

Procedural costs and cumulative pregnancy rate of natural cycle and different minimal stimulation IVF treatments compared to full stimulated IVF

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Abstract

Background

We aimed to calculate costs per protocol and costs to achieve an estimated cumulative clinical pregnancy rate (cumPR) of $\geq 50\%$ for natural cycle IVF (NC-IVF), minimal stimulation IVF (Min stim-IVF) defined as protocols with oral compounds such as clomiphene citrate and aromatase inhibitors with or without gonadotropins ≤ 100 IU/d and conventional full stimulated IVF (cIVF).

Methods

4583 IVF cycles with intended fresh embryo transfer were evaluated in an international multicenter cohort study performed 01/2022–03/2023. Procedural costs such as medication, blood tests, lab costs and salary calculated for an average European price index and treatment failures such as premature ovulation were considered. Costs and number of cycles to achieve a $\geq 50\%$ cumPR were calculated, with an average anti-Müllerian-hormone (AMH) concentration of 2.0 ng/ml.

Results

Average costs per initiated cycle were: NC-IVF € 539, Min stim-IVF € 595 to € 1262, cIVF €2827, thawing cycle €475. To achieve an estimated $\geq 50\%$ cumPR, 5 NC-IVF cycles (total € 2695), 5 Min stim-IVF cycles with oral compounds (total €3135), 4 Min stim-IVF cycles with low dose gonadotropins (total €5272), 3 Min stim-IVF cycles with oral compounds combined with low dose gonadotropins (total €3582) and 1 cIVF plus 1 thawing cycle (total €3413) are needed.

Conclusion

NC-IVF appears to be the cheapest but least efficient treatment strategy. cIVF requires the lowest number of cycles. Min stim-IVF with oral compounds and low dose gonadotropins and cIVF are similar in terms of costs to achieve a $\geq 50\%$ cumPR.

Trial registration

Clinicaltrial.gov: NCT05125497, Registration date 03.11.2021.

Introduction

Since the birth of Louise Brown in 1978 as a result of a natural cycle In vitro fertilization (NC-IVF) [1], IVF treatments have steadily evolved. To enhance per cycle success rates, gonadotropins were increasingly

incorporated into stimulation regimens, initially within gonadotropin releasing hormone (GnRH) agonist protocols and, due to the associated risk of ovarian hyperstimulation syndrome (OHSS) [2] more frequently within antagonist protocols from the early 2000s onwards. Integration of additional patient-specific parameters - such as anti-Müllerian hormone (AMH) concentration, age, and body weight - has progressively enabled the avoidance of severe complications, including OHSS, ovarian torsion and hospitalization, and has improved cycle outcomes. Despite the effectiveness of these treatment strategies, evidence is clear that gonadotropins remain a major cost driver in conventional full dose stimulated IVF cycles (cIVF).

However, in recent years, evidence has demonstrated that IVF treatments employing lower-dose ovarian stimulation aiming to collect fewer oocytes are equally efficient, while being associated with a reduced incidence of side effects [3]. Accordingly, the OPTIMIST trial demonstrated in 2017 that low-dose ovarian stimulation with a maximum of 150 IE/d in women with reduced ovarian reserve -defined as AFC < 11- resulted in live birth rates that were not significantly different from those achieved with high-dose stimulation with 225 or 450 IE/d [4, 5]. Accordingly, a range of alternative IVF protocols have been developed and reported in recent years including unstimulated approaches such as NC-IVF, as well as mixed protocols utilizing minimal gonadotropin stimulation (Min stim-IVF) combined with oral compounds such as clomiphene citrate (CC) and aromatase inhibitors (AI). These protocols showed better fertilization rates and cleavage stage embryo morphology [6] and a higher pregnancy rate per zygote and per transfer [6]. Furthermore, due to the limited number of oocytes obtained, consecutive cycles are possible [8], anesthesia is not required [9] and treatment related stress is consequently reduced [10]. Notably, these findings suggests that Min stim-IVF protocols might be an alternative to fully stimulated cIVF protocols.

However, measuring the cumulative pregnancy rates per treatment period and the clinical applicability are only some aspects when choosing an IVF treatment strategy. In times of increasing healthcare costs – in public as well as in private fertility clinics - the financial burden is also a very important factor and should remain comparable to cIVF therapies with regard to success rates.

Consequently, we utilized data from a large, international multicenter study conducted by our group [7, 9, 11], to evaluate the procedural treatment costs of five different treatment protocols, including NC-IVF, several mini-stimulated IVF protocols and fully stimulated IVF. This study compared a wide range of IVF treatment protocols.

Materials and methods

Objective

The protocols evaluated included NC-IVF, three different Min stim-IVF protocols and the cIVF protocol. The costs for each IVF protocol were calculated based on the number of consultations, number of oocytes and further technical procedural activities. The pregnancy rates per initiated cycle were also

calculated. To better compare the treatment costs across different IVF protocols we set an arbitrary cumulative clinical pregnancy (cumPR) rate cut-off $\geq 50\%$. Total costs were calculated according to the procedural treatment costs required by each protocol to achieve an $\geq 50\%$ cumPR rate.

The following four study questions were addressed:

1. What is the clinical pregnancy rate (cPR) per initiated cycle for each IVF protocol?
2. How many cycles are required to achieve an estimated cumPR of $\geq 50\%$ for each IVF protocol?
3. What are the costs of one IVF cycle for each IVF protocol?
4. What are the costs for an estimated cumPR of $\geq 50\%$ for each IVF protocol?

Study design

This is a secondary analysis of a retrospective observational study of 4583 IVF/ICSI cycles performed between January 2022 and March 2023. Three Swiss and five German IVF centers were involved, all participating centers were part of the same network [12] and used the same treatment protocols for NC-IVF, Min stim-IVF and cIVF. Detailed information regarding the source of the setting and patient characteristics of our source study were published elsewhere [7, 9, 11]. The “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE) criteria were followed [13].

Medication

The medication used per protocol in our study is summarized here and in Supplement I:

- Recombinant human chorionic gonadotropin (hCG): Ovitrelle®, Merck, Weiterstadt, Healthcare GmbH Germany,
- Micronized progesterone: Utrogest® 200 mg, Berlin, Besins Healthcare GmbH Germany,
- Selective estrogen receptor modulator (SERM) clomiphene citrate (CC): Clomifen-ratiopharm® 50 mg, Ulm, Ratiopharm GmbH Germany,
- Aromatase inhibitor (AI), letrozole: Letrozol-ratiopharm® 2.5 mg, Ulm, Ratiopharm GmbH Germany,
- Gonadotropin releasing hormone (GnRH)-antagonist ganirelix 0.25mg: Orgalutran®, Oss, Organon Healthcare GmbH Netherlands,
- Human menopause gonadotropin (hMG): Menogon®, Kiel, Ferring GmbH Germany,
- Recombinant follitropin alpha (rFSH): Gonal-F®, Amsterdam, Merck Europe B. V. Netherlands,
- Recombinant follitropin alpha (rFSH): Ovaleap®, Dublin, Theramex Ireland Limited.

IVF treatment protocols

The definition and description of the different in vitro fertilization (IVF) protocols used in this study can be found elsewhere [7, 9, 11]. Patients were free to choose the IVF protocol they preferred. The IVF protocol could be changed throughout the IVF treatment process.

In summary, treatment cycles were monitored by transvaginal ultrasound and the concentration of serum estradiol (E2) and luteinizing hormone (LH), which were measured by CLIA (Chemiluminescence Immunoassay). The number of measurements is outlined in Supplement II. Ovulation was triggered with recombinant human chorionic gonadotropin (hCG) when the lead follicle reached ≥ 18 mm diameter. Follicle aspiration was performed 36 h after ovulation triggering. Follicle aspiration was performed without anesthesia in all protocols except cIVF. Micronized progesterone was administered for luteal phase support. IVF protocols and medications are described below, further information can be derived from Supplement I and II.

FET was performed in spontaneous cycles, if possible, and hCG trigger and progesterone 400 mg/day was given for 14 days.

Natural Cycle IVF (NC-IVF)

NC-IVF was defined as an IVF treatment without any ovarian stimulation and a single GnRH (gonadotropin releasing hormone) antagonist injection, if required. Medications used were hCG to trigger the ovulation and micronized progesterone for luteal phase support, 200mg/day for 14 days.

Minimal stimulation IVF (Min stim-IVF)

Min stim-IVF was defined as IVF treatment with either oral compounds such as clomiphene citrate (CC) or aromatase inhibitors such as letrozole (AI) and/or additional 75–100 IU human menopausal gonadotropins (hMG) or recombinant human follicle-stimulating hormone (rFSH) per day.

Min stim-IVF with CC/AI

25 mg of CC per day was started around day 4 of the cycle (average 5 tablets) until the day of the ovulation trigger. Alternatively, 5 mg of AI per day was started around day 4 of the cycle for 5 days. Further medications used were hCG trigger and micronized progesterone, 400mg/day for 14 days.

Min stim-IVF with hMG/rFSH

75–100 IU of hMG or rFSH per day was started around day 4 of the cycle until the day before the ovulation trigger was given. On average 100 IU of hMG/rFSH for 8 days were given. Further medications used were one hCG trigger and micronized progesterone, 400mg/day for 14 days.

Min stim-IVF with CC/AI + hMG/rFSH

The medication dosages of “Min stim-IVF with CC/AI” and “Min stim-IVF with hMG/rFSH” were combined. On average 75 IU of hMG/rFSH were given for 8 days. Further medications used were hCG trigger and micronized progesterone, 400mg/day for 14 days.

Conventional IVF (cIVF)

cIVF was defined as any IVF treatment with hMG or rFSH stimulation with dosages of 150 to 300 IU per day. LH surge was controlled by GnRH antagonists. On average, 225 IU of hMG/rFSH for 10 days and 5 GnRH antagonist injections were used. Further medications used were hCG trigger and micronized progesterone, 800mg/day for 14 days.

Data sources

The study was derived from the cohort study mentioned above and published elsewhere [7, 9, 11]. Almost all data required were derived from that study [7, 9, 11] and are shown in Tables 1 and 2.

If additional data were required, the following resources were used:

- The mean pregnancy rate after frozen embryo transfer (FET) was derived from the German IVF-Registry D·I·R® 2024 [14] which was 31.5% per transfer.
- The mean blastulation rate from zygotes in cIVF cycles was n derived from the literature [15–17] and found to be 50%.

Clinical pregnancy rate (cPR) per initiated cycle for each IVF protocol

The cPR was defined as a sonographically diagnosed intrauterine gestational sac per initiated cycle (Table 2).

Number of cycles required to achieve an estimated cumPR of $\geq 50\%$ for each IVF protocol

Number of cycles required to achieve a cumulative pregnancy rate (cumPR) of $\geq 50\%$ was calculated using a binomial formula described by Guzick et al and Malizia et al. [18, 19] assuming that the probability of achieving pregnancy after the first cycle of IVF treatment remains constant across subsequent cycles:

$$(1 - p)^n = 0,5$$

or

$$n = \ln(0,5) / \ln(1 - p)$$

(p = probability of pregnancy per cycle; n = number of cycles)

Consecutive cycles were cumulatively added until the cumPR $\geq 50\%$ was statistically reached as shown in Fig. 1.

For cIVF cumPR of $\geq 50\%$ was based on one fresh cycle and one frozen embryo transfer (FET) cycle. It was assumed that in cIVF one embryo was frozen and was transferred in the consecutive cycle after the failed transfer of the fresh embryo (Suppl. IV). In all other protocols the number of frozen embryos was very small.

Costs of one IVF cycle per IVF protocol

Estimates for medication, consumables and laboratory were based on German price levels. Based on the *Price Level Index for Consumer Goods and Services in the European Union Member State 2023* [20], prices in Germany are very close to the European average and were therefore used as a reference. Medication prices were taken from a pharmaceutical database [21] (Suppl. I). For protocols using gonadotropins, the average price of three gonadotropins (Menogon®, Gonal-F®, Ovuleap®) were calculated. Quantity of medications used are shown in Suppl. I and are described above.

Costs for ultrasound examinations, blood tests, follicle aspiration, fertilization, and embryo transfer were calculated based on the German Medical Fee Schedule [22]. Costs for salary were estimated according to a German salary data platform [23]. Cost calculations for individual treatment components were based on data from three private IVF centers: Fertility Centre Bonner Bogen, Germany, Yuna Praxis AG, St. Gallen, Switzerland and Fertility Center Baden, Switzerland. To calculate costs for oocyte fertilization it was assumed that 50% of oocytes were fertilized by insemination and 50% by intracytoplasmic sperm injection (ICSI). Embryo transfer was performed on day 3 or day 5 after follicle aspiration. For cIVF, additional costs for anesthesia were included.

Costs were calculated separately for each treatment component, including stimulation medication, follicular monitoring, blood tests, follicle aspiration, embryo transfer, and cryopreservation (Suppl. II). Additional costs such as room rental, laboratory equipment, gas for incubators, energy, cleaning, and accreditation fees were not included because these costs vary substantially between centers and were assumed to affect all stimulation protocols equally. The study was designed to analyze treatment-related costs of stimulation protocols rather than to provide a full economic evaluation. Cycles with premature ovulation, follicle aspiration without oocyte retrieval, or no zygote development were included in the analysis and accounted for in the cost-per-cycle calculations (Suppl. III).

Results

Baseline patients' characteristics (Table 1)

The analysis included a total of 2380 patients undergoing different IVF protocols: NC-IVF (n = 578), Min stim-IVF (n = 824; subdivided into CC/AI-IVF, n = 352; hMG/rFSH-IVF, n = 102; and CC/AI + hMG/rFSH-IVF, n = 370), and cIVF (n = 1,422).

The mean $\pm$ standard deviation (SD) female age at first oocyte pickup was 36.0 ± 4.4 years, with higher ages observed in Min stim-IVF groups (up to 37.2 ± 3.7 years) and a younger population in the clIVF group (35.6 ± 4.4 years).

The mean $\pm$ standard deviation (SD) body mass index was 24.1 ± 4.7 kg/m² and was comparable across all protocols.

The median duration of infertility was consistently 3.0 years across all protocols.

Regarding infertility causes, male factor infertility was most common overall (40%), particularly in the clIVF group (47%). Female factors accounted for 25% of cases, combined male and female factors for 21%, and idiopathic infertility for 15%.

Median [interquartile range (IQR)] AMH levels were around 2 ng/ml [0.9–3.6].

Table 1
Baseline characteristics of patients overall and stratified by IVF protocol

	Overall	NC-IVF	Min stim-IVF			cIVF
			CC/AI-IVF	hMG/rFSH-IVF	CC/AI + hMG/rFSH-IVF	
Number of patients, n	2380 ¹	578 ²	352 ²	102 ²	370 ²	1422 ²
Number of cycles per patients, Median [IQR]	1.0 [1.0, 2.0]	2.0 [1.0, 3.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	1.0 [1.0, 1.0]	1.0 [1.0, 2.0]
Female age at 1st follicle aspiration in years, Mean (± SD)	36.0 (± 4.4)	36.6 (± 3.8)	36 (± 4.6)	37.2 (± 3.7)	37 (± 4.5)	35.6 (± 4.4)
BMI (kg/m2), Mean (± SD)	24.1 (± 4.7)	23.0 (± 4.1)	23.7 (± 4.6)	23.0 (± 4.7)	24.2 (± 4.9)	24.5 (± 4.9)
Missings	9	2	1	0	0	7
Duration of infertility, years, Median [IQR]	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]	3.0 [2.0, 5.0]	3.0 [2.0, 4.0]
Missings	2	0	0	0	0	2
Causes of infertility, n (%)						
Male factor	948 (40%)	156 (27%)	61 (32%)	36 (35%)	53 (29%)	673 (47%)
Female factor	595 (25%)	174 (30%)	36 (22%)	27 (26%)	60 (32%)	314 (22%)
Male and female factor	490 (21%)	111 (19%)	50 (29%)	18 (18%)	45 (24%)	269 (19%)
Idiopathic	347 (15%)	137 (24%)	30 (18%)	21 (21%)	29 (16%)	166 (12%)
AMH level (ng/ml), Median [IQR]	2.0 [0.9, 3.6]	1.8 [0.7, 3.1]	1.9 [0.4, 3.9]	1.6 [0.8, 3.3]	1.5 [0.4, 3.2]	2.1 [1.1, 3.9]

¹Number of patients.

²Number of patients per protocol. As some patients underwent different IVF protocols, the overall population is not the sum of each IVF protocol population.

NC-IVF: natural cycle IVF; *IVF*: in vitro fertilization; *Min stim-IVF*: minimal stimulation IVF; *AI*: aromatase inhibitor; *CC*: clomiphene citrate; *cIVF*: conventional IVF; *rFSH*: recombinant follicle-stimulating hormone; *hMG*: human menopausal gonadotropin; *AMH*: Anti-Müllerian Hormone; *BMI*: body mass index; *IQR*: interquartile range; *SD*: Standard Deviation.

cPR per initiated cycle for each IVF protocol (Table 2).

A total of 4,583 IVF cycles were analyzed across different stimulation protocols: NC-IVF (n = 1483), CC/AI-IVF (n = 583), hMG/rFSH-IVF (n = 153), CC/AI + hMG/rFSH-IVF (n = 472), and cIVF (n = 1892).

The overall rate of premature ovulation was 3.7%, with the highest incidence observed in NC-IVF (8.4%) and the lowest in cIVF (0.5%).

The median [interquartile range (IQR)] number of retrieved oocytes increased with stimulation intensity, ranging from 1.0 [1.0–1.0] in NC-IVF to 7.0 [4.0–12.0] in cIVF. A similar pattern was observed for zygote numbers, with median of 1.0 in NC-IVF and Min stim-IVF and up to 4.0 [2.0–6.0] in cIVF.

The median number of transferred embryos was 1.0 across all groups. Fresh embryo transfer was performed in 67% of all cycles, with lowest rates in NC-IVF (53%) and highest rates in CC/AI + hMG/rFSH-IVF (78%) and cIVF (77%).

The clinical pregnancy rate per initiated cycle was 20% overall. The highest pregnancy rates were observed in the cIVF group (27%) and in the Min stim-IVF with CC/AI + hMG/rFSH group (24%), whereas lower rates were found in NC-IVF (14%) and Min stim-IVF with CC/AI (13%).

Population and cycle characteristics

Patient and cycle characteristics including clinical outcomes are described per IVF treatment protocol without any formal statistical test. Categorical variables are summarized as number and proportion, continuous variables as median with interquartile range (IQR) and mean with standard deviation (SD).

Table 2
Cycle outcome characteristics per protocol

Cycles, n	Overall	NC-IVF	CC/AI-IVF	hMG/rFSH-IVF	CC/AI + hMG/rFSH-IVF	cIVF
	4583	1483	583	153	472	1892
Premature ovulations, n (%)	171 (3.7%)	125 (8.4%)	18 (2.8%)	10 (6.5%)	9 (1.9%)	9 (0.5%)
Number of oocytes, Median [IQR]	2.0 [1.0, 6.0]	1.0 [1.0, 1.0]	1.0 [1.0, 2.0]	2.0 [1.0, 3.0]	3.0 [2.0, 5.0]	7.0 [4.0, 12.0]
Number of zygotes, Median [IQR]	1.0 [1.0, 3.0]	1.0 [0.0, 1.0]	1.0 [0.0, 1.0]	1.0 [0.0, 2.0]	2.0 [1.0, 3.0]	4.0 [2.0, 6.0]
Number of transferred embryos, Median [IQR]	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]	1.0 [1.0, 1.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]
Cycles with at least 1 fresh embryo transfer, n (%)	3057 (67%)	791 (53%)	350 (57%)	102 (67%)	366 (78%)	1448 (77%)
Unknown, n	4	3	0	0	0	1
Clinical pregnancy rate per initiated cycle (%)	20%	14%	13%	16%	24%	27%
Unknown, n	3	2	0	0	1	0

NC-IVF: natural cycle IVF; IVF: in vitro fertilization; AI: aromatase inhibitor; CC: clomiphene citrate; cIVF: conventional IVF; rFSH: recombinant follicle-stimulating hormone; hMG: human menopausal gonadotropin; IQR: interquartile range.

Number of cycles required to achieve an estimated cumPR of $\geq 50\%$ for each IVF protocol (Fig. 1)

According to the data analysis, to achieve a cumPR of 50%, five cycles were required for NC-IVF and Min-stim IVF with CC/AI, four cycles for Min stim-IVF with hMG/rFSH, and three cycles for Min stim-IVF with CC/AI + hMG/rFSH. In the cIVF group, two cycles were sufficient, ideally consisting of one stimulation cycle and one FET cycle.

The black bar indicates the cycle which leads to a cumPR $\geq 50\%$. In NC-IVF and Min stim-IVF only intended fresh transfer cycles are shown. In cIVF 1st fresh transfer cycle and 1st consecutive FET cycle are shown.

NC-IVF: natural cycle IVF; IVF: in vitro fertilization; AI: aromatase inhibitor; CC: clomiphene citrate; cIVF: conventional IVF; rFSH: recombinant follicle-stimulating hormone; hMG: human menopausal gonadotropin; cPR/cycle : clinical pregnancy rate/cycle. FET: Frozen embryo transfer

Costs of one IVF cycle per IVF protocol (Table 3)

The cost per initiated cycle varied across treatment modalities, ranging from €539 for NC-IVF to €2827 for cIVF. Intermediate costs were observed for CC/AI-IVF (€595), CC/AI + hMG/rFSH-IVF (€1134), and hMG/rFSH-IVF (€1262). Additional costs for zygote cryopreservation and storage were lowest in CC/AI-IVF (€32) and increased across treatment types up to €111 in cIVF. A frozen embryo transfer (FET) cycle incurred an additional cost of €475.

Costs for an estimated cumPR of ≥ 50% for each IVF protocol (Table 3)

The corresponding overall costs per protocol to reach cumPR of ≥ 50% were lowest for NC-IVF (€2695), followed by CC/AI-IVF (€3135), cIVF (€3413), and CC/AI + hMG/rFSH-IVF (€3582), while the highest costs were observed for hMG/rFSH-IVF (€5272).

Table 3					
Estimated costs (Euro) per initiated cycles per protocol to achieve a cumPR ≥ 50% per protocol					
Treatment items	NC-IVF	CC/AI-IVF	hMG/rFSH - IVF	CC/AI + hMG/rFSH-IVF	cIVF
Costs per initiated cycle (Euro)	539.00 ¹	595.00 ¹	1262.00 ¹	1134.00 ¹	2827.00 ¹
Costs for zygote cryopreservation and storage	-	32.00	56.00	60.00	111.00
Costs for a FET cycle					475.00
Number of cycles need for a cumPR ≥ 50%	5	5	4	3	2 (1x fresh + 1x FET)
Overall costs for ≥ cumPR 50% per protocol	2695.00	3135.00	5272.00	3582.00	3413.00
¹ Without storage costs					

NC-IVF: natural cycle IVF; IVF: in vitro fertilization; AI: aromatase inhibitor; CC: clomiphene citrate; cIVF: conventional IVF; rFSH: recombinant follicle-stimulating hormone; hMG: human menopausal gonadotropin; cumPR 50%: cumulative pregnancy rate of 50 percent.

Discussion

In this study, the procedural costs of five different IVF protocols were assessed per cycle and per estimated cumPR of $\geq 50\%$ in a group of patients with a median AMH concentration of around 2 ng/ml and an average female age of 36 years. To our knowledge, this is the first study to provide such data based on a broad range of protocols including several Min stim-IVF protocols.

The study showed that either Min stim-IVF protocols such as CC/AI + HMG/rFSH-IVF, combining oral compounds and minimal gonadotropin dosages or conventional cIVF strategies, combining one fresh and one FET cycle were the most efficient treatment strategies in terms of costs and number of IVF cycles to achieve a cumPR of $\geq 50\%$.

Our study has some major strengths. The multicenter and international design and the large number of cycles analyzed, provide robust real-world data. Another strength of our study is that we included the procedural costs per initiated cycle. We also included cycles which were cancelled due to premature ovulation, failed fertilization, or lack of embryo development. This approach reflects the true procedural cost and time effort per chosen strategy.

However, our study has also some limitations. Firstly, the retrospective design introduces inherent bias. Secondly, the medication costs were based on German price levels. Even though these costs reflect the average European cost levels, costs may not be the same in other countries. Thirdly, our analysis focused on procedural costs and excluded expenses such as costs for renting, infrastructure, insurance, accreditation etc. which might be slightly different for the analyzed IVF treatment strategies. Fourthly, to enable a comparison of the cost-effectiveness of different IVF stimulation strategies, an estimated cumPR of $\geq 50\%$ was arbitrarily set as a cut-off point. To reach the target cut-off we assumed the same cPRs across consecutive cycles despite the fact that the success rates decrease with increasing number of cycles.

However, even though we are aware of these limitations, we strongly believe that our study provides a valuable orientation regarding costs and number of cycles needed for the different IVF treatment protocols.

In our study, NC-IVF was the cheapest protocol to reach the target cumPR of $\geq 50\%$, with cumulative costs of €2695 for five IVF cycles. Only 53% of the patients underwent a fresh embryo transfer per cycle due to premature ovulation, empty follicles or failed fertilization and embryo development. This resulted in a low overall PR per initiated cycle of 14% and a longer treatment time needed. Previous studies on modified NC-IVF reported similar pregnancy rates per cycle of 12.4–13.6% [24, 25]. Thus, patients considering NC-IVF should be informed that, despite its lower costs, this treatment strategy requires more treatment cycles and therefore might take longer.

In Min stim-IVF treatment costs were higher to achieve a cumPR of $\geq 50\%$. The CC/AI + hMG/rFSH-IVF protocol was calculated to cost €3582 to reach the target PR of $\geq 50\%$. In this strategy, fresh embryo transfers were performed in 77% of initiated cycles, yielding an overall pregnancy rate per cycle of 24%. Due to the limited number of surplus embryos, FET cycles were rarely possible and three fresh CC/AI +

hMG/rFSH-IVF cycles were required to reach the target cumPR of $\geq 50\%$. However, CC/AI + hMG/rFSH-IVF can be considered patient-friendly due to the low stimulation dosage, almost no risk for overstimulation [26], aspiration without anesthesia which imposes only mild pain [9] and the use of less expensive oral compounds.

cIVF required the lowest number of treatment cycles but highest costs of €2827 per initiated cycle. However, due to the high number of surplus embryos which could be used for FET cycles, cIVF, combining one fresh and one FET cycle turned out to be the most time efficient approach. In the cIVF group, the transfer rate was 78% and the pregnancy rate was 27% per initiated cycle, which is consistent with published data [26–28].

cIVF plus one FET and CC/AI + hMG/rFSH-IVF yielded comparable average procedural costs to achieve a $\geq 50\%$ cumPR (€3413 vs. €3582). However, due to an additional FET with an estimated pregnancy rate of 31.5% per transfer [14], only two cycles were required in cIVF to reach target cumPR of $\geq 50\%$. Therefore, cIVF was the approach with the lowest number of cycles to achieve the target cumPR of 50%. Whether cIVF is also the fastest approach with the shortest time to pregnancy depends on the overall treatment strategy. As NC- and Min stim-IVF protocols can easily be performed on a monthly basis whereas cIVF frequently requires wash-out cycles for medical reasons or at the patient's request [8], the advantage of a lower number of cycles in cIVF does not necessarily lead to a shorter time to pregnancy.

Groen et al. [29] analyzed retrospectively and compared the cost-effectiveness and biochemical PR per cycle of modified natural cycle IVF (mNC-IVF) and cIVF. Data from 1994 mNC-IVF and 392 fresh cIVF cycles were analyzed in ovulatory, subfertile women < 36 years. mNC stimulation was performed with 150 IU of gonadotropins per day and antagonist injections were started when the lead follicle reached 14 mm and was given until the trigger was applied. They performed double embryo transfers (DET) if more than one embryo was available. cIVF was based on long agonist protocols with 150–225 IU gonadotropin per day with dosage adjustment from day 7 onwards if needed. Single embryo transfer (SET) or DET was performed on d3 and cryopreservation of surplus embryos on d4. One to two surplus embryos were transferred in hormone replaced cycles on d5. Total costs per initiated cycle were €1157 in mNC-IVF, €2107 in cIVF and €644 in FET cycles. Biochemical pregnancy rates were 9.6% in mNC-IVF, 35.7% in cIVF cycles and 20% in FET cycles. Cryopreservation of surplus embryos was possible in 43% of cIVF cycles and 1–4 FET cycles were performed after the fresh transfer.

The authors stated that mNC-IVF was less expensive than cIVF but also less effective. However, they argued that mNC-IVF is a plausible alternative for couples that are willing to trade off effectiveness with less medication and lower risk for OHSS [29].

Due to higher pregnancy rates in our cohort and lower calculated costs for NC-IVF and Min stim-IVF, our study results and interpretations were slightly different. cPR in Min stim-IVF protocols was 13–24% (see Table 2.) and therefore higher than in the study by Groen et al. Costs per cycles were also different. Costs per cIVF cycles for example were 30% higher than in the study by Groen et al. This price difference might be due to higher costs for medication, salaries and consumables. As cPRs per initiated cycle of

CC/AI+rFSH/hMG-IVF and cIVF were similar (24% vs. 27%), this Min stim-IVF protocol appeared to us as an alternative to cIVF.

Similar cPRs for different stimulation protocols along with cost calculations have been described by Mukherjee et al. [26]. They analyzed 94 normogonadotropic women with an average age of 28.5 years, who had undergone intracytoplasmic sperm injection after testicular sperm extraction due to male infertility. They compared two groups: the study group underwent Min stim-IVF with 5 mg AI for five days plus 75 IU gonadotropins, beginning on day five of the cycle. The control group underwent cIVF and received 150–225 IE of rFSH beginning on day two of the cycle. Both groups received GnRH antagonist injections daily when the lead follicle reached 14mm. They found a cPR per initiated cycle of 36% for Min stim-IVF with AI+rFSH-IVF and 33% for cIVF. Their calculations showed that Min stim-IVF protocols resulted in an overall cost reduction of 34% per cycle due to a 64% reduction in gonadotropins compared to cIVF. They concluded that adding AI to IVF protocols is an effective strategy to reduce costs [26].

In our study, the average cost for cIVF per started cycle was €2827, based on a 10-day stimulation with standard doses of rFSH/hMG. For Min stim-IVF the costs were €1134 per cycle, based on a 8-day low dose gonadotropin stimulation. In terms of costs, a single cycle of CC/AI + hMG/rFSH-IVF cycle was 58% cheaper than one cycle of cIVF, primarily due to a 73% reduction in gonadotropin dosage. The lower costs compared to those reported by Mukherjee et al. can partly be explained by the lower number of antagonist injections given in our CC/AI + hMG/rFSH-IVF protocol. As shown in Suppl. I, we administered only one antagonist injection mainly to prevent preterm ovulation for example to bridge the weekends, resulting in a preterm ovulation rate of 2% (see Suppl. IV).

Karimzadeh et al. [28] performed a similar cost analysis and analyzed the first IVF cycle in 243 normogonadotropic women aged 18–35 years. They compared a standard long GnRH protocol (cIVF) with 150–225 IU of rFSH with a Min stim-IVF protocol combining clomiphene citrate for five days with rFSH 75 IU (CC/rFSH-IVF) beginning on day 5 of the cycle. When the leading follicle was 12mm, GnRH antagonist injections were started and the rFSH dose was increased to 150 IU per day. Even though the cumulative dosage of rFSH was reduced by 55% in CC/rFSH-IVF compared to long GnRH protocols, the cPR per cycle was higher in Min stim-IVF protocol (37% vs. 31%).

Even though cPRs in our Min stim-IVF protocols were not higher than in cIVF as shown by Karimazadeh et al., some Min stim-IVF protocols used in our study were not or not substantially inferior in terms of cPR and costs per fresh cycle.

However, a key advantage of cIVF is the option to cryopreserve embryos for subsequent FETs which increases the chance of a pregnancy without the need for additional expensive stimulation cycles.

In conclusion,

Min stim-IVF protocols such as CC/AI + hMG/rFSH-IVF and cIVF with one FET seem to be associated with comparable costs and time (three vs. two treatment cycles) to achieve a cumPR of $\geq 50\%$ in women

in her mid-thirties and with an average AMH concentration. Both protocols are efficient and clinically comparable strategies. However, these findings need to be confirmed by prospective studies, ideally also considering treatment time and treatment related stress.

Declarations

Ethical approval

Ethical approval was given by the cantonal ethics committee of Bern, for Switzerland (04.10.2021, KEK 2021-01689) and by the four regional ethics committee of Germany (Baden-Württemberg (ID F-2024-068, 22.08.2024), Fertility Centres Ulm and Neckarsulm, Niedersachsen (ID Grae/080/2024, 30.08.2024), Fertility Centre Hildesheim, Bavaria (ID mb24043, 12.09.2024), Fertility Centre kiz, Munich and Nordrhein-Westfalen (ID 2024194, 30.10.2024), Fertility Centre Bonner-Bogen, Bonn). Written informed consent was provided from participants. The study was registered at Clinical Trial.Gov, study number NCT05125497.

Consent for publication

Not applicable.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

M. Nordin., I. Siercks., C. Huober-Zeeb.: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing.

R. Popovici., U. Bohlen., S. Eisenhardt., J-S. Lanowski.: Data curation, Project administration, Validation, Writing – review & editing.

M. von Wolff, I. Magaton: Conceptualization, Funding acquisition, Methodology, Writing – review & editing.

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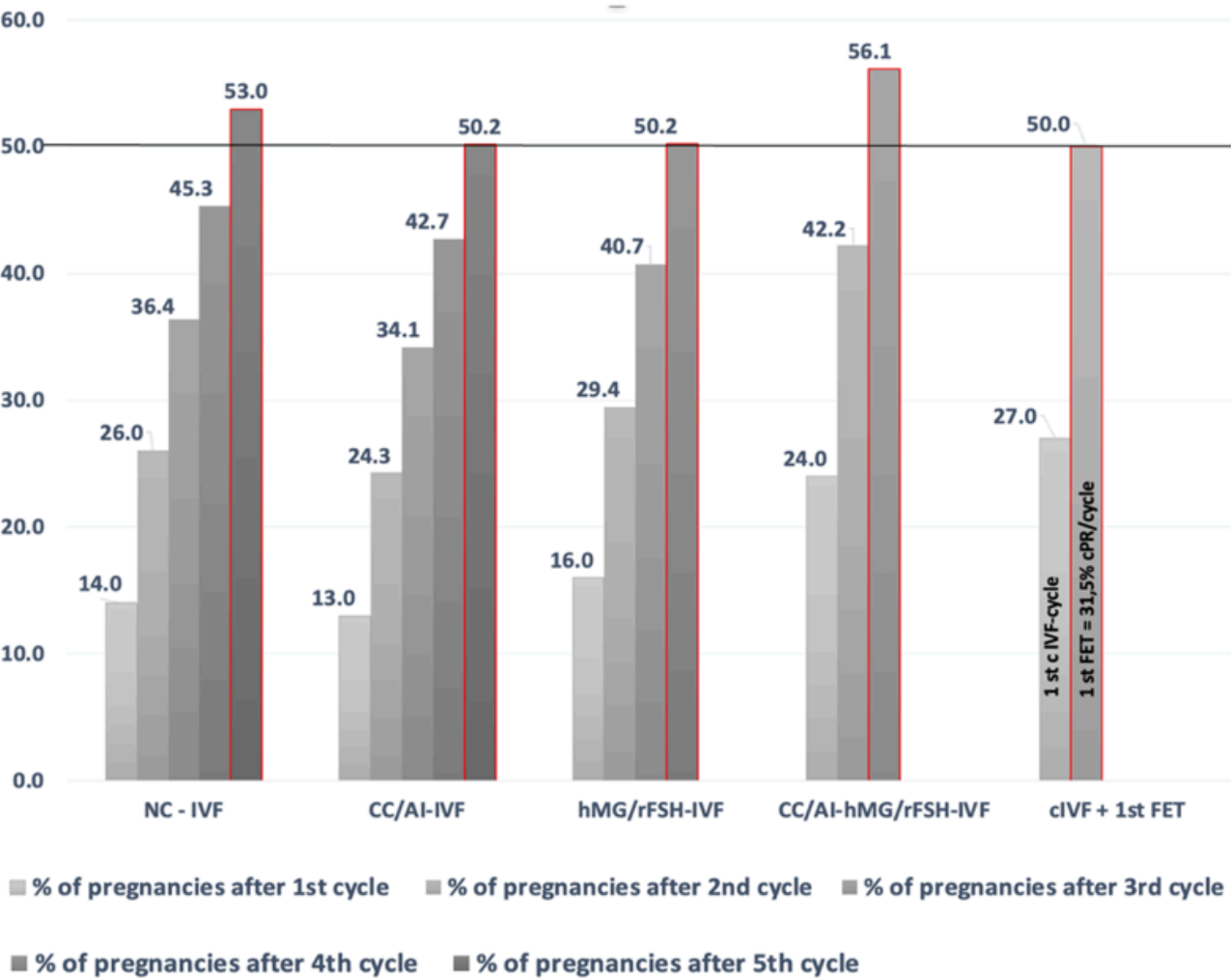
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Figures

Figure 1. Number of initiated cycles to reach a cumPR of $\geq 50\%$ per protocol



The black bar indicates the cycle which leads to a cumPR $\geq 50\%$. In NC-IVF and Min stim-IVF only intended fresh transfer cycles are shown. In cIVF 1st fresh transfer cycle and 1st consecutive FET cycle are shown.

NC-IVF: natural cycle IVF; IVF: in vitro fertilization; AI: aromatase inhibitor; CC: clomiphene citrate; cIVF: conventional IVF; rFSH: recombinant follicle-stimulating hormone; hMG: human menopausal gonadotropin; cPR/cycle : clinical pregnancy rate/cycle. FET: Frozen embryo transfer

Figure 1

See image above for figure legend.

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