

Associated Factors Affecting The Successful Pregnancy Rate of Intrauterine Insemination at International Islamic University Malaysia (IIUM) Fertility Centre

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SUMMARY

Purpose: The aim was to determine pregnancy rate and its associated factors in Intrauterine Insemination (IUI) at IIUM Fertility Centre. **Methods:** A retrospective analysis of 504 IUI cycles was conducted on all available records of infertile couples who had undergone IUI treatment at IIUM Fertility Centre between 2004 until 2008. The data was collected and then analyzed with multivariate logistic test with a significant level of 0.05. **Results:** The overall clinical pregnancy rate was 14.5% (73/504). Among 73 pregnancies, 44 cases were live births (60%), 23 cases were miscarriages (32%) and 6 were ectopic pregnancies (8%). Analysis from logistic regression revealed two predictive variables which influence the pregnancy; female age (OR:0.580, CI:0.338-0.996, $p=0.046$) and male sperm count (OR:0.506, CI:0.304-0.843, $p=0.008$). Pregnancy weren't related to the etiology of infertility, duration and type of infertility, cycle number of IUI, ovarian stimulation protocol and the number of dominant follicle. **Conclusion:** IUI remain as a convenient and useful treatment option in women of younger age (<30 years) and male with higher sperm count (≥ 100 million per ml).

KEY WORDS:

IUI, Pregnancy rate, Maternal age, Motile sperm count

INTRODUCTION

Intrauterine insemination (IUI) is a technique where the semen is processed into highly concentrated motile sperm and then inseminated into the uterus through the cervix using a fine catheter. It is the first line of assisted conception methods that is least invasive and most cost effective¹. This technique has been widely used for the treatment of infertility patients. The indications for IUI are unexplained infertility factors, low sperm quality, unilateral tubal blockage, cervical factors, ovulatory dysfunction and endometriosis^{2,3,4}.

The overall successful pregnancy rate of IUI varies from as low as 5% to as high as 70%^{5,6}. The pregnancy rate depends very much on the underlying aetiological factors^{5,6}. Although many researchers have reported the success rate of IUI, not many have correlated specific variables with the success of IUI treatment. The aim of this study is to evaluate and analyze

the IUI outcome from our 5 years experience (April 2004-December 2008). The successful pregnancy rates are assessed according to women's age, etiological factors, duration and type of infertility, cycle number of IUI, ovarian stimulation protocol, number of dominant follicle and sperm quality.

MATERIALS AND METHODS

Patients

A total of 504 cycles of IUI attempted during a 5 years period from 2004 until 2008 were analyzed. The patients received fertility treatment at Fertility Centre, International Islamic University Malaysia (IIUM), Kuantan, Pahang. All couples underwent infertility investigations prior to the IUI procedure. This included seminal fluid analysis, hormonal tests, a baseline gynaecological scan and hysterosalpingography or 'lap & dye' before IUI. Only single IUI procedures were included in the analysis.

Ovarian stimulation and follicle rupture timing

All female patients were treated with ovarian stimulation agents either clomiphene citrate (CC) alone or gonadotrophin alone (Gonal-F or Puregon) or using combination of CC and gonadotrophin. A serial transvaginal scan (TVS) were performed to monitor the growth of the follicles. Human chorionic gonadotrophin (HCG) was administered to the patient when the size of the follicles reached ≥ 18 mm. IUI was performed 36-40 hours post HCG injection.

Sperm preparation and IUI

All semen samples from male patients were collected either by masturbation or coitus interruptus following an abstinence period of 3-4 days and left to liquefy for less than 1 hour. The samples were assessed according to WHO (1987, 1992) criteria. The sperm count before wash were divided into two groups: < 100 million per ml and ≥ 100 million per ml.

Puresperm media was used for sperm preparation. In the gradient method, 45% and 90% solutions were prepared and then top layered with the semen samples. The samples were then centrifuged at 1200rpm for 20 minutes, the pellet was left to sink at the bottom and the supernatant discarded. The pellet was then washed with 2ml of media wash and centrifuged again at 2000rpm for 10 minutes. For

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oligospermia samples, the mini gradient method was used with the same techniques. The final pellet was re-suspended with 0.3ml IVF medium.

The uterine insemination was carried out using a soft IUI catheter (Laboratoire CCD / Gynetics Medical Products/ Select Medical Systems/ Cook K-Jets) with the patient in the lithotomy position. Sterility of the procedure was strictly observed. All patients were given oral progesterone for luteal support for three weeks (Duphaston; Solvey Pharmaceuticals). Three weeks after the IUI procedure, if patients remained amenorrhoeic, urine pregnancy test was done and if it was positive, transvaginal ultrasound scan was performed a week later to observe for the gestational sac.

Statistical analysis

The data was analyzed using SPSS version 18. The selected variables for the analysis were female age, duration and type of infertility, number of IUI cycle, etiological factors of infertility, ovarian stimulation protocol, number of dominant follicle (more than 16 mm in diameter) and male sperm count. The Independent t- test was used to study the correlation between two variables. Multivariate logistic regression was used to identify the significant variables that contribute to the IUI success rate. The chosen level of significant was p<0.05.

RESULTS

From a total of 504 cycles, the clinical pregnancy rates of IUI at IIUM Fertility Centre were 11.1% (2004), 15.7% (2005), 9.1% (2006), 17.7% (2007) and 18.5% (2008). The overall clinical pregnancy was 14.5% per cycle. The success rate was 25.6% per cycle started. The take home baby rate was 8.7% per cycle and 15.4% per cycle started. There were 55 singleton, 10 were twin and 2 were triplet in the early part of the pregnancy. Out of these, 44 delivered live birth babies (60%), 23 were miscarriages (32%) and 6 were ectopic pregnancy (8%) (see Figure 1). Out of 44 babies delivered, 37 (84%) were singleton, 6 (13.6%) were twin and 1 (2.4%) was triplet (see Figure 2).

Our result showed that the clinical pregnancy rate was reduced when the woman's age increased. For age less than 30, there were 34 pregnancies out of 182 cycles, declining to 3 pregnancies out of 43 cycles in woman age more than 40.

We found that 3-5 years duration of infertility had the highest clinical pregnancy rate (15.3%). The clinical pregnancy rate for duration less than 3 years was 12.1%. The clinical pregnancy rate reduced to 11.2% after 5 years of infertility.

Most of the pregnancies were obtained within the first few IUI cycles. The clinical pregnancy rate increases until third cycle attempt but decreased after the fourth (see Table 1). Patient with secondary infertility had a higher successful pregnancy rate (21.1%) compared with primary infertility (12.6%).

The highest clinical pregnancy rates were in patients with ovarian/anovulation factors (16.3%) and unexplained factors (16.1%) (see Table 1).

Table I: Demographic of Intrauterine insemination pregnant patients

Characteristic		Numbers (%)
Age (years)		
<30	*(n=182)	34 (18.7)
30-34	(n=136)	20 (14.7)
35-39	(n=143)	15 (10.5)
>40	(n=43)	3 (7.0)
Cycle number		
1	(n=286)	38 (13.3)
2	(n=133)	21 (15.8)
3	(n=60)	11 (18.3)
>4	(n=25)	3 (12.0)
Duration of infertility (years)		
<3	(n=123)	15 (12.1)
3-5	(n=131)	20 (15.3)
>5	(n=250)	28 (11.2)
Type of infertility		
Primary	(n=395)	50 (12.6)
Secondary	(n=109)	23 (21.1)
Aetiology factors		
Unexplained	(n=217)	35 (16.1)
Ovarian/anovulation	(n=153)	25 (16.3)
Endometriosis	(n=92)	10 (10.9)
Others	(n=42)	2 (4.8)
Drug regime		
Clomiphene	(n=139)	9 (6.5)
Clomiphene & Gonal-F	(n= 88)	15 (17.1)
Clomiphene & Puregon	(n= 30)	8 (26.7)
Gonal-F	(n=159)	28 (17.6)
Puregon	(n=85)	13 (15.6)
Gonal-F & Puregon	(n=3)	0 (0)
Number of dominant follicle (≥16mm)		
1	(n=250)	24 (9.6)
2	(n=128)	17 (13.2)
3	(n=49)	11 (22.4)
≥4	(n=77)	15 (19.5)
Sperm count (×10⁶/ml)		
≤20	(n=72)	4 (5.5)
20.1 – 99.9	(n=223)	27 (12.1)
≥100 *	(n=209)	41 (19.6)

*Logistic regression shown significant differences with p<0.05

Table II: Predictive variables affected the IUI pregnancy rate

	OR	95% CI
Age (years)		
≥30	0.580	0.338, 0.996
<30	1.000	
Sperm count (×10⁶/ml)		
<100	0.506	0.304, 0.843
≥100	1.000	

Recombinant follicle stimulation hormone (rFSH); Gonal-F were the main ovarian stimulation agent used (39.4%) followed by Puregon (18.3%). The rest were minimal stimulation with Clomiphene citrate (CC) (14.1%), CC and Gonal-F (18.3%) and CC and Puregon (9.9%). The clinical pregnancy rate was better in patients with rFSH ovarian stimulation. However, there was no significant difference between patients treated with rFSH or minimal stimulation.

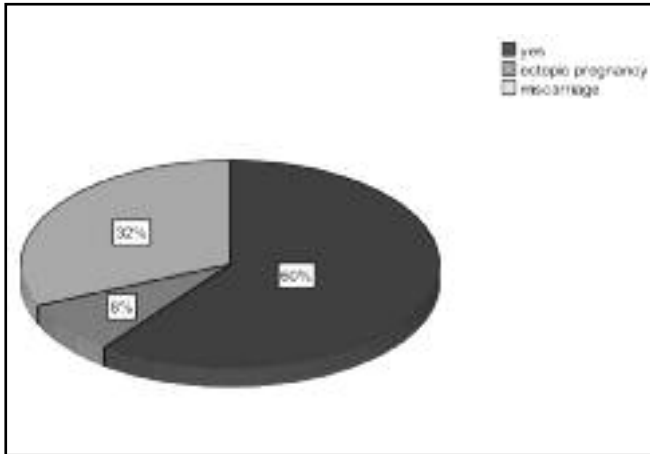


Fig. 1: The outcome of clinical pregnancy following IUI (n=73).

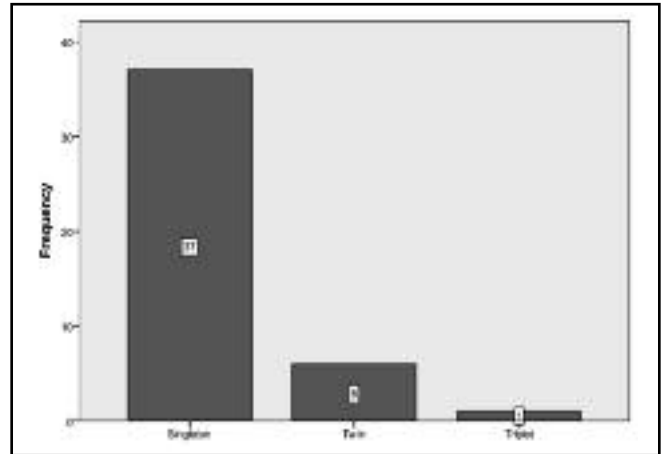


Fig. 2: Number of delivered babies.

The pregnancy rate in cycle with only one single dominant follicle (>16mm in diameter) was lower (9.6%) as compared to cycles with more follicles. The highest clinical pregnancy rate was observed in cycle with three dominant follicles (22.4%). There was a slight decreased in clinical pregnancy rate with four or more dominant follicles.

Our results showed that the pregnancy rate increased with patients that had more than 20 million per ml of sperm count (per milliliters). The clinical pregnancy rate was much higher in patients that have more than 100 million per ml sperm count (see Table I). Patients with oligospermia (less than 20 million per ml) had the lowest clinical pregnancy rates (5.5%).

From logistic regression analysis, it was found that among all the factors, two variables were found to significantly influences the success rate; age and sperm count (see Table 3). In other words, chances of getting pregnant from IUI cycle were female patients with younger age (less than 30 years) and male patients that had a better sperm count (more than 100 million per ml).

DISCUSSION

This study attempted to determine the factors that predict successful pregnancy for IUI. The female’s age is the most important predictor of IUI success. The clinical pregnancy rate decreases as the age increases⁷. In our study, there was a significant difference in pregnancy rates between patients aged less than 30 and aged more than 30 years (p=0.046). The clinical pregnancy rate was higher in those aged less than 30 years and declined to 50% with those aged 30 years and above (OR:0.580, CI:0.338-0.996). Women with age more than 40 has less than 5% pregnancy and age more than 45 had only a 0.5% pregnancy rate⁸. Our study has shown that for women aged 40-44 years, 3 out of 39 patients became pregnant (7%). None of the patient with age 45 years and above achieved pregnancy. This is perhaps due to decreasing of oocyte quality and endometrial receptivity².

Our study has also shown that patients infertility of less than 5 years duration have a better chance of getting pregnant

compared to longer duration. Zadehmodarres *et al* (2009) reported a similar finding and suggested that IUI was not recommended for patients with long infertility⁹. Our results also demonstrate that patients need to undergo a few cycles of IUI to be successfully pregnant. However, more than 4 cycle of IUI will not significantly increase the clinical pregnancy rate. It would be advisable for a patient who has failed IUI after several attempts to consider other options of treatment such as in vitro fertilization (IVF) or intra cytoplasmic sperm injection (ICSI).

The etiology of the infertility is one of the contributing factors that influence the IUI outcome. In our study, ovarian/anovulation and unexplained infertility are the factors with the highest clinical pregnancy rate. Some studies found that unexplained factors have a better prognosis in clinical pregnancy compared to other etiological factors¹⁰. However, some studies noted that moderate male factors and anovulation have the highest clinical pregnancy rates in IUI¹¹. There were 23 cases of miscarriages where 11 were associated with unexplained factors, 10 were ovarian/anovulation factors and 2 were endometriosis.

An unexplained infertility couple may have problems with egg quality, the ability of the sperm to fertilize the egg, undiagnosed tubal dysfunction, implantation failure or genetic causes⁹. Ovarian factors maybe related to elevated luteal hormone (LH) levels that affects the egg quality by resumption of early meiosis and premature oocyte maturation that will lead to inability to be fertilized or miscarriages¹².

Ovarian stimulating agents for controlled ovarian hyperstimulation (COH) affected the clinical pregnancy rate of IUI. According to Guzick *et al.* (1999), the chances of getting pregnant in IUI using COH were double with the addition of COH compared with IUI alone¹³. The drug regimens that are mainly used for IUI were Clomiphene Citrate (CC) and gonadotrophins (rFSH, HMG, hCG)¹⁴. In our centre, we used CC, rFSH alone or both combinations for ovarian stimulation. In most of the studies, the use of gonadotrophins has a better clinical pregnancy rate compare to CC¹⁵. However, this regime would increase the risk of

multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). Therefore, the use of gonadotrophin in unexplained factors may not be appropriate for these reasons¹⁶.

Minimal stimulation using combination of both CC and gonadotrophins in IUI seems to be the ideal regime. This protocol could reduce the risk of multiple pregnancies and achieve the main objective is to obtain a few dominant follicles with less complication of OHSS. In our study, the number of patient who had mild-moderate of OHSS complication is low 5.6% (using both protocols). No severe of OHSS case was observed. The ovarian stimulation using the rFSH seems to have the effects on the number of gestational sac and mostly related to the unexplained factor patients.

The other most prognostic factor for IUI success is the sperm quality. We assessed our results based on the sperm count and it had significant influence in the clinical pregnancy rate. Our study showed that oligozoospermia patients (<20 million per ml) had the lowest clinical pregnancy rate (5.5%). This proves that male patients with oligozoospermia (low count in sperm) and asthenozoospermia (low progressive motility in sperm) were associated with poor outcome; between 0 and 3% pregnancy rate¹⁷. IUI is not a good option for these patients. Intracytoplasmic sperm injection (ICSI) should be considered instead.

There was a significant difference where the clinical pregnancy rate was increased in sperm count ≥ 100 million per ml ($p=0.008$). The clinical pregnancy rate decreased to 50% if sperm count less than 100 million per ml (OR:0.506, CI:0.304- 0.843). The sperm preparation method did not result in difference in the clinical pregnancy rate. Pregnant following density gradient method was 14.6% and swim up method 12.0%.

In most studies, the density gradient method has been shown to confer advantages in sperm recovery compared to swim-up method. This method not only yields the highest number of motile sperm but also reduces the bacterial contamination and processing time¹⁸. Furthermore, this technique has a higher percentage of morphological sperm recovery, better DNA quality and chromatin packaging^{19, 20, 21}.

There are many studies that stated the suitable number motile sperm recovery after preparation. The minimum number of motile sperm varies from 0.8 to 10 million per ml^{22, 23}. In our cases, patients with more than 100 million per ml have a good recovery of motile wash compared with oligozoospermia patients. However, the sperm recovery after post-wash for oligozoospermia patient in gradient method did not improve the count and motility.

We concluded that the female age and sperm count have the most predictive value for IUI clinical pregnancy outcome in our centre. Other factors such as type of infertility, etiology factors, stimulation protocol, number of dominant follicle and cycle number of IUI does not have a significant effect on

the IUI successful rate. Hence, female patient with advanced age group and male patient with low sperm count would benefit from in vitro fertilization (IVF) / intra cytoplasmic sperm injection (ICSI) than IUI.

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