La Prensa Medica Argentina

Research Article

The Pregnancy Outcomes Comparison on Natural or Controlled Ovarian Stimulation Cycles in Intrauterine Insemination Treatment: An Analysis of 8,893 Cycles

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Rec date: Oct 26, 2015 **Acc date**: Jun 18, 2016 **Pub date**: Jun 23, 2016

Abstract

Objective: To evaluate the intrauterine insemination pregnancy outcomes both in nature and controlled ovarian stimulation cycles

Design: Retrospective analysis.

Setting: A single university medical center.

Intervention: After controlled ovarian stimulation or nature cycle follicle monitoring, IUI performed 24-36 hours after ovulation triggering.

Main Outcome Measure: The pregnancy rate, live birth rate, miscarriage rate.

Result: The clinical pregnancy and live birth rate was statistically significantly higher in the stimulated cycles than nature cycles as well as that of abortion rate. The pregnancy rate and live birth rate of combination CC with HMG and LE with HMG was higher than other protocols ($P<0.05$). The abortion rate was higher in stimulated cycles than that in nature cycles with unexplained infertility ($P<0.05$). There were no statistical significance in pregnancy outcomes between nature and ovarian stimulation cycles in normal ovulation patients ($P>0.05$).

Conclusion: Ovarian stimulation could significant increase pregnancy and live birth rate accompany with a higher abortion rate compared with nature cycles in intrauterine insemination treatment. Letrozole combined gonadotropins stimulation protocols showed higher pregnancy rates and live birth rate in comparison to natural cycle and other stimulation protocols. The ovary stimulation was failed to improve the pregnancy outcome of women who have good natural cycles. Nature cycles were still favorable to recommend for safety factors.

Keywords: Intrauterine insemination; Stimulated cycles; Nature cycles; Mild ovary stimulation

Introduction

Intrauterine insemination (IUI) is considered the oldest first-line procedure in assisted reproductive techniques due to its simplicity, easy management and low cost. Moreover, the acceptable pregnancy rates and relatively lower incidence of complications lead most clinicians to direct patients to IUI in routine infertility management plans. Intrauterine insemination involves timed insemination of spermatozoa into the uterus in natural cycles or insemination following stimulation of the ovaries. Although the fact that controlled ovarian stimulation (COS) is routinely used in many infertility centers, there was no clear evidence for a superior effect of ovarian stimulation combination with IUI compared to nature cycles(NC) [1,2]. A role for the agents used to ovarian stimulation as a contribution to the multiple births, ovarian hyper-stimulation syndrome and abortion is still discussed. Till now there is no consensus about the best drug and treatment option used for ovarian stimulation [3]. The controversy over whether the couples should undergo nature cycles or ovarian stimulation cycles was opinions vary. The aim of this study is to evaluate the IUI pregnancy outcomes both in nature and ovarian stimulation cycles through a retrospective analysis of our hospital recent five years IUI cycles to guide physicians to develop individualized and safe and effective protocols for infertility couples.

Material and Methods

Patients

This is a retrospective study performed between 2006 and 2012 on 5109 couples with infertility problems, who were enrolled in this study, aged 21-46 years old and averaged 30.8 ± 4.3 years old, infertility ranged from 1 to 17 years with an average of 5.5 ± 2.9 years. Clinical information was from the database of our department (CCRM). Infertility factors included female pelvic inflammation, endometriosis, an ovulatory infertility, unexplained infertility and male factors. The inclusion criteria were included: infertility for over 1 year, at least one healthy fallopian tube is diagnosed. This study was approved by the hospital medical ethics committee.

Ovarian stimulation and follicle monitoring

Patients with normal ovulation cycle underwent IUI in natural cycles, while for patients with anovulation, irregular menstruation, follicular dysplasia or some pregnant failure with nature cycle IUI in controlled ovarian stimulation, clomiphene (CC), letrozole (LE), and human menopausal gonadotropin (HMG) were used for ovarian stimulation. The stimulation took place from the fourth day of the cycle and continued until ovulation triggering. The initial dose was 50 mg/day for clomiphene citrate (days 4–8) or of 70 IU/day for HMG and 2.5 mg/day for letrozole, the dosage and project was modulated by the woman's previous responses to stimulation. Follicle growth and endometrium were monitored with vaginal ultrasound, when at least one mature follicle diameter was 18 mm or higher, we performed ovulation triggering via intramuscular injection of urinary human chorionic gonadotropin (5,000-10,000U IU of hCG; Schering-Plough), underwent IUI the next day or the day of follicular rupture. Ovulation

stimulation protocols included: 1. CC; 2. combination CC with HMG; 3. HMG; 4. LE; 5. combination LE with HMG. The specific drug usages were carried out on a regular basis. In out center, we controlled the dominant follicle within three in ovulation stimulation, so as to control the occurrence of multiple pregnancies to a minimum, also called mild ovulation stimulation. We cancelled the IUI cycle when no mature follicles were monitored or when more than four mature follicles were monitored. Insemination was performed 36 to 40 hours after hCG injection

Semen preparation

The semen samples were analyzed using WHO guide-lines from 1999. Semen for the insemination was collected by masturbation, after abstinence for 3-7 days and prepared with 2-layer density gradient centrifugation after liquefaction.

Single IUI was carried out by slowly injected 0.3-0.5 ml well-prepared semen suspension into uterus with disposable artificial insemination tube. The end of the soft catheter (Frydman type; CCD) or hard catheter if the soft catheter could not pass (TDT; CCD) was inserted into the center of the uterine cavity

Postoperative luteal support and follow-up

Ultrasound examination was carried out at 48 hours after HCG injection, to determine whether the follicle was ruptured or not. Luteal phase was supported if follicular rupture occurred. Daily treatment with micronized progesterone (Utroge-stan, 400 mg/day; Cassenne-Aventis) was prescribed for 13 days after the IUI. A serum hCG assay was performed 14 days after insemination. Ultrasound examination was performed 3 weeks later to confirm the presence of a gestational sac in the uterine cavity. A clinical pregnancy was defined as a fetal heartbeat on ultrasound.

Statistical treatment

SPSS16.0 software was used for data analysis, x^2 test was for rate comparison between groups, with P<0.05 for the difference was statistically significant.

Results

Pregnancy outcomes of stimulated cycles and natural cycles

A total of 8893 cycles were for IUI treatment, with 2591 cases underwent IUI in nature cycles, and 6302 in stimulated cycles. The mean age of nature cycles patients was 30.44 ± 3.57 years old, and 30.58 ± 3.45 years old for stimulated cycles patients, there was no statistical significance in age (P>0.05); the mean number of dominant follicle was 1.06 ± 0.27 and 1.68 ± 0.81, respectively, the difference between groups was of statistically significance (P<0.05).

In nature cycles group, 241 cases were of clinical pregnancy with a pregnancy rate of 9.3%. In stimulated cycles group, 734 cases were of clinical pregnancy with a pregnancy rate up to 11.65%, the statistical significance was also observed in live birth rate (P<0.05). There was no statistical significance between stimulated cycles and nature cycles groups in ectopic rate, no twinning pregnancy was present in nature cycles group, so the twins rate was not included in statistic. The abortion rate in stimulated cycles group was higher than that in nature cycles group, (P<0.05) (Table 1).

	NC	COS	P value
Cycles	2591	6302	
Pregnancy rate	9.3 (241/2591)	11.65(734/6302)*	0.001
Abortion rate	14.52(35/241)	19.62(144/734)*	0.045
Twins rate	0(0/241)	4.9(36/734)	NS
Ectopic rate	4.15(10/241)	5.99(44/734)	NS
Live birth rate	7.56(196/2591)	8.66(546/6302)*	0.047

Table 1: Comparison of pregnancy outcomes between natural and stimulated cycles (%) *compared with NC: P<0.05

Comparison of pregnancy outcomes between different IUI protocols

The pregnancy rate and live birth rate of combination CC with HMG and LE with HMG was higher in stimulation cycles group than that in nature cycles group, with statistical significance. The abortion rate of CC was also higher in stimulation group than that in nature cycles group, with statistical significance. There were no statistical significance in twins and ectopic pregnancy rates between stimulated cycles and nature cycles groups for 6 subgroups (P>0.05), among them no twining pregnancy present in nature and LE treatment. No triplet pregnancy and OHSS in stimulated cycles for five subgroups as shown in Table 2.

	NC	CC	LE	HMG	CC + HMG	LE + HMG	P value
Pregnancy rate	9.3 (241/2591)	9.92 (274/2761)	7.87 (27/343)	10.56 (68/644)	13.47* (270/2005)	17.3* (95/549)	0.000
Abortion rate	14.52 (35/241)	23.36* (64/274)	25.93 (7/27)	14.71 (10/68)	15.19 (41/270)	23.16 (22/95)	0.037
Twins rate	0 (0/241)	4.01 (11/274)	0 (0/27)	4.41 (3/68)	6.3 (17/270)	5.3 (5/95)	NS
Ectopic rate	4.15 (10/241)	5.11 (14/274)	11.11 (3/27)	5.88 (4/68)	8.15 (22/270)	1.05 (1/95)	NS

Live birth rate	7.56 (196/2591)	7.1 (196/2761)	4.96 (17/343)	8.39 (54/644)	10.3* (207/2005)	13.11* (72/549)	0.000

Table 2: Comparison of pregnancy outcomes between different IUI protocols (%) *compared with NC: P<0.05

Clinical outcomes comparison of IUI between stimulated cycles and nature cycles with various infertility factors

According to the infertility reasons, all cases were divided into five groups: endometriosis, tubal and pelvic inflammation, anovulation, male factors, and unexplained infertility. There were no statistical significance in pregnancy rate in stimulated cycles(exclude anovulation), but a higher pregnancy rate was showed in male factors group with stimulated cycles, however, this outcome has no statistical difference in live birth rate, as shown in Table 3. The comparison of abortion rate in different etiologies showed that it was higher in stimulated cycles than that in nature cycles with unexplained infertility, as shown in Table 4.

	NC	COS	P value
Endometriosis PR LBR	10.82(29/268) 6.72(18/268)	10.61(33/311) 8.68(27/311)	NS NS
Tubal and pelvic inflammation PR LBR	8.35 (69/826) 6.3 (52/826)	9.87 (140/1418) 7.48 (106/1418)	NS NS
Anovulation PR LBR	0 (0/0) 0 (0/0)	15.8 (247/1563) 12.73 (199/1563)	
Male factors PR LBR	14.22 (60/422) 12.56 (53/422)	19.2 (125/651)* 16.13 (105/651)	0.021 NS
Unexplained infertility PR LBR	9.49 (83/875) 8.69 (76/875)	10.41 (189/1815) 7.44 (135/1815)	NS NS

Table 3: Comparison of pregnancy rates/ live birth rate between different groups (%) * compared with NC: P<0.05 PR: pregnancy rates LBR: live birth rate

	NC	COS	P value
Endometriosis	31.03 (9/29)	15.15 (5/33)	NS
Tubal and pelvic inflammation	18.84 (13/69)	17.86 (25/140)	NS
Anovulation	0 (0/0)	18.22 (45/247)	NS
Male factors	10 (6/60)	13.6 (17/125)	NS
Unexplained infertility	8.43 (7/83)	27.51 (52/189)*	0.000

Table 4: Comparison of abortion rates between different groups (%) *compared with NC: P<0.05

Pregnancy outcomes comparison in stimulation group

Divided stimulated cycles into anovulation and ovulation two groups, the abortion and ectopic pregnancy rates and twins rate in two groups showed no statistical significance (P>0.05), there was statistical significance higher in pregnancy rates and live birth rate compared anovulation with ovulation groups as shown in Table 5.

	An ovulation	Ovulation	P value
Pregnancy rate	15.8(247/1563)*	10.28(487/4739)	0.000
Abortion rate	19.03(47/247)	19.92(97/487)	NS
Ectopic rate	3.64 (9/247)	7.19(35/487)	NS
Twins rate	6.48(16/247)	4.11(20/487)	NS
Live birth rate	12.22(191/1563)*	7.49(355/4739)	0.000

Table 5: Comparison of pregnancy outcomes between two different groups (%)* compared with ovulation: P<0.05

Pregnancy outcomes comparison in ovulation group between stimulated cycles and nature cycles

There were no statistical significance in pregnancy rate, live birth rate, abortion rate and ectopic pregnancy rate between stimulated and nature cycles groups in ovulation (P>0.05), as shown in Table 6.

	NC	COS	P value
Pregnancy rate	9.3(241/2591)	10.28 (487/4739)	NS
Abortion rate	14.52 (35/241)	19.92 (97/487)	NS
Ectopic rate	4.15 (10/241)	7.19 (35/487)	NS
Twins rate	0 (0/241)	2.26 (11/487)	NS
Live birth rate	7.56 (196/2591)	7.49 (355/4739)	NS

Table 6: Comparison of pregnancy outcomes excluded anovulation (%).

Discussion

Although more invasive therapies like in vitro fertilization show good results, the intrauterine insemination (IUI) still plays a role in assisted reproductive technologies (ART). IUI is considered the first therapeutic option for a large group of infertile or sub fertile patients. But it still remains to be discussed whether the pregnancy outcomes of IUI in stimulated cycles is superior to nature cycles. Moreover, when and which protocols of controlled ovarian stimulation is necessary.

Clinical pregnancy rate of IUI in stimulated and nature cycles

The analysis results showed that there was no significant difference in pregnancy rate of IUI between stimulated and nature cycles [4,5]. In 2008 The Cochrane Collaboration reported that no statistically significant of difference between pregnancy rates (PR) per couple for IUI with ovary stimulation versus IUI could be found [4]. In a prospective randomized trial Goverde could not find an influence of mild FSH stimulation in comparison with a natural cycle in IUI treatment for patients with idiopathic sterility [1]. In a later study, in 2005 these results were confirmed. They described IUI on natural cycle as equally effective as stimulation protocols avoiding the multiple pregnancy risks [6]. However, the statistical results showed that stimulation can improve the pregnancy rate of IUI when compared with nature cycles. There is further evidence that IUI with stimulated increases the live birth rate compared to IUI alone for unexplained subfertility [7].

The data in our center suggesting the pregnancy rate and live birth rate in ovary stimulation showed to offer significantly higher outcome in comparison to the natural cycle. The increase of dominant follicles number in stimulated cycles is one of the main causes responsible for the increasing pregnancy rate, the standards in different medical centers are different on limiting the dominant follicles numbers, and this may be the reason for different conclusions [8]. In our ovary stimulation protocols, the dominant follicles were basically controlled at 1.68 ± 0.81, this relatively mild ovulation induction may be one of the reasons responsible for avoiding the multiple pregnancy and OHSS risks.

Dankert [9] could not demonstrate any significant difference in live birth rates between clomiphene and recombinant FSH. In another small prospective randomized trial no difference in pregnancy rates either in clomiphene or in hMG stimulation [10]. In a prospective study that there is no significant difference in pregnancy rate after intrauterine insemination comparing stimulation with clomiphene and hMG and clomiphene in combination with recombinant FSH [11]. A tendency can be seen, as the pregnancy rate is higher after stimulation with clomiphene and recombinant FSH but the difference did not reach any statistical significance. There is no difference in the outcome if stimulation was performed with HMG, recombinant FSH, urinary FSH or in a natural cycle [12].

Meta-analysis results of Papageorgiou showed that the pregnancy rates of IUI in nature cycles and with oral medicines for ovarian stimulation (CC or LE) were significantly lower than those in gonadotropin group [13]. As recently as last year a systematic intervention review of the Cochrane Database on ovarian stimulation protocols concluded that although " robust evidence is lacking gonadotropins might be the most effective drugs when IUI is combined with ovarian hyper stimulation [14]."

In our research, the pregnancy rate and live birth rate of combination CC/LE with HMG was significantly higher than nature cycles ($P<0.05$). Among five ovarian stimulation protocols, the pregnancy rates and live birth rate of CC or LE combined with HMG and HMG lonely were higher than those of single application of CC or LE, suggesting that the stimulation effect of gonadotropin may be contributed to increased pregnancy rates. Although easy to be taken, its high LH level, anti-estrogen role and effect on the quality of oocytes may decrease the pregnancy rate of CC. For gonadotropin, it's more likely to obtain oocyte to mature, the application of CC or LE in early follicular phase, can play a role in follicular recruitment, and reduce the potential risk of more follicular initiation and mature caused by HMG alone, indicating more advantages of combination CC or LE with HMG in clinical application. Clomiphene citrate is a long-standing, standard drug for ovulation induction and is still considered as first-line option in PCOS women [15]. However, clomiphene has certain well-defined disadvantages. Treatment with CC is associated with discrepancy in ovulation and pregnancy rates (60-85%; 10-20%). Miscarriage rate is higher than general population, and 20-25% PCOS women are resistant to clomiphene. Anti-estrogenic effect of CC leads to prolonged depletion of estrogens receptors, adversely affecting endometrial growth and development as well as quantity and quality of cervical mucus [16]. As letrozole does not deplete estrogen receptors in the brain, Furthermore, letrozole causes temporary accumulation of androgens in the ovarian follicles by blocking the conversion of androgens to estrogens. The accumulated androgens may increase the sensitivity of the growing follicles to FSH by increasing the expression of FSH receptors [17], which makes it suitable alternative for CC in resistant patients with polycystic ovarian syndrome or poor responder patients [16].

The results of our study revealed that the extended letrozole combined HMG regimen has an excellent efficacy as compared with other protocols both in pregnancy rate and live birth rate. Letrozole should be considered as first line drug for ovulation induction in infertile women. However it needs to be further explored the long-term effects of the optimum dose and time of LE on IUI.

Abortion rate of IUI in stimulated cycles and nature cycles

The analysis results of Papageorgiou suggested that there was no significant difference in abortion rate of IUI in stimulated and nature cycles [13]. Stimulation could result in a higher abortion rate [18]. Our results indicated that the abortion rate of stimulated cycles was higher than nature cycles, and the difference reach statistical significance ($P<0.05$). In various ovary stimulation protocols, the abortion rate of CC was significantly higher than nature cycles ($P<0.05$), in different etiologies, the abortion rate of unexplained infertility in stimulation was significantly higher than other factors ($P<0.05$). Spontaneous triggering of ovulation is associated with significantly higher ongoing pregnancy rates compared with administration of HCG in patients undergoing IUI in nature cycles [19]. It has been reported that endometrial receptivity is higher in non-stimulated compared with stimulated IVF cycles. The higher ongoing pregnancy rate in the spontaneous cycles might also be associated with the degree of follicle/oocyte maturity during the LH rise compared with the case of HCG administration [19]. The anti-estrogen role of CC can result in the antagonism to endometrium, which may be responsible for the high abortion rate. The clomiphene citrate induces prolonged estrogen receptors depletion and therefore exerts anti-estrogenic effect on estrogen target tissues as endocervix and endometrium [3]. Several studies revealed that clomiphene citrate has a deleterious effect on cervical mucus quantity and quality and endometrial development resulting in decreased uterine blood flow, endometrial thinning, luteal phase defect and implantation failure [20]. Increasing the diameter of follicle was unable to improve the high abortion rate of unexplained infertility patients, might be associated with endometrial factors [18]. Embryo chromosome abnormality rate in natural abortion after IUI pregnancy was up to 85.7%. The development driven of follicles in stimulated cycles is from the stimulation of exogenous drugs, different from the follicular development under normal cycles, which may also result in the high abortion rate. Although ovary stimulation drugs can

improve the oocyte development in morphology, we still cannot give further quality assessment, so the risk of oocyte dysplasia still exists, underdeveloped oocyte and its endocrine environment may lead to decreased fertilization ability or further developmental ability even fertilization implantation happens, affecting the embryonic development, leading to the occurrence of spontaneous abortion [21]. The NICE fertility guide lines recommended IUI without OH for couples with unexplained sub fertility because of the increased risk of multiple pregnancies and OHSS associated with stimulation [7]. To sum up, IUI in nature cycles is much safer to be recommended for those have good natural cycles or unexplained infertility patients, who seem not to profit from any ovarian stimulation.

Twins rate comparison of IUI in stimulated cycles and nature cycles

The twin's rate in stimulated cycles was 4.9%, higher than that in nature cycles, which might be associated with increasing dominant follicles; meanwhile, multiple pregnancy risk was also increased. It reported that there was no significant difference in pregnancy rate with 1-3 or more than 3 dominant follicles in IUI cycles [8]. So it's should strictly dominate the indications of ovary stimulation drugs, control 1-2 dominant follicles in stimulated cycles, cancel the cycle or take an alternative to IVF-ET if more than 3 follicles, so as to avoid multiple pregnancy or OHSS. The multiple pregnancies caused by stimulation were primarily because of the significantly more follicles at the HCG injection day or the day with endogenous LH peak than nature cycles [6]. However this increase of follicles before ovulation was unable to increase pregnancy rate, but only lead to higher risk of multiple pregnancies. The reported multiple pregnancy rates at home and abroad of IUI in stimulated cycles ranged from 13% to 33% [7]. In this study, we controlled the dominant follicles less than or equal to three with mild stimulation proposal, no triple and OHSS was present in clinic, and the twins rate of IUI in stimulated cycles was only 4.9%, indicating a higher safety, but it's still need more statistical data to make prospective conclusions.

IUI outcomes of different subgroups

We found that in all kinds of infertility factors, there was no statistical significance in pregnancy rate of IUI between stimulated cycles and nature cycles, excluded male factors. Multi follicular growth following ovarian stimulation may be associated with an increase in pregnancy rates in male factor sub fertile couples. For those anovulation in stimulated cycles, the pregnancy rate was 15.8%, whose pregnancy rate and live birth rate were higher than those ovulation in stimulated cycles ($P<0.05$). If dividing ovulation into stimulated cycles and nature cycles two groups, there were no statistical significance in pregnancy rate, live birth rate, abortion rate and ectopic pregnancy between two groups.

The use of IUI in male subfertility with or without ovary stimulation has been under debate. The question regarding the effectiveness of IUI with or without stimulation as a treatment for male subfertility has been addressed repeatedly, yet a definitive conclusion has never been drawn [4]. The most recent NICE Guidelines state that for male subfertility, ovarian stimulation should not be offered because it does not improve treatment outcome while increasing the risk of multiple pregnancy [4]. Our outcomes also indicated that stimulation cannot improve the live birth rate for male subfertility. It has been suggested that IUI in male subfertility would be advantageous over other assisted reproductive techniques only when a certain threshold value of motile sperm count can be achieved [4,22].

Main reasons for infertility from anovulation are no mature follicles or rare ovulation; ovary stimulation drugs can improve oocyte development so as to improve the pregnancy rate. Advantages of controlled ovarian stimulation include the possibility to correct endocrine dysfunction and to increase fertility rate by stimulating more follicles. In the case of female endocrine dysfunction, a controlled ovarian stimulation is necessary [12]. The synchronous development of multiple follicles may be one reason for higher twins' rate. The follicular development must be monitored with vaginal ultrasound.

In our center, there had 10 cases of ectopic pregnancy in NC and 44 cases of ectopic pregnancy in stimulated cycles, with relatively small sample size. And the reports of ectopic pregnancy in IUI cycles are also fewer reports, so it's still unable to make a conclusive statistical result.

In conclusion, the results of our study revealed that the controlled ovarian stimulation has a significant increasing pregnancy rate and live birth rate followed with a higher abortion rate compared with nature cycles in intrauterine insemination treatment. The ovary stimulation proposal used in our center was a kind of effective method to improve the pregnancy rate and live birth rate in case of female anovulation, which was failed to improve the pregnancy outcome of women who have good natural cycles. For those couples with unexplained sub fertility, nature cycles were still favorable to recommend making sure safety. Mild ovary stimulation protocols were had better to use as far as possible. Letrozole combined gonadotropins stimulation showed to offer significantly higher pregnancy rates and live birth rate in comparison to the natural cycle and other stimulation protocols in IUI treatment, however, which need to collect further robust evidence to appraise on the benefits and disadvantages.

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