The stimulation with gonadotrophins strengthens this effect and thus has a negative impact on oocyte quality. In regard to the concentration of cytokines in serum and follicular fluid in natural cycle IVF and gonadotrophin-stimulated IVF cycles, the team of Bersinger et al. [34] could not find any differences between the two groups in follicular fluid but in serum concentrations. In the authors' opinion, this may suggest that the gonadotrophin stimulation does not affect the follicular immune system.

Summary

Due to patients asking for a more natural IVF treatment option, natural cycle IVF relives a renaissance. Several studies deal with this renewed approach.

Completely non-stimulated cycles were reported as well as modified or mild stimulated natural cycles. A yet unsolved problem in natural cycle attempts is the spontaneous LH-surge and therefore the premature ovulation. Different therapy strategies are tested including GnRH antagonists as well as clomiphene citrate. In recent years also, NSAIDs attract notice, but divergent results were found.

For patients, the natural cycle IVF is a patient-friendly, cost-effective option which is monthly repeatable. The risk of multiple pregnancies is minimized, also the hazard of an ovarian hyperstimulation syndrome. Possible negative long term-side effects of hormonal stimulation, which are yet not fully ruled out, can be avoided.

From the scientific view, oocytes yielded from a natural cycle seem to be of better quality and might offer higher chances for fertilization and implantation than oocytes retrieved by conventionally stimulated cycles.

Natural cycle IVF seems to be also a last chance for patients with POR before alternatives such as adoption or oocyte donation must be considered.

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