

COMPARISON OF THE INFLUENCE OF DIFFERENT OVULATION INDUCTION PROTOCOLS ON CUMULATIVE PREGNANCY RATES IN AN IVF/ET PROGRAM

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Original paper

Key words: ovulation induction, IVF/ET, cumulative pregnancy rate

SAŽETAK. Objective: The aim of this study was to compare the cumulative pregnancy rate of in vitro fertilization (IVF) per cycle in patients in whom the ovulation induction was conducted in a modified natural cycle and in cycles with mild and standard ovarian stimulation. **Methods:** Retrospective analysis was carried out on 126 consecutive IVF cycles in patients who matched the inclusion criteria, performed at our institution from January 2012 to July 2013. **Results:** In a modified natural cycle after 12th week of pregnancy, three pregnancies in five cycles were achieved (60.0%), in mild stimulation 16 pregnancies in 40 cycles (40.0%), and in standard stimulation 24 pregnancies in 81 cycles (29.6%). These were followed by eight cryoembryotransfers after mild stimulation, resulting in three clinical pregnancies (37.5%) and 29 cryoembryotransfers after standard stimulation, resulting in 15 clinical pregnancies (51.7%). The cumulative clinical pregnancy rate in mild stimulation cycles was 47.5%, and in standard stimulation cycles 48.1%, which was not statistically significant ($p=0.95$). **Conclusion:** In this study, mild ovarian stimulation proved to be equally successful in achieving clinical pregnancy as the standard ovarian stimulation.

Introduction

Ovulation induction in women about to start their process of assisted reproduction (ART) is the key part of the whole process. The aim of a controlled ovarian stimulation is to retrieve an optimal number of mature oocytes and to provide a success of lab procedures¹ which can be achieved through procedures in a modified natural cycle, protocols with mild ovarian stimulation and protocols with standard ovarian stimulation.²

A modified natural cycle where one spontaneously developing follicle is aspired is recommended as an alternative to standard controlled ovarian stimulation in IVF procedures.³ However, in a modified natural cycle there is a possibility of failure – no oocyte is retrieved, no fertilization is achieved or, in cases of a successful fertilization, an embryo stops developing. Consequently stimulated cycles are a preferred method of choice. In cycles with mild ovarian stimulation a lower dosage of gonadotropins in combination with antiestrogen agents or aromatase inhibitors are used in order to limit the number of oocytes to less than eight.⁴ A number of studies have shown that the optimal number of oocytes for a successful IVF procedure is over 10,^{5,6} which is achieved through standard protocols of ovarian stimulation.

However, a mild ovarian stimulation has been recommended in recent literature⁷ as mild ovarian stimulation cycles may be more successful than the standard ones.⁸ Since stronger ovarian stimulation, unlike non-stimulated cycle, may affect the endometrial receptivity,^{9,10} cryopreservation of embryos and then replacing them during a non-stimulated cycle has been more often recommended in recent times.

This retrospective study was conducted in patients with whom all of the above stimulation protocols were used in order to test these claims. The primary aim of

this study was to compare cumulative pregnancy rate of IVF per cycle in patients in whom the ovulation induction was conducted in a modified natural cycle, with mild and with standard ovarian stimulation.

The secondary aim of this study was to determine the success rate of each particular treatment approach per cycle and embryo transfer (ET) performed and to establish the number of eggs retrieved, fertilization rate, the total number of embryos and the number of cryopreserved embryos per each treatment method.

Materials and methods

This retrospective study was carried out at BetaPlus Center for Reproductive Medicine in Zagreb. It included consecutive IVF cycles in patients treated for infertility in the period between 1 January 2012 and 1 July 2013, and who matched our inclusion criteria.

The inclusion criteria were the following: age up to 38, anti-Müllerian hormone (AMH) >5 pmol/L, IVF/ICSI carried out with fresh semen sample and body-mass index (BMI) <30 kg/m². The exclusion criteria were chronic and/or system diseases (diabetes mellitus, rheumatoid arthritis, malign diseases, etc), anomalies of reproductive organs, inflammatory diseases of genital and urinary organs, untreated thyroid disorders, follicle-stimulating hormone (FSH) >12 UI/L on the day 3 of the cycle, ovarian cysts and endometriosis.

Before entering the IVF procedures all of patients went through diagnostic tests, including anamnesis, gynecological examination, cytological smear tests, cervical smear tests for aerobes, chlamydia, mycoplasma and ureaplasma, ultrasound scan and hormone tests (AMH, FSH, luteinizing hormone (LH), estradiol (E2), prolactin (PRL), thyrotropin (TSH) on days 2–5 of the cycle). Women's partners gave semen for semen analysis, and

microbiologic analysis in cases when leukocytes were found in the samples.

The data were collected by researching database with detailed description of procedures over the subject period of time. The patients were divided into three groups: the first were patients treated in a modified natural cycle, the second patients treated in a mild ovarian stimulation and the third in a standard ovarian stimulation protocol. Both short and long agonists protocols and antagonists protocols were designated as standard stimulation procedures.

Serial ultrasound scans were used to monitor the growth of the leading follicle in patients in a modified natural cycle. When follicle reached 17 mm, 250 mcg of recombinant human chorionic gonadotropin (rhCG) was applied (Ovitrelle, Merck Serono). Egg retrieval was performed within 38 hours after the application of rhCG. The same procedure was followed in all ovulation stimulation protocols.

Patients in a mild stimulation cycle were administered 100 mg/d of clomiphene citrate (Clomiphene, Bruno Pharmaceuticals) or 5 mg/d of letrozole (Femara, Novartis Pharma) from days 3 to day 7 of the cycle, and then 75–225 IU/d of gonadotropin (Menopur, Ferring GmbH ili Gonal F, Merck Serono) from day 7 until the leading follicle reached 19–20 mm when rhCG injection was administered, as previously described.

During the long agonist protocol the application of GnRH agonist started on day 21 of the previous cycle: 0.1 mg/d of triptorelin (Decapeptyl, PharmaSwiss) or 3x2 inhalations of busserelin (Suprefact spray, Sanofi), on daily basis until the application of rhCG. A short agonist protocol differs from the long protocol in that rhCG agonist was used from day 1 of the cycle.

Gonadotropin in a personalized dosage was introduced into the therapy on day 2 of the cycle and administered on a daily basis until the application of rhCG. When at least three follicles over 17 mm in diameter were observed, rhCG was administered.

In antagonist protocol gonadotropin was applied in a personalized dosage from day 2 of the cycle until the leading follicle reached 14 mm. Then 0.25 mg/d of GnRH antagonist was introduced into the therapy and applied until at least three follicles of 17 mm were observed. Then rhCG injection was administered.

Gametes and embryos were cultivated in incubators adjusted to 6% CO₂ and 5% O₂. All culture media were prepared a day earlier; the culture was performed in drops of oil covered medium. The equipment used in the procedures was as follows: disposable plastic material for IVF procedures (Nunc Art IVF Product Line, Thermo Scientific™), 17G needles (Kitazato Opu Needle 327350, Kitazato Medical, Japan; K-OSN-1735-B-60 Ova–Stiff Ovum Aspiration Needle, Cook Medical, Australia), and Sydney IVF catheters for embryo transfer (K-JETS-7019-SIVF, Cook Medical, Australia).

The ejaculate was centrifuged at 80% / 40% of density gradient for 15 minutes at 300 g (PureCeption™

Sperm Separation Media, CooperSurgical, USA), then washed out twice with a washing medium (Quinns Advantage® Sperm Washing Medium, CooperSurgical, USA) for 7 minutes at 600 g. Obtained sperm pellet was layered with fertilization medium (Quinns Advantage® Fertilization Medium, CooperSurgical, USA) and placed into an incubator until the insemination.

After the retrieval from a follicular liquid, oocytes were washed with fertilization medium, granulosa cells were mechanically removed up to corona radiata, after which oocytes were placed into Petri dishes with culture medium (Quinns Advantage® Fertilization Medium, CooperSurgical, USA) covered with oil (SAGE Oil for Tissue Culture, CooperSurgical, USA). After a 3-hour period of pre-incubation, oocytes were inseminated. Sperm concentration per an oocyte depended on semen quality and ranged from 6×10³ to 20×10³. In cases of severe male infertility or previous failed fertilization, ICSI was performed. In Petri dishes with oil covered, stabilized medium granulosa cells were first cleared out through enzymatic removal (Hyaluronidase 80 U/mL in HEPES-HTF, CooperSurgical, USA) and then oocytes were washed out through series of drops and placed in 10 µl drops (Quinns Advantage® Fertilization Medium, CooperSurgical, USA) for ICSI procedure. Sperm were added to drops containing polyvinylpyrrolidone (PVP 7%, Cooper Surgical, USA). A sperm with best kinetic and morphologic features from phase boundaries was chosen, immobilized and injected into oocyte cytoplasm by an ICSI micropipette. After 16–20 hours culture medium was changed (Quinns Advantage® Cleavage Medium, CooperSurgical, USA) and fertilization checked. After 48 hours another quality grading of embryonic development was performed. If up to 2 embryos developed, the transfer was carried out on day 3. In cases of a multiple embryonic development the cultivation was prolonged up to 5 days in a changed medium for blastocyst development (Quinns Advantage® Blastocyst Medium, CooperSurgical, USA). The embryonic development was checked and assessed on day 4. On day 5, after examination and assessment, one or two viable embryos were returned; other embryos of sufficient quality were vitrified and cryopreserved in liquid nitrogen as per manufacturer's instructions (Kitazato Vitrification Kit, Dibimed, Spain). If no pregnancy occurred thawing of embryos (Kitazato Thawing Solutions, Dibimed, Spain) and their transfer were performed in the following cycle.

As corpus luteum support progesterone was used (Utrogestan, Laboratoires Besins International)– 3×200 mg/d vaginally after egg retrieval until pregnancy test that was performed 14 days after the retrieval. Biochemical pregnancy was established if beta hCG levels reached over 50 IU/L 14 days after the retrieval. This study defined clinical pregnancy as a uterine pregnancy after the week 12.

The data were analyzed using SPSS 17.0 program. The results are expressed as mean values and standard deviations. Considering the number of procedures and

variable distribution, non-parametric tests were used – Kruskal-Wallis H test for the comparison of three groups and Mann-Whitney U test for the comparison of two groups. Statistical significance was accepted at $P < 0.05$.

Results

In 103 patients undergoing IVF 126 cycles were analyzed. In 81 cycles (64.3%) standard stimulation was used (43 cycles in the antagonist protocol, 38 in agonist protocol), in 40 cycles (31.7%) mild stimulation, and 5 procedures (<1%) were in a modified natural cycle. In the standard stimulation group there were 78 ETs (96.3%), in the mild stimulation group 38 ETs (95%), and in the modified natural cycle group there were 4 ETs (80%). *Table 1* features basic characteristics of subjects in three groups, where there was no statistical significance observed.

With standard stimulation average gonadotropin use per cycle was 22.1 vials (SD 7.3), and with mild stimulation it was 9.6 vials (SD 5.2), which is statistically significant ($P < 0.001$). The endometrial thickness on the day of rhCG administration in a modified natural cycle was 7.4 (SD 1.0), in a mild stimulation cycle it was 7.8 (SD 1.7), and in a standard stimulation cycle it was 9.8 (SD 1.6). There are statistically significant differences between the modified natural cycle and the standard stimulation ($p = 0.01$), and the difference between the mild and standard stimulations ($P < 0.001$).

The comparison of the retrieved and fertilized oocytes and the number of transferred and cryopreserved embryos in individual groups is featured in *Table 2*. The difference in the number of transferred embryos between the mild and standard stimulation shows borderline significance ($P = 0.05$).

Table 1. Basic characteristics of study groups.

	Modified natural cycle N=5 Mean value (SD)	Mild stimulation N=40 Mean value(SD)	Standard stimulation N=81 Mean value(SD)	P
Age (in years)	31.8 (3.7)	32.8 (3.7)	33.0 (3.7)	0.71
BMI (kg/m ²)	20.9 (1.9)	21.6 (1.6)	22.8 (2.9)	0.20
Duration of infertility (years)	3.0 (1.7)	3.2 (1.5)	3.8 (2.6)	0.68
Number of IVF attempts	3.3 (2.2)	3.0 (2.4)	2.7 (2.2)	0.76
FSH (IU/L)	8.0 (2.9)	6.8 (1.6)	6.8 (2.0)	0.72
LH (IU/L)	5.4 (1.5)	5.3 (1.7)	5.4 (2.8)	0.82
E2 (pg/mL)	206 (0)	121.6 (75.7)	182.0 (169.5)	0.27
TSH (mIU/L)	2.4 (1.0)	1.7 (0.7)	1.9 (0.9)	0.43
PRL (mIU/L)	254.5 (232.3)	202.4 (127.3)	272.7 (211.8)	0.26
Day of rhCG introduction	11.4 (1.3)	11.7 (1.2)	11.4 (1.8)	0.37

(BMI – body mass index, IVF – in vitro fertilization, FSH – follicle-stimulating hormone, LH – luteinizing hormone, E2 – estradiol, TSH – thyrotropin, PRL – prolactin, rhCG – recombinant human chorionic gonadotropin)

Table 2. Comparison of number of retrieved and fertilized oocytes, transferred and frozen embryos in different ovulation stimulation protocols, per cycle.

	Modified natural cycle N=5 Mean value (SD)	Mild stimulation N=40 Mean value (SD)	Standard stimulation N=81 Mean value (SD)	P
Number of retrieved oocytes	0.8 (0.4)	4.3 (2.3)	8.7 (4.2)	<0.001 ^{a,b,c}
Number of fertilized oocytes	0.8 (0.4)	2.9 (1.4)	5.9 (3.3)	<0.001 ^{a,b,c}
Day of the embryo transfer	3.0 (0.0)	3.9 (1.0)	4.7 (0.8)	<0.001 ^{b,c}
Number of transferred embryos	0.8 (0.4)	1.6 (0.6)	1.8 (0.5)	<0.001 ^{a,b}
Number of cryopreserved embryos	0.0 (0.0)	0.7 (1.0)	1.5 (1.7)	0.01 ^{b,c}

^aNatural cycle – mild stimulation ($P < 0.05$)

^bNatural cycle – standard stimulation ($P < 0.05$)

^cMild stimulation – standard stimulation ($P < 0.05$)

Table 3. Pregnancy rates per started cycle, aspiration and embryo transfer, analyzed by stimulation protocol.

Pregnancy rate	Ovulation induction			P
	Modified natural cycle	Mild stimulation	Standard stimulation	
Per cycle	60.0%	52.2%	35.8%	0.153
Per aspiration	75.0%	53.8%	36.3%	0.081
Per embryo transfer	75.0%	55.3%	36.7%	0.073

Pregnancy rates per started cycle, per performed aspiration and per performed ET are featured in *Table 3*. A total of 53 biochemical pregnancies were achieved: 3 in a modified natural cycle, 21 in a mild stimulation and 29 in a standard stimulation. There were 5 miscarriages (biochemical and clinical) before week 12 (24%) in a mild stimulation, which amounts to 40% of clinical pregnancies, and 5 miscarriages (17%) in a standard stimulation ($P = 0.57$), which amounts to 29.6% of clinical pregnancies.

In mild stimulation cycles 27 embryos were cryopreserved, and 119 embryos were cryopreserved in standard stimulation cycles. ET of cryopreserved embryos was performed in 37 patients by the date of the analysis – 8 in mild stimulation (three pregnancies) and 29 in standard stimulation (fifteen pregnancies), and no miscarriages were reported by week 12. The cumulative biochemical pregnancy rate for 40 cycles of mild stimulation was $21+3=24/40$, i.e. 60.0%. There were five miscarriages making the cumulative clinical pregnancy rate 47.5%. The cumulative biochemical pregnancy rate for 81 cycles of standard stimulation was $29+15=44/81$, i.e. 54.3%. Considering the five miscarriages, the cumulative clinical pregnancy rate was 48.1%.

Two patients developed ovarian hyperstimulation syndrome (OHSS) over the subject period in standard stimulation cycles.

Three multiple pregnancies (twins) were recorded in cases of mild stimulation (14.3%) and seven in standard stimulation (24.1%).

Discussion

This study showed that conclusions from recent literature suggesting that mild stimulation cycles are equally successful as standard stimulation were confirmed in our patients. Mild ovarian stimulation reduces the risk of complications such as OHSS and multiple pregnancies,^{11,12} without changing the quality of endometrium; it is cheaper than the standard stimulation, making it more acceptable for both patients and the system.¹¹ Our results, with cumulative pregnancy rate in these two types of stimulation being equal, confirm such hypothesis. Similar results with comparative cumulative pregnancy rates have been published previously.¹³

Furthermore, claims that strong ovarian stimulation has adverse effects on endometrial receptivity¹⁴ were also partially confirmed as we had the lowest pregnancy rates with ETs in fresh cycles after standard ovarian stimulations. This difference, however, did not reach statistical significance. In freshly stimulated cycles there is often an asynchrony of endometrium and embryos preventing pregnancy to occur,¹⁵ which is attributed to prolonged hCG activity in fresh cycles leading to endometrial damage. This is a probable cause of lower pregnancy rate.

It is known that implantation rate is lower in stimulated cycles in comparison with natural cycles¹⁶ and that the stimulation shifts implantation window which reduces the chances of pregnancy in freshly stimulated cycles.¹⁷ In our study we analyzed only five cases of modified natural cycles and although a high pregnancy rate was achieved we cannot draw conclusions from such a small sample. However a pregnancy rate achieved in cycles with mild ovarian stimulation is rather high, and nowadays it is considered a better environment for successful assisted reproduction procedures.¹⁸ In comparison with the widely preferred standard stimulation, high pregnancy rate after cryo-procedures confirmed the above claims.

Furthermore, in younger women mild ovarian stimulation results in the same aneuploidy rate in embryos as in non-stimulated cycles, as opposed to standard stimulation where aneuploidy number is increased,¹⁹ which explains equal pregnancy rate in all of our three test groups, regardless the fact that the number of retrieved oocytes and fresh and cryopreserved embryos differed significantly. It is obvious that high levels of estradiol and progesterone, resulting from stimulation with high dosages of gonadotropin, have an adverse influence on pregnancy rates in fresh standard stimulation cycles,²⁰ unlike cryoprocures from the same standard stimula-

tion where high success rate was achieved as it is carried out in a non-stimulated cycle.

Protocols of mild stimulation have been showing a high success rate over the recent years, probably due to advanced IVF technology in laboratories. A decade ago a success rate per cycle was 10–35%,^{21,22} and in 2007 it increased to 43.4%,¹² which is a little lower than the above results, but also 5 years earlier. In comparison to similar retrospective studies²³ fewer oocytes were retrieved in this one. The probable reason is that during the first 8 months of the study the laws of the Republic of Croatia restricted the number of oocytes to be fertilized to no more than 3 in a single IVF procedure. Current laws allow fertilization of up to 12 oocytes so physicians are prone to milder stimulations. However clinical pregnancy rates in the subject study and on the subject patients are comparable, probably due to the above reasons.

The disadvantage of the study is the retrospective nature of the research which prevented us from controlling the patients' entries into the study. This may have induced us to choose patients with higher pregnancy probability for mild stimulation cycles although this is, considering the comparative basic group characteristics, not very likely. Also, only 5 patients were treated in a modified natural cycle so the results are not conclusive. Therefore this group was not particularly considered, although the statistics were adjusted to a small sample as a comparison of all three groups was the objective of observation. The results are still incomplete – there are still 109 cryopreserved embryos left from the above stimulation cycles. The cumulative success rate per standard stimulation cycle, after all embryos are used (the biggest number has remained in this group), is expected to increase. This does not change the fact that mild stimulation success rate is satisfactory.

Individualized protocols of mild stimulation, especially if followed by a single – embryo ET for the purpose of reducing the risk of multiple pregnancies can represent an important step to simplifying IVF procedures, if it retains acceptable pregnancy rate. We believe we have proved that mild stimulation cycles in young and healthy women with normal hormonal status are a good alternative solution to standard stimulation, because the availability of good laboratory at present provides a comparative pregnancy probability.

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USPOREDBA UTJECAJA RAZLIČITIH PROTOKOLA INDUKCIJE OVULACIJE NA KUMULATIVNE STOPE TRUDNOĆA U IVF/ET PROGRAMU

Izvorni članak

Ključne riječi: indukcija ovulacije, IVF/ICSI, kumulativna stopa trudnoća

SUMMARY. Cilj rada. Cilj ovog istraživanja bio je usporediti kumulativnu stopu trudnoća in vitro fertilizacije (IVF) po jednom ciklusu, u pacijentica u kojih je indukcija ovulacije provedena u modificiranom prirodnom ciklusu te u ciklusima s blagom i standardnom stimulacijom jajnika. **Metode.** Učinjena je retrospektivna analiza 126 uzastopnih ciklusa IVF-a u pacijentica koje su zadovoljavale kriterije uključivanja, provedenih u našoj ustanovi od siječnja 2012. do srpnja 2013. godine. **Rezultati.** U modificiranom prirodnom ciklusu nakon 12-og tjedna trudnoće ostvarene su tri trudnoće iz pet ciklusa (60.0%), kod blage stimulacije 16 trudnoća iz 40 ciklusa (40.0%), te kod standardne stimulacije 24 trudnoće iz 81 ciklusa (29.6%). Ove postupke slijedilo je osam krioembriotransfera nakon blage stimulacije gdje je bilo 3 kliničke trudnoće (37.5%) i 29 krioembriotransfera nakon standardne stimulacije gdje je bilo 15 kliničkih trudnoća (51.7%). Kumulativna stopa kliničkih trudnoća u ciklusima blage stimulacije iznosila je 47.5%, a u ciklusima standardne stimulacije 48.1%, što nije statistički značajno ($P=0.95$). **Zaključak.** U ovom istraživanju blaga stimulacija jajnika se pokazala jednako uspješnom u ostvarivanju kliničke trudnoće kao i standardna stimulacija jajnika.