

# Intrauterine insemination IUI: the effect of ovarian stimulation and infertility diagnosis on pregnancy outcome

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## Summary

We determined the intrauterine insemination (IUI) pregnancy outcome in the same group of patients when applying different methods of ovulation induction. A group of patients with unexplained (no. 46) and male factor infertility (no. 101) consented to have the following treatment protocol at the American University of Beirut - Infertility Center: IUI to be performed in three natural ovulatory cycles in all patients, then in three clomiphene citrate (CC) stimulated cycles in the remaining non-pregnant patients, and then three cycles with controlled ovarian hyperstimulation (COH) in the remaining group. Of the total 147 patients 130, 138 and 123 underwent 273 natural, 278 CC and 266 COH IUI cycles, respectively. Semen processing for IUI was done by washing the sperm twice and using the swim-up technique. The chi-square test was used for statistical analysis. Pregnancy rate per cycle of IUI with COH (9.8%) was significantly higher than that of IUI in natural cycles (3.3%) but approached significance when compared to IUI with CC cycles (5.4%). Also unexplained infertility cases had a significantly higher pregnancy rate (58.7%) when compared to that of male factor cases (22.8%). IUI still has a place in the treatment of infertility due to selective causes. Combined with COH, IUI gives the best pregnancy rate although its benefit with natural or CC cycles remains obvious.

**Key words:** IUI; Ovulation induction; Unexplained infertility; Male infertility.

## Introduction

Intrauterine insemination (IUI) with the husband's spermatozoa has been widely used for the treatment of infertile couples. The major indications for performing IUI are unexplained infertility, cervical factor and male factor infertility [1]. In spite of its long term use, many aspects of IUI are still controversial. There appears to be lack of agreement as to whether IUI is an appropriate treatment for couples with sperm dysfunction [1]. Several studies have shown that IUI is of limited value in patients with poor sperm motility [2, 3]. However, recent work by Burr *et al.* suggests that sperm morphology rather than motility is a more sensitive guide to outcome [4].

There is also no consensus about the role of ovulation induction with IUI. Several reports show improved pregnancy rates when IUI is performed in human menopausal gonadotropin (hMG) stimulated cycles [5, 6], but others do not support these data [7]. In addition, the overall success of IUI varies, with pregnancy rates ranging from as low as 5% to as high as 66% [8]. Much of these controversies may stem from differences in the treatment groups, diagnostic criteria and techniques used in the various studies.

In this study, we present our IUI results in relation to hormonal treatment for ovulation induction, and the indication for performing IUI, applying a unified protocol in all treatment cycles.

## Materials and Methods

**Patients:** A total of 147 patients with primary infertility range of 2 to 15 years duration, underwent 817 cycles of IUI during a 3-year period from January 1, 1994 to December 31, 1996.

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Treatment was performed at the infertility unit of the American University of Beirut - Medical Center. Indications for IUI included male factor infertility (101 patients) and unexplained infertility (46 patients). Patients with male factor infertility were divided into two groups: severe male factor when  $< 5 \times 10^6$  motile sperm were obtained by the swim-up technique, and mild male factor when  $> 5 \times 10^6$  motile sperm were present in the swim-up sample. All the female partners of the male factor cases had documented ovulatory cycles and documented patent fallopian tubes (by hysterosalpingogram (HSG) and/or laparoscopy). Unexplained infertility was defined in couples who underwent extensive infertility evaluation consisting of at least two normal semen analyses [9], documentation of ovulation and adequate luteal phase, normal postcoital test, normal HSG, and normal pelvic organs by laparoscopy.

**Treatment protocol:** Women with normal ovulatory cycles consented to the following protocol: IUI would be performed in three spontaneous and natural ovulatory cycles, then in three clomiphene citrate (CC) stimulated ovulation cycles, and finally in three cycles of controlled ovarian hyperstimulation (COH) using human menopausal gonadotropins (hMG). Patients with anovulation underwent IUI in three cycles of CC stimulation followed by three cycles of COH. In natural and CC stimulated cycles ovulation was detected using urinary LH surge kits. Intrauterine insemination was performed 24 hours after a positive LH surge test. Clomiphene citrate was given from day 3 to 7 of a cycle in doses ranging from 50 to 150 mg daily. In the hMG stimulated cycles, two ampoules of hMG (Humegon; Organon Ltd) were administered daily as of the third day of a menstrual cycle. Patients were followed up by serial ultrasounds and the dose of hMG was regulated depending on the response. When the leading follicle reached a mean diameter of  $\geq 18$  mm, 5,000 IU hCG were given. Intrauterine insemination was performed 36-40 hours after hCG injection.

**Sperm preparation and IUI:** Semen samples were collected by masturbation into sterile containers and allowed to liquefy for about 30 minutes at room temperature. Prior to preparation, sperm characteristics were assessed according to WHO criteria [9]. The ejaculates were washed twice by centrifugation at 300 x g in Ham's F-10 (GIBCO, Grand Island, NY, USA) supple-

mented with 7.5% human fetal cord serum. After the second wash, the supernatant was removed, and 0.3 to 0.5 ml of fresh medium was gently layered over the final pellet and incubated in 5% CO<sub>2</sub> in air at 37 °C for one hour. The supernatant was then collected and analyzed for count and motility. This "swim-up" specimen was used for IUI using the Tom Cat catheter (Sherwood, St. Louis, MO, USA). Patients were asked to rest in the supine position for 20-30 minutes post-IUI.

**Statistics:** Only on-going pregnancies and deliveries were included in the statistics. The chi square test was used to compare the differences in pregnancy rates parameters and significance was set at  $p < 0.05$ .

## Results

Of the 147 patients, 130 underwent 273 cycles of IUI during natural ovulatory cycles. Seventeen patients were anovulatory. Nine patients got pregnant [pregnancy rate (PR) of 6.9% per patient and 3.3% per cycle]. In the stimulated cycles, 278 cycles were done in the remaining 138 patients using CC and resulted in 15 pregnancies (PR of 10.9% per patient and 5.4% per cycle), and 266 cycles were done in the remaining 123 patients using COH and resulted in 26 pregnancies (PR of 21.1% per patient; 9.8% per cycle). There was a significant difference in the number of patients who got pregnant with ovulation induction using COH than those with natural cycles (Table 1). Pregnancy rates achieved when applying IUI with CC were higher when compared to those of IUI in natural cycles, but lower as compared to those with COH. These differences however did not reach significance (Table 1). Unexplained infertility cases had significantly higher pregnancy rates than cases of male factor infertility when almost the same relative number and type of IUI procedures were performed in both groups (Table 2). Mild male factor cases expectedly had significantly higher pregnancy rates compared to severe male factor ones (Table 2). Moreover, in each infertility diagnostic group, IUI cycles done with COH gave the highest pregnancy rates compared to almost the same number of natural and CC stimulated IUI cycles (Table 2).

There was a decrease in IUI pregnancy rates with increasing age of the patient. This decrease becomes significant after age 40 when compared to pregnancy rates achieved before age 35 (Table 3).

Table 1. — IUI outcome vs Type of ovulation induction.

Type of cycle	No. of patients	No. of cycles	No. of pregnancies	PR/cycle
Natural	130	273	9	3.3% <sup>ab</sup>
CC	138	278	15	5.4% <sup>ac</sup>
COH	123	266	26	9.8% <sup>bc</sup>

a:  $p = 0.318$ ; b:  $p = 0.004$ ; c:  $p = 0.075$ .

Table 2. — Infertility diagnosis and type of cycle vs IUI outcome.  
No. of pregnancies (percentages)

Diagnosis	No. patients	Natural	CC	COH	Total	PR/dx
Male	101	3 (13.0%)	7 (30.0%)	13 (57.0%)	23	22.8% <sup>b</sup>
Severe	44	0	2 (50.0%)	2 (50.0%)	4	9.1% <sup>bc</sup>
Mild	57	3 (15.8%)	5 (26.3%)	11 (57.0%)	19	33.3% <sup>bd</sup>
Unexpl.	46	6 (22.2%)	8 (29.6%)	13 (48.2%)	27	58.7% <sup>acd</sup>
Total						
no. of pts.	147	9 (18.0%)	15 (30.0%)	26 (52.0%)	50	34.0%

a:  $p = 0.000$ ; b:  $p = 0.008$ ; c:  $p = 0.000$ ; d:  $p = 0.017$ .

Table 3. — IUI outcome vs Age.

Age	No. of patient	No. of pregnancies (rate)
< 35	103	44 (42.7%) <sup>ab</sup>
36-39	23	5 (21.7%) <sup>ac</sup>
> 40	21	1 (4.8%) <sup>bc</sup>
Total	147	50

a:  $p = 0.103$ ; b:  $p = 0.002$ ; c:  $p = 0.233$ .

## Discussion

This study describes the pregnancy rates achieved by IUI and tries to identify the different clinical variables that might affect these rates. Two main controversial issues were evaluated in this study: first IUI outcome versus the indication (the infertility diagnostic category) and second the outcome as related to the ovulation induction method (natural vs CC vs COH).

As to the first issue, the literature is still controversial as to which diagnostic group would benefit more from IUI. In the guidelines issue 91 of the American Fertility Society (now the American Society for Reproductive Medicine) it was stated that IUI success rate was almost zero when less than one million motile spermatozoa were used [8]. Malarewicz *et al.* had a 0% pregnancy rate when IUI was applied to male factor cases [2]. Similarly Kossakowski *et al.* found that IUI was not beneficial for either male factor or unexplained infertility cases [10]. The only benefit was in cervical factor cases. Contrary to this, Check *et al.* found that IUI was beneficial for both cervical and male factor cases [6]. Sperm morphology was not found to affect IUI outcome by Matorras *et al.* [11], but it was by Burr *et al.* [4]. Increasing the number of motile sperm increased the prep rate of IUI as reported by Brash *et al.* [9] but had no such effect as shown by Burr *et al.* [4].

In this study all the diagnostic groups have similar mean age which eliminates the effect of age on outcome. IUI was very beneficial for unexplained infertility cases (PR: 58.7%), but it was significantly less so for male factor (PR: 22.8%). Also the number of motile sperm used did affect the outcome significantly as shown from the PR of both severe (9.1%) and mild male factor cases (33.3%).

As to the second issue, namely the effect of the ovulation induction method on IUI outcome, many authors reported better pregnancy rates when IUI was performed with HmG as compared to IUI with CC or natural cycles [12, 13]. Moreover, Arici *et al.* showed that IUI with CC is better than IUI with natural cycles [14]. Some authors showed that the reported superiority of IUI with hMG is due to the administration of hMG per se and not to the IUI procedure itself [7, 15]. But this theory has been refuted by others [5, 13]. In our study, IUI with COH pregnancy rate (9.8%) was better than that of IUI with CC (5.4%) (the difference did not reach significance) and significantly better than that of IUI with natural cycles (3.3%). Also the IUI outcomes with both CC and natural

cycles were not different (5.4% vs 3.3%). These findings do not concur with many of the previously reported studies [12-14]. This disagreement with previous studies, especially when comparing COH and CC cycles outcomes, may be secondary to the fact that our study was not a crossover one. This means that a relatively lesser number of patients conceived from IUI with COH because the good prognostic cases had already achieved pregnancy by IUI with natural or CC cycles.

In conclusion, we believe that IUI still has a place in the treatment of infertility due to selective causes. Whether to recommend it for severe male factor cases depends on the availability of other alternative means such as the assisted reproductive technologies. Combined with hMG, IUI gives the best pregnancy rate although one cannot deny its benefit even with natural cycles or CC in certain diagnostic categories.

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