CLINICAL ASSISTED REPRODUCTION

Effect of Clinical and Semen Characteristics on Efficacy of Ovulatory Stimulation in Patients Undergoing Intrauterine Insemination¹

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Purpose: We measured the effect of ovulatory stimulation (OS) upon intrauterine insemination (IUI) success rates, particularly among patients with risk factors for IUI failure.

Methods: Retrospective review of medical and laboratory results from 512 patients who underwent 1576 cycles of IUI with partner's sperm over a 3 year period. Data were collected on 3 risk factors for IUI failure (advanced female age >37.7 years, prior corrective pelvic surgery, and poor post-wash sperm motility), and on method of OS (none, clomiphene citrate, or gonadotropin).

Results: Patients who underwent OS had significantly higher pregnancy rates (7.6%) than those who did not (4.7%, $p = 0.02$). However, when patients were stratified by their risk factors, OS made a significant difference only for patients without risk factors. These patients had a 15.5% per cycle pregnancy rate with OS, compared to 7.9% in unstimulated IUI cycles ($p = 0.04$).

Conclusions: Ovulatory stimulation doubles IUI pregnancy rates among young patients without a prior pelvic surgery and with good post-wash semen quality. The benefit of OS for patients with risk factors for IUI failure is unclear. These patients should be counseled that their chances for success with IUI are limited, with or without OS.

KEY WORDS: infertility-female; ovulation induction; pregnancy rate; insemination-artificial; sperm motility.

INTRODUCTION

Because ovulatory stimulation increases fertility with some types of assisted reproductive techniques, it is believed to increase the chances of success in intrauterine insemination (IUI). Therefore, many centers that use IUI routinely stimulate ovulation with clomiphene citrate or injected gonadotropins (1–4). However, few reports are available to show whether this practice really does raise pregnancy rates or birth rates, and if so, in which types of patients.

In a concurrent study, we determined that the success of intrauterine insemination (IUI) is influenced by patient characteristics as well as by semen quality (5–6). We identified 3 pre-treatment variables that are major determinants of IUI cycle outcomes: the woman's age, her history of corrective pelvic surgery, and the post-wash sperm motility.

In this retrospective analysis, we compared the rates of full-term pregnancies following IUI among patients who underwent ovulatory stimulation and those who did not. We also compared pregnancy rates among

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patients with and without the 3 risk factors identified above.

MATERIALS AND METHODS

Study Design

This study was approved by the Institutional Review Board. In this retrospective study we reviewed the records of women who had undergone IUI at the Cleveland Clinic Foundation between January 1993 and December 1995. These were the first 3 years in which data collection for these patients was standardized at our institution. During this period, 533 women underwent 1728 IUI cycles using sperm from their partner. In our concurrent study, full-term pregnancy rates were analyzed for relationship with pre-treatment clinical and semen characteristics (preceding manuscript).

In this study, we restricted the sample to patients for whom all ovulatory management, age, pelvic surgery, and sperm motility were available. We identified 512 such patients who had undergone 1576 IUI cycles.

Patient Evaluation

All medical records included findings from pre-treatment history and physical examinations. Menstrual disorders were diagnosed if cycle duration was >32 days or <21 days, or if the duration of menstrual flow was >7 days. Dysmenorrhea was assessed for presence and severity, and was graded as absent, mild, moderate, or severe based on subjective patient reporting. Prior contraceptive use, and the type of contraception were recorded. Prior fertility history was elucidated. History of previous laparoscopy or open pelvic surgery, and pertinent surgical findings and treatments were obtained.

Pelvic examinations were performed on all patients. Hysterosalpingograms were obtained when clinically indicated. Endometrial biopsies were also obtained when clinically indicated. Diagnostic laparoscopy was performed when clinically indicated, and corrective pelvic surgery was performed by laparoscopic or open surgical procedures as appropriate. We also collected data on ovulatory management, defined as the modality of hormonal ovulatory stimulation used in each IUI cycle. Three categories of management were defined: 1) no ovulatory stimulation; 2) stimulation with clomiphene citrate at any dosage; and 3) stimulation with injectable gonadotropins at any dosage.

Women with a significant luteal phase defect on endometrial biopsy were treated with clomiphene citrate. Patients who ovulated were treated first with clomiphene citrate and then with gonadotropins if no follicles were induced or if pregnancy did not occur. Pergonal (Serono Laboratories, Randolph, Massachusetts) was used exclusively for the gonadotropin stimulation. The dose was determined by a protocol in which patients were started on 150 IU of Pergonal per day for 4 days, with the dosage adjusted subsequently. The dose of clomiphene citrate was based on physician preference, but was used in increasing doses up to 200 mg daily.

Sperm Preparation

Semen specimens were obtained by masturbation after 2–3 days of sexual abstinence. Both manual and computer-assisted semen analysis were performed. Complex motion parameters were assessed using a Motion Analysis VP-50 semen analyzer (Motion Analysis Corporation, Santa Rosa, California). Endtz test (myeloperoxidase staining) was performed on all specimens in which round cell concentrations exceeded 1×10^6 mL, in order to measure the presence of granulocytes. Sperm were isolated using a modified Percoll-wash (Irvine Scientific, Santa Ana, California). The final sperm pellet was then re-suspended in a volume of 0.4 ml human tubal fluid. Post-wash analysis was performed on a small, well-mixed aliquot of the specimen, and repeat manual analysis was performed on all specimens which had $>1 \times 10^6$ round cells on pre-wash analysis.

Insemination Procedures

Intrauterine insemination was performed using a simple catheter with the patient in lithotomy position. Insemination procedures were performed 36 hrs following gonadotropin administration or on the day after urinary LH kit readings were positive.

Statistical Analysis

Cycles of IUI that did not result in a live delivery were considered unsuccessful. Multivariate GEE (generalized estimating equation) logistic regression models tested the effect of stimulation in addition to other significant risk factors. Odds ratios and their 95% confidence intervals were calculated. Fisher's exact test was used to determine if stimulation affected live birth rates within each group classified by the risk factors.

Table I. Results of 1576 Cycles of Intrauterine Insemination with and Without Ovulatory Stimulation

Ovulatory stimulation	IUI cycles (n)	Live deliveries resulting from IUI	Per cycle delivery rate (%)	Patients* (n)	Per patient delivery rate (%)
None	489	23	4.7	155	14.8
Clomiphene	302	25	8.3	104	24.0
Gonadotropin	785	58	7.4	318	18.2
Total	1576	106	6.7	512	20.7

* Some patients attempted more than 1 of the 3 methods of ovulatory management, so totals in this column do not add up to 512.

Significance was assumed when $P < 0.05$. All calculations were performed with SAS version 6.12 (SAS Institute, Cary, North Carolina).

RESULTS

There were 1576 IUI cycles among 512 patients for which all data were available on patient age, prior pelvic surgery, semen quality, and ovulatory stimulation. Most patients (430, undergoing 1053 IUI cycles) utilized only one form of ovulatory management (either clomiphene citrate, gonadotropins, or no hormonal stimulation). Multiple forms of ovulatory management were used for 82 patients who received a total of 523 treatment cycles. Treatment results for the entire study population are summarized in Table I. Overall, 106 out of 1576 IUI cycles (6.7%) resulted in live deliveries. Ovulatory stimulation provided an overall benefit ($P = 0.02$), with 83 deliveries resulting from 1087 stimulated IUI cycles (7.6%), compared with 23 deliveries out of 489 unstimulated cycles (4.7%).

Treatment results for patients who underwent single-modality ovulatory management (a single method used throughout their treatment period) are summarized in Table II.

No ovulatory stimulation was used among 100 patients, who received 286 cycles of IUI, and achieved 23 pregnancies, resulting in 18 deliveries. Their per cycle pregnancy rate was 8.0%, and the individual

patient delivery rate was 23%. Clomiphene citrate was used exclusively among 63 patients over a total of 157 IUI cycles. These patients achieved 22 pregnancies and 21 deliveries, for a per cycle pregnancy rate of 14%, and a per patient success rate of 33.3%.

Gonadotropin administration alone was used among 246 patients who underwent 610 IUI cycles, and achieved 67 pregnancies, 48 of which resulted in live deliveries, yielding a per cycle delivery rate of 11.0%, and a per patient delivery rate of 19.5%.

Table III summarizes the multivariate logistic regression results. The odds ratio of successful pregnancy with clomiphene compared with no stimulation was 1.82 (95% CI, 1.01 to 3.34), and the comparable odds ratio for gonadotropin was 1.89 (95% CI, 1.05 to 3.40); the difference was not significant ($p = 0.88$). Subset analyses were performed to compare outcomes with and without ovulatory stimulation in patients with different combinations of the 3 risk factors (Figure 1). Five subsets were considered: 1) those with no risk factors; 2) women older than 37.7 years with a history of corrective pelvic surgery; 3) women with a history of corrective pelvic surgery and no other risk factors; 4) women older than 37.7 with a history of corrective pelvic surgery; and 5) all women whose partner's post-wash sperm motility was less than 40%.

In IUI cycles with no risk factors, 34 pregnancies were achieved from 220 stimulated cycles (15.5%), compared to 10 pregnancies among 127 unstimulated cycles (7.9%). The difference of 7.6% was statistically

Table II. Results of Intrauterine Insemination with and Without Ovulatory Stimulation Among 409 Patients Undergoing Single-Modality Ovulatory Management

Ovulatory stimulation	IUI cycles (n)	Live deliveries resulting from IUI	Per cycle delivery rate (%)	Patients (n)	Per patient delivery rate (%)
None	286	18	6.3	100	18.0
Clomiphene	157	21	13.4	63	33.3
Gonadotropin	610	48	7.9	246	19.5
Total	1053	87	8.3	409	21.2

Table III. Multivariate Logistic Regression Results

Variable	Parameter estimates	Odds ratio	Odds ratio (95% CI)	P
Intercept	-3.304			
Age at IUI cycle (yr)	-0.051	0.95	0.91-0.999	0.01
No pelvic surgery	0.917	2.50	1.65-3.79	0.0001
Post-wash motility (%)	0.010	1.01	1.002-1.02	0.046
Ovulatory induction	0.626	1.87	1.09-3.22	0.02

significant ($p = 0.03$). In the remaining subsets, none of the differences between stimulated and unstimulated cycles were statistically significant.

When the only 2 risk factors were advanced female age and pelvic surgery, 18 pregnancies were achieved out of 320 stimulated cycles of IUI (5.6%), versus 1 pregnancy achieved among 86 unstimulated cycles (1.2%; $P = 0.09$). Because this difference was relatively large, yet not statistically significant, we performed a post-hoc power calculation to determine whether we could have found a significant difference. We found that our sample had only 72% power to detect the observed difference. Nomograms were constructed to compare predicted live delivery rates by age with and without ovulatory stimulation among patients with different combinations of pre-treatment risk factors (Figure 2).

DISCUSSION

We found older women had less success with IUI, a finding consistent with that of other studies (1-3). When advanced age was the sole risk factor, ovulatory stimulation did not substantially improve live delivery

Fig. 1. Observed live birth rates following intrauterine insemination, stratifying patients by risk factors. **Fig. 2.** Predicted live birth rates following intrauterine insemination.

rates. Surgical correction for pelvic abnormalities also lowered the chance of success with IUI; again, when pelvic surgery was the only risk factor, ovulatory stimulation conferred no benefit. Poor sperm motility after therapeutic semen wash was virtually always associated with IUI failure, regardless of whether or not ovulatory stimulation was employed. The only patients with pre-treatment risk factors who may have benefited from ovulatory stimulation were older patients who had a history of corrective pelvic surgery. However, our study lacked the necessary statistical power to prove a difference in percycle delivery rates between stimulated (5.6%) and unstimulated (1.2%) IUI cycles in this group, largely because of the discrepancy in the numbers of stimulated and unstimulated cycles (320 and 86, respectively).

The majority of patients tried only one method of ovulatory management during their attempts to become pregnant. Our data suggest patients who tried more than one method of ovulatory management had results similar to those of the patients who stayed with a single method, and hence we believe they probably constitute similar populations. The age at which the woman presents for assisted reproduction is beyond the physician's control, as is her history of pelvic surgery. Of the 3 pre-treatment risk factors which we identified, only sperm motility might potentially be improved by the fertility clinic. As demonstrated by our treatment outcomes, this factor appears to carry the highest risk of failure. Anecdotally, among our entire study population (from both studies) of 533 women undergoing 1728 IUI cycles, only one live delivery was achieved with sperm having a post-wash motility of less than 40%, and in that case, the post-wash motility was 39%.

Our study has several of the inherent limitations of retrospective research. We did not assess patient's treatment histories prior to the 3-year study period.

Although previous treatment failure might be an independent risk factor for future failures, data from our multivariate analysis of pre-treatment risk factors does not appear to support this; the 12% of patients who underwent more than 6 IUI cycles continued to achieve per-cycle success rates comparable to those of their initial cycles. Conversely, patient's at the highest risk for IUI treatment failure may have been selectively moved on to IVF. Treatment biases were present as well, as patients physicians employed ovulatory stimulation when they empirically believed it would be beneficial.

The failure to demonstrate a benefit to ovulatory stimulation among IUI patients with multiple pre-treatment risk factors may indicate their risk factors were poorly quantifiable and eluded identification during an otherwise exhaustive retrospective review of their clinical records. Also, as noted above, the lack of statistically significant benefit to ovulatory stimulation in some patient subsets may simply reflect an inadequate sample size to provide the necessary statistical power.

We had hoped to validate the use of ovulatory stimulation to increase our "at-risk" patient's delivery rates, but the effectiveness of this therapy is not supported by our results. In light of our results, we now advise patients without any of the 3 risk factors that ovulatory stimulation may double their chances of success with IUI. However, when sperm motility is low and when the woman has at least one risk factor, we recommend in vitro fertilization or intracytoplasmic sperm injection.

CONCLUSIONS

Ovulatory stimulation clearly increases IUI pregnancy rates among a select group of patients: young patients without any history of pelvic surgery and whose partner's sperm has good post-wash motility. In these patients, per-cycle IUI pregnancy rates doubled with ovulatory stimulation.

The benefits of ovulatory stimulation are unclear among patients affected by multiple risk factors. Advanced age or a history of corrective pelvic surgery

in the woman and poor post-wash sperm motility are all predictors of poor IUI success rates, and the risks of multiple factors are cumulative. Poor post-wash sperm motility in combination with either of the other two risk factors has been associated with a 0% success rate.

Men with poor post-wash sperm motility should be evaluated for correctable conditions. If none is present, and if the woman has one or both of the female risk factors, the couple should be counseled that IUI will have little chance of success, regardless of whether ovulatory stimulation is employed, and they should be advised to consider IVF or ICSI.

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