Factors predicting the outcome of intrauterine insemination

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ABSTRACT

Background: Intrauterine insemination (IUI) is a frequently indicated therapeutic modality in infertility and considered to be of low to moderate complexity before the application of more sophisticated assisted reproductive technologies (ART). It is simple and inexpensive treatment in which processed and concentrated motile sperm are placed directly into uterine cavity. IUI is used together with various controlled ovarian hyperstimulation (COH) protocols for many indications such as male infertility, ovulatory disorders, endometriosis and unexplained infertility. *Aim of study*: Is to identify the important prognostic variables contributing to the successful outcome. *Patients and methods*: A prospective study was carried out at Assisted Conception Unit of Basra Medical College, A total of 203 cycles were analyzed to identify prognostic factors regarding treatment outcome. The variables selected for analysis were female age, duration and etiology of infertility, sperm parameters, number of preovulatory follicles, and number of previous treatment cycles and the method of COH. *Results*: The overall pregnancy rate per cycle was 9.3% (19/203). Of 19 pregnancies, 68.4% resulted in live birth, 26.3% in spontaneous abortion, and 5.3% were ectopic pregnancy. The multiple pregnancy rate was 15.8 % (3 twin pregnancies). Three significant variables for successful outcome were total motile sperm count ($>10 \times 10^6$), the method of ovarian stimulation (use of r-FSH alone being superior to Clomiphen Citrate (CC) with r-FSH and CC alone), and multifollicular response. There was a tendency to a higher pregnancy rate in women <40 years and shorter duration of infertility (< 5 years) but this did not reach a statistical significance. Significant difference was not observed among different etiologies, although lowest pregnancy rate was found in unexplained infertility group. *Conclusion*: IUI may be an option for a selected group of couples prior to considering more sophisticated and expensive assisted reproductive techniques. High total motile sperm count ($>10 \times 10^6$), controlled ovarian hyperstimulation (COH) with r-FSH and multifollicular response are valuable predictors for pregnancy in COH-IUI cycle. (MJBU,30,2: 2012, Page 99-105)

العوامل المؤثرة على نجاح عملية الإخصاب الداخلي (التلقيح الصناعي) في علاج حالات العقم

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خلاصة البحث: تعتبر عملية الإخصاب داخل الرحم (ما يعرف بالتلقيح الاصطناعي) من الوسائل العلاجية المألوفة في علاج العقم وهذه العملية هي قليلة التعقيد والكلفة ويمكن البدء بها قبل التحول إلى عمليات الإخصاب المساعد المتطورة إنها عمليه بسيطة وغير مكلفه والتي تتم عن طريق تحضير الحيامن نشطة الفعالية فقط وتركيزها ثم حقنها إلى داخل التجويف الرحمي. إن عملية الإخصاب داخل الرحم تستخدم مع مختلف برامج تحفيز الاباضه المفرطة لعلاج حالات العقم التي أهم أسبابها ضعف في كمية ونوعية حيامن الرجال, اضطراب عملية الاباضة, انتشار بطانة الرحم وأخيرا حالات العقم مجهولة السبب. طريقة الدراسة: دراسة مستقبلية أجريت في وحدة الإخصاب المساعد في كلية الطب, جامعة البصرة جرى من خلالها تحليل 203 دورة تلقيح اصطناعي لمعرفة العوامل المؤثرة على نتائج هذه العملية. من جملة العوامل التي تم دراستها هي عمر المرأة, سبب العقم ومدته, تحليل السائل المنوي, عدد البويضات الموجودة في المبيض قبل حصول الاباضة , وعدد المحاولات السابقة وأخيرا الطريقة المستخدمة لتحفيز المبيض. النتائج: إن المعدل العام للحمل كان 9,3% وهو يمثل 19 مريضة من أصل 203 دورة تلقيح اصطناعي, من هؤلاء (19) مريضة, 68,4% نتج عنها ولادة طفل حي, 26,3% انتهى حملهم بإجهاض تلقائي و 5,3% كانت نتيجتهم حمل خارج الرحم. كانت نسبة الحمل المتعدد 15,3% (3 حوامل توأم). ثلاثة عوامل مؤثرة لنجاح العملية وهي العدد الكلي للحيامن المتحركة (أكثر من 10* 10 [6]), طريقة تحفيز الاباضة (استعمال عقار r. FSH وحده كان أكثر فائدة من استخدام عقار الكلوميفين ستريت أو الكلوموفين ستريت مع r.FSH). تكثير كمية البويضات المكونة. كان هناك زيادة في نسبة الحمل عند النساء اللواتي عمرهن اقل من 40 سنة ومدة العقم اقل من خمس سنوات لكن هذه النتائج لم تصل إلى قيمة إحصائية, لم يكن هناك اختلاف ذو قيمة بين أسباب العقم بالرغم من وجود اقل معدل للحمل بين حالات العقم مجهولة الأسباب. الاستنتاج: إن عملية الإخصاب داخل الرحم (التلقيح الاصطناعي) تعتبر اختيار علاجي مهم في مجموعة عن حالات العقم قبل التحول إلى عمليات الإخصاب المساعد المعقدة مثل الحقن ألمجهري. زيادة نسبة الحيامن الفعالة (المتحركة) أكثر من (10* 10 [6]), تحفيز المبيض بواسطة (r.FSH) وعدد البويضات المستجيبة هي العوامل الرئيسية في توقع نتائج حمل في عمليات الإخصاب داخل الرحم. هدف الدراسة:– معرفة العوامل المهمة المؤثرة في نجاح عملية الإخصاب داخل الرحم.

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INTRODUCTION

Intrauterine insemination (IUI) is one of the assisted conception techniques and can be used for alleviation of infertility in some selected couples. IUI may offer particular advantages such as minimal equipment required, being less invasive and simpler to start with a reduced cost.[1,2] It is generally considered to be an intermediate step of low to moderate complexity before the application of more sophisticated assisted reproductive technology.[3] IUI is a form of artificial insemination using husband's sperms and it has been recommended for several indications (e.g., male infertility, ovulatory disorders, endometriosis, tubal factor and unexplained infertility).[4-7] Controlled ovarian hyperstimulation (COH) in IUI cycles may improve cycle fecundity rate compared with timed intercourse presumably due to increased number of oocytes available for fertilization.[8,9] Some factors such as sperm count[10] and number of follicles developed have been positively related to pregnancy rate, whereas advanced female age and high cycle number have been negatively associated.[11,12] There are also different findings regarding the effects of woman's age, infertility diagnosis, number of treatment cycles, medication for COH and sperm quality on pregnancy rates with IUI.[13,14] The aim of this study was to identify the important prognostic variables which could provide a better patient selection for IUI treatment with husband's sperm for a successful outcome.

PATIENTS AND METHODS

This study was based on the data of 203 couples' consecutive IUI cycles carried out in Assisted Conception Unit of Basra Medical College between March 2009-December 2010. All couples with one cycle of IUI were included in the study. Couples who attended the center had at least one year of infertility, and had undergone basic infertility evaluation consisting of at least two semen analysis, monitoring of ovulation by ultrasound and assessment of prolactin, TSH, FSH and mid-luteal serum progesterone levels. Tubal patency was investigated by hysterosalpingography or laparoscopy prior to IUI treatment. Inclusion criteria were euthyroid, normoprolactinemic female partner with bilateral tubal patency, age less than 43 years with normal ovulation. Male partner with a quantity of $> 5 \times 10^6$ of total motile sperm count in sperm analysis. Women with previous IUI in other centers were also included in the study. Women who had previous pelvic surgery or developed Ovarian Hyperstimulation Syndrome (OHSS) during ovulation induction were excluded. The categories of infertility etiology were unexplained infertility (65 couples), male factor (58 couples), ovulatory disorders (67 couples) and endometriosis (13 couples). Mild male factor was defined as a semen analysis showing a concentration of $<20 \times 10^6$/mL or motility of $<50\%$. The types of infertility whether primary (123 couples) or secondary (80 couples), and infertility duration < 5 years (88 couples) or ≥ 5 years (115 couples) were also analyzed in this study. All women in the study had transvaginal ultrasound performed on the third day of the menstrual cycle as a baseline then underwent ovarian stimulation protocols. Three types of ovarian stimulation protocols were carried out and analyzed as three different groups. In the first group, 64 women were stimulated with clomiphene citrate (CC) in a dose of 100 mg./day daily from cycle day 2 to 6. In the second group (87 women) CC of 100 mg/day was used between cycle day 2-6, then the recombinant FSH (Gonal F[R], Serono) 75 IU was started on day 7 until day 12 every other day. The third group (37 women) used FSH alone (Gonal F[R],Serono) 75 IU daily from day 2 of the cycle until the dominant follicle reached to 17 mm in diameter. Follicular development and endometrial thickness were monitored by transvaginal ultrasound, starting on day 12 for group 1, and on day 9 for the other two groups.

Human chorionic gonadotropin (HCG) (5,000-10,000 IU) was administered when at least one follicle was more than 16 mm in mean diameter and endometrial thickness was >6mm. A single IUI was performed at approximately 34- 36 hours after administration of HCG. Semen was collected by masturbation into a sterile container in the same day of insemination, after 2-4 days of sexual abstinence. After liquefaction and initial sperm analysis using World Health Organization guidelines, the standard swim up technique was used for preparation, employing Earle's balanced salt solution. The sperm sample was centrifuged at 500 g (relative centrifugal force) for 15 minutes. The supernatant was discarded and the pellet diluted in 2.5ml of medium and re centrifuged. After removing supernatant the final pellet was gently covered with medium and incubated for one hour at 37 °C. Catheter (Cook, Australia) was inserted gently through cervical os, and 0.5-1 ml prepared semen with motile spermatozoa was injected into the uterus approximately 0.5 cm below the fundus. A serum βHCG test was performed 12 days after missing period to establish a biochemical pregnancy. Clinical pregnancy was defined as detection of gestational sac confirmed by ultrasound. Statistical analysis was done SPSS version 15 (statistical package for social sciences) was used for data input and analysis. Fisher`s Exact and X^2 test were used to test the association between discrete variables such as female age, duration of infertility, type of infertility, etiology of infertility, total motile sperm count, number of preovulatory follicles, number of treatment cycles and method of ovulation stimulation. Statistical significance was assumed at p< 0.05.

RESULTS

A total of 203 consecutive IUI cycles of 203 couples were evaluated. The female age ranged from 17 to 42 years (mean±SD: 31.3±3.2) and the mean duration of infertility was 6.94±3.8 years (range, 1-25). The overall pregnancy rate per cycle was 9.3% (19/203). Miscarriage and ectopic pregnancy rates were 26.% (5/19) and 5.3% (1/19), respectively. Multiple pregnancy rate was 15.8% (3/19) and all of them were twins. Of these one was diagnosed in CC-rFSH cycle and 2 in rFSH alone cycle. Pregnancy rate per cycle was higher in couples with a total motile sperm count of $\geq 10 \times 10^6$ (12.8%) compared to those with $5\text{-}10 \times 10^6$ (p<0.05). (Table-1) COH-IUI produced a better pregnancy rate in women with two or more preovulatory follicles (≥ 16 mm) than those with single follicle (P<0.05). Significantly higher pregnancy rate was observed in those who received r-FSH (24.3%) compared to those who used CC+ r-FSH (6.9%) or CC alone (6.3%) (p<0.05) (Table-I). Although most patients underwent their first 2 trials of IUI, there were also pregnancies in the third and fourth attempts but no pregnancy occurred in the fifth attempt. The pregnancy rate in women <40 years old was higher than those women ≥ 40 years (10.3% versus 5.3%). However, the difference did not reach to a statistical significance (p=0.26). A higher pregnancy rate was observed among those with primary infertility compared with secondary infertility (11.4% versus 6.3%), although the difference was not statistically significant (p=0.22). Pregnancy rate in women with the duration of infertility less than 5 years was higher than in those with ≥ 5 years (11.4% versus 7.8%), although the difference was not statistically significant (P=0.39). There was no difference in pregnancy rates among different infertility etiologies, although lower, but statistically insignificant pregnancy rate was observed in couples with unexplained infertility (6.2%).

Table 1. Distribution of cycles and cycle fecundity according to different variables.

Age (y)	No. of patients (%)	No. of pregnancy (%)
<40	165 (81.3)	17 (10.3)
≥40	38 (18.7)	2 (5.3)
Type of infertility		
Primary	123 (60.6)	14 (11.4)
Secondary	80 (39.4)	5 (6.3)
Infertility duration (y)		
<5	88 (43.3)	10 (11.4)
≥5	115 (56.7)	9 (7.8)
Cause of infertility		
Male factor	58 (28.5)	6 (10.3)
Ovulatory dysfunction	67 (33)	8 (11.9)
Endometriosis	13 (6.4)	1 (7.7)
Unexplained	65 (32)	4 (6.2)
Cycle no.		
1	140 (68.9)	7 (5)
2	49 (24.1)	8 (16.3)
3	7 (3.4)	2 (28.5)
4	5 (2.5)	2 (40)
5	2 (1)	0
Follicle number (≥ 16 mm)		
1	103 (50.7)	*5 (4.9)
2	67 (33)	7 (10.4)
3	20 (9.8)	4 (20)
≥4	13 (6.4)	3 (23.1)
Total motile sperm count ($x10^6$)		
10	133 (65.5)	*17 (12.8)
5-10	70 (34.5)	2 (2.9)
Method of Ovulation Induction		
CC	72 (35.4)	4 (5.5)
CC with r-FSH	92 (45.3)	6 (6.5)
r-FSH alone	39 (19.2)	*9 (23)
		*P<0.05

DISCUSSION

This study demonstrated that high motile sperm number, multifollicular ovarian response and the type of ovulation induction are variables associated with higher pregnancy rates in COH-IUI cycles. In our study, total progressive motile sperm number $>10x10^6$ was found to be a good predictor and yielded a better pregnancy rate compared to lower count ($5-10x10^6$). This finding is in agreement with many other studies demonstrating the importance of sperm number.[15-17] Since we excluded men with total motile sperm count less than $5x10^6$ it is not possible to make a comment on pregnancy rate in couples with severe male factor. Regarding the effect of age on IUI outcome, we found a better cycle fecundity rate in women <40 years than that obtained in women ≥40 years (10.3% versus 5.3%), although the difference was not statistically significant. Age related decline in female fecundity has been well documented in natural and artificial reproduction. This decline has been suggested to be the result of reduced uterine receptivity and/ or decreased oocyte.[18] Many other studies found that women`s age significantly influenced the outcome of IUI.[19,20] The overall pregnancy rate in our study was 9.3%, which was lower than the results reported by other studies Zadehmodarres et al. (22%), Merviel et al. (14.7%), Nuojua-Huttunen, et al. (12.6%).[19-21] The reported pregnancy rates achieved by IUI usually vary between 8-22%, but may be as low as 2.7% and

as high as 66% owing to several different factors.[22] The relatively low success rate in our study may be due to ovarian stimulation protocols and/or characteristics of subjects. In our study spontaneous abortion rate was 26.3% which was similar to that reported by Noujua–Huttunen, *et al* [21] but higher than recently published results of Zadehmodarres, *et al*. (7.5%) and Merviel *et al*. (13.5%).[19,20] Due to the differences of method of ovarian stimulation and subject characteristics, it is not easy to determine a cause to account for such a high number of miscarriages. The ectopic pregnancy rate in the present study is (5.3%) similar to the result reported by Noujua-Huttunen *et al*. (5.9%). [21] Multiple pregnancy rate in the present study was 15.8%, which seems higher than the rates reported in the previous studies (3.9%,13.5%,13.7%).[19-21] Since all multiple pregnancies occurred in CC-rFSH and rFSH alone cycles, this high rate may be on account of high follicle numbers. However, because of low number of observations in our study we cannot make definitive conclusions on this subject. Regarding the method of ovarian stimulation, higher pregnancy rate was observed among those who received r-FSH (24.3%) for COH protocol compared to those who received CC + r-FSH (6.9%) or CC alone (6.3%). This result is in line with the result reported by Cantineau *et al*,[23] who found that pregnancy rate was higher with gonadotropins than that with anti-estrogens. IUI combined with FSH for ovarian stimulation aimed at developing multiple dominant follicles, leading to availability of multiple oocytes for fertilization.[24-26] Number of preovulatory follicles was found to be a good predictor for successful IUI outcome in our study. Multifollicular development provided a better cycle fecundity rate than monofollicular ovarian response. This result is in accordance with the results of other studies.[19,21,27] Multifollicular development may result in an increased number of fertilized oocytes and a better quality of endometrium and luteal phase, thereby improving fertilization and implantation. Regarding the duration of infertility, our results demonstrated higher pregnancy rate for those with short duration of infertility < 6 years compared to those with ≥6 years (11.4% vs. 7.8%) but the difference was not statistically significant. Many studies reported negative effect of long duration of infertility.[19,21] Although there is no precise time limit for recommending IUI, according to several studies including ours , pregnancy rate may be severely compromised in long –standing (≥5 years) infertility. Higher pregnancy rate was observed in those with primary infertility than secondary infertility (11.4% versus 6.3%) although the difference was statistically not significant. Our results are in agreement with the results reported by some studies but disagree with some others.[20,21,28] A number of studies have examined cycle fecundity rates in couples undergoing an IUI cycle with different etiologies. Success rates in patients with unexplained infertility and endometriosis have been found higher than those with male factor infertility and tubal factor infertility.[29,30] In our study pregnancy rate was higher in cases of ovarian dysfunction (11.9%) and male factor infertility (10.3%). These results are in accordance with the study of Merviel *et al.*, who found highest pregnancy rate in anovulatory infertility, followed by male factor infertility.[15] In the present study the pregnancy rates in women with endometriosis and unexplained infertility were 7.7% and 6.2%, respectively. This results are also similar with the results of other studies which found the lowest pregnancy rate in case of endometriosis.[19,21] The causal relationship between reduced fertility and endometriosis without tubal involvement may be related to cytokines and growth factors secreted by the ectopic endometrial tissue which might interfere with ovulation, fertilization, implantation and embryonic development.[31] Cycle fecundity has been reported to be similar for the first 3 to 6 cycles, although decreasing with an increased number of treatment

cycles.[32] Accordingly, most of our pregnancies were obtained within the first 4 cycles. Since most of our patients underwent their first two IUI attempts, drawing a conclusion about cycle fecundity rate and IUI attempt seems difficult in our study.

CONCLUSIONS

IUI may be an option for a selected group of couples prior to considering more sophisticated and expensive assisted reproductive techniques. Couples with high total motile sperm count (>10 x10^6), those having controlled ovarian hyperstimulation with r-FSH with multifollicular response may benefit from IUI treatment better.

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