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Original Research Article

Risk factors for multiple pregnancies in intrauterine insemination cycles with ovarian stimulation: a predictive approach

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ABSTRACT

Background: The aim of this study was to predict the risk of multiple pregnancies during ovarian stimulation (OS) followed by intrauterine insemination (IUI) as a treatment for infertility and to identify risk factors associated with multiple pregnancies in IUI cycles.
Methods: This prospective observational study was conducted on 358 couples who underwent OS with IUI between January 2022 and July 2023. Data on maternal and paternal age, type of infertility, gonadotropin dosing, follicular size, and total motile sperm concentration (TMSC) were collected. The primary outcome was clinical pregnancy, defined as the presence of a gestational sac on transvaginal ultrasound (TVS). Descriptive and regression analyses were performed to examine the relationship between these variables and the incidence of multiple pregnancies.
Results: A total of 358 IUI cycles resulted in 57 clinical pregnancies, yielding a pregnancy rate of 15.9%. Among these, 87.7% were singleton pregnancies, and 12.3% were multiple pregnancies. No significant association was found between maternal age, paternal age, or type of infertility and multiple pregnancy outcomes. However, regression analysis revealed that the presence of follicles between 13-15 mm, in combination with larger follicles (>15 mm), significantly increased the likelihood of multiple pregnancies ($p=0.007$). Additionally, a significant relationship was found between gonadotropin dosing and multiple pregnancy rate ($p<0.05$), whereas TMSC did not significantly correlate with multiple pregnancy outcomes ($p=0.57$).
Conclusions: The risk of multiple pregnancies in IUI cycles is significantly associated with follicle size, particularly the presence of follicles in the 13-15 mm range, and higher gonadotropin dosing. While TMSC did not affect multiple pregnancy rates, careful monitoring of ovarian response, especially follicle size, is crucial for minimizing the risk of multiple pregnancies and optimizing clinical outcomes in controlled OS (COS)-IUI cycles.

Keywords: TMSC, IUI, Infertility, Gonadotropin, Follicles

INTRODUCTION

Infertility is a complex medical condition with profound psychological, economic, and demographic implications, affecting 8-12% of couples in developed societies.[1] Approximately half of these cases are attributed to female factors (e.g., endocrine, tubal, uterine, and oocyte factors), while the other half are due to male infertility factors (e.g., poor spermatogenesis, cryptorchidism, and genetic syndromes).[2,3] In the face of infertility, assisted reproductive technologies (ART), particularly *in vitro* fertilization (IVF) and IUI, have become common treatment options.[4] IUI is considered a simpler, less invasive, and more cost-effective alternative to IVF, particularly in cases of cervical, male factor, and unexplained infertility.[5] However, while IUI may improve pregnancy rates, it also carries risks, particularly the increased likelihood of multiple gestations.[2,6]

Multiple gestation is a well-known adverse outcome of infertility treatments, particularly when OS and ART are used. The incidence of multiple pregnancies has notably increased since the 1980s, largely due to the widespread use of COS with oral medications and injectable

gonadotropins, which induce the growth of multiple follicles.[7,8] In the United States, approximately 28.7% of ART cycles in 2011 resulted in multiple births, and studies have shown that multiple gestations are more likely with OS protocols, especially those using high-dose gonadotropins.[9,10] Multiple pregnancies are associated with significantly increased maternal and fetal morbidity, including preeclampsia, gestational diabetes, preterm delivery, low birth weight, and perinatal mortality.[11,8]

Given these risks, reducing the incidence of multiple pregnancies remains a key goal in infertility treatment. The ultimate aim of infertility treatments, including ART and OS, is to achieve a singleton pregnancy at term.[12] As such, strategies like single embryo transfer (SET) have been proposed to minimize the multiple pregnancy rate, particularly in ART cycles.[13] However, in OS cycles, especially when combined with IUI, controlling the number of embryos or mature follicles is more challenging, and the risk of multiple pregnancies remains a significant concern.[4,5]

The use of OS with IUI, although less invasive and costly compared to IVF, has its own set of challenges. A major issue is the higher rate of multiple pregnancies, with studies reporting twin rates of 7.2-9% and triplet rates of 0.4-0.5% in high-dose gonadotropin cycles.[1,2] The presence of multiple mature follicles is a key predictor of multiple gestation, and the risk increases with the number of follicles greater than 10-14 mm in diameter.[7,10] Therefore, it is critical to identify predictive factors that may help in the optimization of OS protocols to reduce the risk of multiple pregnancies, while maintaining or improving pregnancy success rates. Some studies suggest that factors such as the woman's age, the number of mature follicles, and serum estradiol (E2) levels may be useful in predicting the likelihood of multiple gestation in COS-IUI cycles.[13,3] However, clear guidelines for predicting and managing the risk of multiple pregnancies following OS and IUI remain lacking.

Objectives

Objectives were to predict the risk of multiple pregnancies during OS followed by IUI as a treatment for couples subfertility/infertility and to study the risk factors for multiple pregnancies in IUI cycles.

METHODS

The present prospective observational study was conducted on 358 couples who underwent IUI after proper informed consent. The study was done with effect from 1st January 2022 to 31st July 2023 over 19 months.

Inclusion criteria

All couples who consented for the study and underwent OS with IUI were included.

Exclusion criteria

Couples who underwent OS but procedure withheld due to ovarian hyperstimulation syndrome (OHSS) were excluded.

Methodology

Prior approval was obtained from the institutional ethical committee, and written informed consent was obtained from all participants. OS was initiated with oral letrozole and injectable gonadotropins, starting with a weight-adjusted low dose for at least 3 days, with dose escalation if no response was observed. IUI was scheduled after human chorionic gonadotropin (hCG) was administered at a standard dose, following the documentation of ovulation. All follicles with a diameter greater than 10 mm on TVS on the day of the hCG trigger were taken into account. The TMSC was measured, and additional data collected included male and female ages, and total gonadotropin dose used during the stimulation cycle. Data obtained was saved in Microsoft excel spreadsheet 2010/above and analyzed using statistical package for social sciences (SPSS Ver. 20). Descriptive statistics were used to summarize baseline characteristics of study population, including mean ± standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables. A $p<0.5$ considered as statistically significant.

RESULTS

A total of 358 IUI cycles were performed during the 19-month study period, with each cycle meeting the aforementioned inclusion criteria for insemination. The primary outcome of the study was the achievement of clinical pregnancy, defined as the presence of an identifiable gestational sac on TVS. Out of the 358 cycles, 57 cycles resulted in clinical pregnancies, corresponding to a per-cycle pregnancy rate of 15.9%. Among the clinical pregnancies, 87.7% (50) were singleton pregnancies, and 12.3% (7) were multiple pregnancies.

The mean maternal age of the study participants was 27.6±4 years, while the mean paternal age was 32.7±4.4 years. There were no significant differences in maternal or paternal age between the singleton and multiple pregnancy groups ($p=0.833$ and $p=0.798$, respectively). Additionally, the type of infertility (primary or secondary) did not show a significant association with the occurrence of multiple pregnancies in this study ($p=0.639$). Regression analysis revealed that likelihood of achieving both clinical pregnancies and multiple pregnancies increased as size of mature follicle cohort grew. While a minimal difference in rate of multiple pregnancies was observed when >2 follicles >15 mm were present (beta<0), presence of follicles in 13-15 mm range, when present alongside follicles >15 mm, significantly influenced likelihood of multiple pregnancies ($p=0.007$). The regression coefficient (beta=+0.6) indicated a strong effect for this cohort.

Table 1: Association between independent factors and multiple pregnancy.

Independent factors		Multiple pregnancy, (n=7)	Singleton pregnancy, (n=50)	P value
Maternal age (in years)		28±4.3	27.5±4.0	0.833*
Paternal age (in years)		33±4.5	32.6±4.4	0.798*
Type of infertility	Primary	6 (13.3%)	39 (86.7%)	0.639*
	Secondary	1 (8.3%)	11 (91.7%)	

*NS-not significant.

Table 2: Regression analysis showing multiple pregnancies based on follicle size.

Follicle size	Mean no. of follicles		Beta	T	P value
	Singleton pregnancy	Multiple pregnancy			
≥18 mm	1.3±0.6	1.7±1.2	-0.091	-0.416	0.682
16-17 mm	1.3±1.0	1.7±1.2	-0.056	-0.225	0.824
13-15 mm	0.65±0.8	2.2±1.7	0.601	3.044	0.007*
10-12 mm	0.68±0.8	1.8±2.4	0.029	0.127	0.901

*p value significant.

The findings suggest that while maternal and paternal age, as well as the type of infertility, did not significantly influence the rate of multiple pregnancies, the size of the follicles played a significant role. Specifically, the presence of follicles between 13 and 15 mm in diameter, when combined with larger follicles (>15 mm), was found to significantly increase the risk of multiple pregnancies. This emphasizes the importance of closely monitoring follicular growth during OS cycles, as these follicle size cohorts seem to be a predictive factor for multiple gestation outcomes.

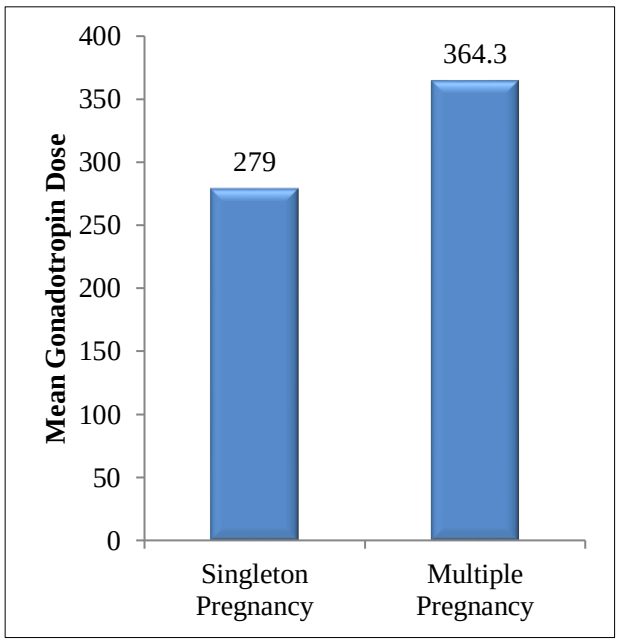

Figure 1: Mean dosing consumption and multiple pregnancy rate.

Mean dosing consumption and multiple pregnancy rate were 279 and 364.3, respectively with a significant statistical difference (p<0.05).

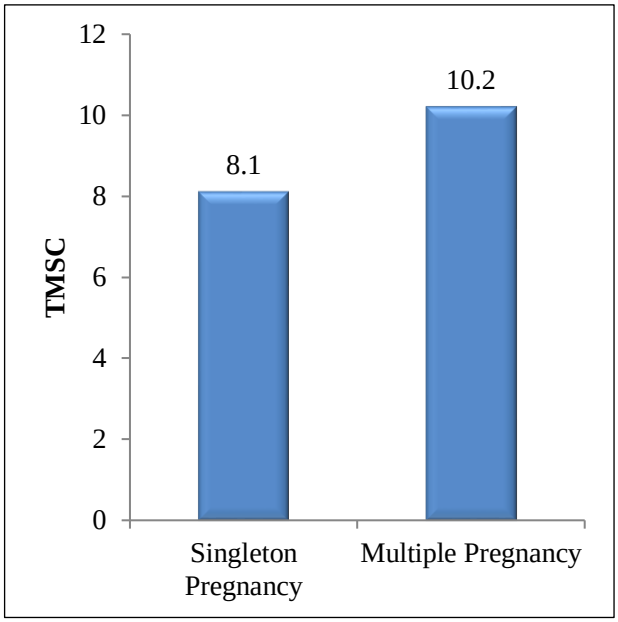

Figure 2: TMSC and multiple pregnancy rate.

Mean TMSC and multiple pregnancy rate observed were 8.1 and 10.2, respectively with a statistically insignificant difference (p=0.57).

DISCUSSION

The present study's findings on multiple pregnancies in IUI cycles with OS are consistent with several key points from existing literature, but also reveal some novel insights that contribute to the ongoing discussions about follicular response and risk factors in COS-IUI cycles.

In our study, 358 IUI cycles were performed over a 19-month period, resulting in a clinical pregnancy rate of 15.9%, with 87.7% of clinical pregnancies being singleton and 12.3% multiple pregnancies (7 cases). These figures

are comparable to other studies in the literature, where pregnancy rates and multiple pregnancy rates have been consistently reported, though with some variations depending on protocols, population, and inclusion criteria. Gleicher et al reported a 9% multiple pregnancy rate in a cohort of 441 pregnancies following COS-IUI.[14] This is lower than 12.3% multiple pregnancy rate observed in our study. The difference may stem from the distinct protocols used across centers. Tur et al reported a 15.6% twin pregnancy rate and a 5.7% higher-order multiple pregnancy (HOMP) rate in 1878 pregnancies following COS-IUI, with the HOMP rate increasing significantly when E2 levels exceeded 862 pg/ml and when more than 5 follicles >10 mm were present.[15] In our study, the multiple pregnancy rate of 12.3% is somewhat consistent with their twin pregnancy rate but lower than their HOMP rate, which suggests a difference in the follicular response thresholds used in our protocols and the application of the predictive model.

In our study, maternal age (mean 27.6±4 years) and paternal age (mean 32.7±4.4 years) did not show significant differences between singleton and multiple pregnancies (p=0.833 and 0.798, respectively). These findings align with the results reported by Tur et al who also found no significant association between maternal age and multiple pregnancy incidence.[15] The influence of maternal age on pregnancy outcomes is well-documented in the literature, but as observed in this study, the direct association with multiple pregnancy occurrence is not always evident. The maternal age finding also reflects Gleicher et al results, where age did not significantly influence the likelihood of achieving a clinical pregnancy in their cohort, although they noted that advanced maternal age is a known risk factor for pregnancy loss after the establishment of pregnancy.[14]

In this study, there was no significant association between the type of infertility (primary or secondary) and the occurrence of multiple pregnancies (p=0.639). This is in line with findings from Tur et al who also found that infertility type did not significantly affect multiple pregnancy rates.[15] This suggests that factors such as follicular development and ovarian response might have a more direct impact on multiple pregnancy outcomes than the underlying cause of infertility itself.

One of the most important findings of our study is the significant association between follicle size and the likelihood of multiple pregnancies, especially when follicles between 13-15 mm were present alongside larger follicles (>15 mm). Specifically, the presence of follicles in the 13-15 mm range was found to significantly increase the risk of multiple pregnancies (p=0.007, beta=+0.6). This result mirrors findings from other studies, including Tur et al which emphasize that multiple follicles of larger than 10 mm are associated with higher risks of multiple pregnancies in COS-IUI cycles.[15] The role of smaller follicles (13-15 mm) in increasing the likelihood of multiple gestation has been underreported in some studies, but our findings suggest that these follicles may contribute significantly to the final pregnancy outcome, particularly when present in combination with larger follicles. Gleicher et al also found that greater follicular numbers were associated with an increased risk of multiple pregnancies, although their focus was primarily on serum E2 levels and pre-ovulatory follicle counts.[14] Our study provides additional clarity on the importance of follicle size and suggests that follicular size may be a more critical factor than simply follicle count in predicting multiple gestation outcomes.

While gonadotropin dosage was not directly examined in our study, our findings on the follicular cohort and pregnancy rates suggest that more careful monitoring of follicle size, especially in patients with multiple follicles of varying sizes, could help reduce the risk of multiple pregnancies. Studies like those by Tur et al and Gleicher et al have indicated that higher gonadotropin doses and excessive follicular response can lead to higher risks of multiple pregnancies, which aligns with our understanding that follicle size, rather than just follicular count, plays a crucial role in the risk of multiple gestation.[14,15] Tur et al also emphasized that lower gonadotropin doses might reduce the incidence of multiple pregnancies without negatively impacting pregnancy rates, which is consistent with our use of a stricter monitoring protocol to reduce the multiple pregnancy rate while maintaining reasonable success rates for singleton pregnancies.[15]

In our study, we emphasize that careful monitoring of follicular development, particularly when follicles between 13 and 15 mm are observed, is essential for minimizing the risk of multiple pregnancies. This finding is consistent with the literature, which suggests that predicting multiple pregnancies requires not only counting the number of follicles but also considering their size. Similar to Tur et al findings, our results underscore the importance of avoiding excessive follicular development, particularly in younger patients with a good ovarian reserve, as the presence of multiple mature follicles (especially in the 13-15 mm size range) can lead to an increased likelihood of multiple gestations.[15] Moreover, the regression analysis in our study supports the concept that size cohorts of follicles (particularly the 13-15 mm range) can be predictive of multiple pregnancy outcomes, which can help guide clinical decisions about cycle cancellation or proceeding with insemination. This can be especially helpful when counselling patients about their risks and making decisions about cycle management.

In existing literature, higher gonadotropin doses are known to increase the likelihood of multiple pregnancies. However, there is also evidence suggesting that overstimulation, which is often associated with higher doses, can lead to OHSS and multiple pregnancies. Tur et al observed that higher gonadotropin doses, especially those exceeding 150 IU, increased the risk of multiple pregnancies, though they did not specify a significant threshold for dosing differences in relation to multiple

pregnancy outcomes.[15] Gleicher et al also acknowledged the relationship between higher gonadotropin doses and the increased risk of multiple pregnancies, noting that more pre-ovulatory follicles and higher estradiol levels can contribute to higher multiple pregnancy rates.[14] Their findings suggested that higher gonadotropin doses, which increase the number of mature follicles, are strongly linked to higher pregnancy rates, but they also carry a significantly higher risk of multiple gestations.

In our study, a significant association was found between higher dosing consumption and the multiple pregnancy rate ($p<0.05$). This suggests that as gonadotropin doses increased, the likelihood of multiple pregnancies also increased. This finding aligns with existing literature, supporting the notion that higher gonadotropin doses increase the risk of multiple gestations in IUI cycles. However, the $p<0.05$ in our study indicates that this relationship is statistically significant, suggesting that careful monitoring and regulation of gonadotropin doses may be key in minimizing the risk of multiple pregnancies without compromising the success rates of IUI cycles.

In our study, the mean TMSC and multiple pregnancy rate were reported as 8.1 million sperm/mL and 10.2%, respectively, with a statistically insignificant difference ($p=0.57$). TMSC is an important factor in assessing male fertility. A higher TMSC can improve the chances of successful conception because it increases the number of motile sperm available for fertilization. Multiple pregnancy rates may be influenced by both male and female factors, including sperm quality and the number of mature follicles present after OS. Gleicher et al discussed the role of male factor infertility in pregnancy outcomes, noting that while male factors such as low sperm count or low motility can lower the chances of achieving pregnancy, they do not have a direct impact on the likelihood of multiple pregnancies.[14] In fact, in the case of IUI, a higher TMSC generally increases the probability of success, but it does not necessarily influence the multiple pregnancy rate. Tur et al also found that male factor infertility (e.g., low sperm count or motility) was not significantly associated with the occurrence of multiple pregnancies in COS-IUI cycles.[15] Instead, the primary determinant of multiple pregnancy outcomes in their study was ovarian response (i.e., the number of follicles) rather than sperm quality.

Our finding of a statistically insignificant difference ($p=0.57$) between TMSC and multiple pregnancy rate aligns with the existing literature, which suggests that sperm quality, while crucial for achieving pregnancy, does not appear to have a strong direct impact on the incidence of multiple pregnancies. It is likely that other factors, such as follicular development and gonadotropin dosing, play a more significant role in determining the likelihood of multiple pregnancies, as evidenced by the significant relationship observed between gonadotropin doses and multiple pregnancy rates in our study.

CONCLUSION

There is hardly any increase in the probability of achieving pregnancy with more than 2 of >15 mm size follicles combined with a substantially increased multiple pregnancy risk if more than 2 mature follicles are present especially if 13-15 mm cohort is neglected. The risk of multiple pregnancy was higher in women who consumed more units of gonadotropins compared to women who achieved singleton pregnancies. Although the mean TMSC was found higher in multiple pregnancy cohort over singleton cohort (10.2 m/ml vs 8.1 m/ml; $p=0.57$ NS), it didn't reach statistical significance.

The findings therefore further emphasize the importance of the holistic management of COS-IUI cycles, where careful monitoring of ovarian response is crucial in defining gonadotropin dosing and hence minimizing the risk of multiple pregnancies while optimizing the chances of a successful clinical pregnancy.

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