Clarifying the relationship between total motile sperm counts and intrauterine insemination pregnancy rates

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Objective: To study the relationship between postwash total motile sperm count (TMSC) and intrauterine insemination (IUI) outcomes.
Design: Retrospective review
Setting: Large fertility clinic
Patient(s): A total of 92,471 insemination cycles from 37,553 patients were included in this study.
Intervention(s): All stimulated clomiphene citrate, letrozole, and/or injectable gonadotropin IUI cycles performed at a single institution from 2002 through 2018 were reviewed. Generalized estimating equations (GEE) analysis was used to account for multiple cycles by individual patients and to adjust for female partner age, body mass index, and stimulation protocol.
Main outcome measure(s): Successful clinical pregnancy was defined as ultrasound confirmation of an intrauterine gestational sac with fetal cardiac activity.
Result(s): A total of 92,471 insemination cycles were available to evaluate the relationship between postwash TMSC and clinical pregnancy. Pregnancy rates were highest with TMSC of $\geq 9 \times 10^6$ and declined gradually as TMSC decreased. Complete data for the adjusted GEE analysis were available for 62,758 cycles. Adjusted GEE analysis among cycles with TMSC of $\geq 9 \times 10^6$ ($n = 46{,}557$) confirmed that TMSC in this range was unrelated to pregnancy. Conversely, TMSC was highly predictive of pregnancy (Wald $\chi^2 = 39.85$) in adjusted GEE analysis among cycles with TMSC of $<9 \times 10^6$ ($n = 16{,}201$), with a statistically significant decline.
Conclusions: IUI pregnancy is optimized with TMSC of $\geq 9 \times 10^6$, below which the rates gradually decline. Although rare, pregnancies were achieved with TMSC of $<0.25 \times 10^6$. Since the decline in pregnancy is gradual and continuous, there is no specific threshold above which IUI should be recommended. Rather, these more specific quantitative predictions can be used to provide personalized counseling and guide clinical decision making. (Fertil Steril® 2021;115:1454–60. ©2021 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Intrauterine insemination, male infertility, sperm count

Infertility is a common disease characterized by the failure to establish a clinical pregnancy after 12 months of regular intercourse. Up to 13% of couples attempting pregnancy remain unable to conceive after 1 year (1). Several treatment strategies from minimally invasive to more aggressive are used to assist infertile couples. Intrauterine insemination (IUI) is an assisted reproductive treatment that places a processed semen sample into the uterine cavity. This simple procedure aims to increase the likelihood that a greater density of motile sperm enters the upper female reproductive tract. IUI is a valid, cost effective, minimally invasive first-line treatment in select patient populations (2).

Several studies have aimed to delineate the factors that predict successful IUI outcomes, including female partner age, duration of infertility, ovarian stimulation protocol, infertility etiology, number of treatment cycles, timing of insemination, and follicle

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number (3). Historically, research has focused primarily on female factor infertility; however, recent evidence suggests that male factor infertility contributes significantly to IUI outcomes (4, 5). Importantly, the prognostic value of semen parameters and IUI outcomes is yet to be fully explored. Total motile sperm count (TMSC) is an important and readily available preinsemination parameter on semen analyses. The prewash total motile count has been shown to be a poor predictor of live birth in IUI treatment (6), and data regarding postwash TMSC have been mixed. Some analyses demonstrate no relationship with pregnancy rates (7, 8), and others indicate a clear association between postwash TMSC and ongoing pregnancy (9–13).

In regard to the TMSC of the final insemination sample, the recommended lower limit for treatment ranges widely from 3×10^6 to 10×10^6 motile sperm (14). Previous reports have been limited by small sample sizes and have generally attempted to identify clinically meaningful thresholds rather than define pregnancy rates across a continuum of TMSC (9–11). We aim to clarify the relationship between postwash TMSC at the time of insemination and IUI clinical pregnancy rates utilizing our large single-institution cohort.

MATERIALS AND METHODS

This study was a retrospective cohort analysis of all patients who underwent natural and controlled ovarian stimulation IUI at a single high-volume fertility practice from 2002 to 2018. Approval for the analyses of these data was obtained from the Schulman Institutional Review Board under protocol 00027148. All patients undergoing ovarian stimulation with a single IUI using fresh or cryopreserved sperm were included in the study.

Ovarian Stimulation

Ovarian stimulation was achieved with letrozole, clomiphene citrate (CC), follicle-stimulating hormone (FSH), or a combination of CC and FSH using protocols described in detail elsewhere (15, 16). Ovulation was induced using subcutaneous human chorionic gonadotropin hormone unless natural luteinizing hormone surge was noted either by positive home ovulation predictor kit or by appropriate rise in serum luteinizing hormone concentration over baseline. IUI was performed approximately 36 hours after injection. Patients who were noted to have a spontaneous luteinizing hormone surge underwent IUI approximately 24 hours after the surge was detected.

Sperm Retrieval and Wash Protocol

Fresh ejaculated semen samples were collected via masturbation into a laboratory-approved specimen cup the day of IUI and allowed to liquefy for 15 minutes before processing. Frozen samples were thawed 15–20 minutes at room temperature with an additional 5–10 minutes in an incubator or thawed for 20 minutes in a dry heat block. To achieve maximum recovery of motile sperm, 2 methods were used. For fresh samples with TMSC of $\geq 10 \times 10^6$, 12-minute centrifugation on a density gradient column (80% Enhance-S Pure sperm and 20% Modified Human Tubal Fluid Medium) followed by 5-minute wash media (95% modified Human Tubal Fluid and 5% serum protein substitute) was used. For frozen samples and fresh samples with TMSC of $<10 \times 10^6$, a 5-minute wash with 95% modified Human Tubal Fluid and 5% serum protein substitute was used. The final postwash TMSC was calculated by multiplying final semen volume by total sperm concentration and percent motile.

IUI Protocol

A SoftPass insemination catheter (Cook Medical) was utilized for intrauterine insemination. Subjects were asked to remain supine for 5 minutes after the insemination procedure.

Serum quantitative human chorionic gonadotropin hormone concentration was assessed approximately 15 days after IUI and repeated 48 hours later to assess for an appropriate rise of at least 66%. Clinical pregnancy, defined as an intrauterine gestational sac with fetal cardiac activity, was confirmed by transvaginal ultrasound at approximately 6–7 weeks' gestation.

Statistics

Clinical pregnancy was modeled by using generalized estimating equations (GEEs) to account for repeated cycles and adjusted for age, body mass index (BMI), and stimulation protocol. Variables were collected via automated extraction from the electronic medical record. For couples who underwent multiple IUI cycles, only the first 3 cycles were utilized in the analysis. Natural IUI cycles and cycles stimulated with letrozole were excluded from the GEE analysis due to low relative utilization.

Descriptive statistics were used to demonstrate the mean with SD or median with interquartile range for continuous variables, and categorical variables were expressed as case number and percentages. Parametric (independent samples *t* test) tests were performed after normality analysis to determine the differences between the groups. Proportions were compared with χ^2 test and Fisher exact test where appropriate. Statistical significance was defined as $P<.05$. GEE modeling steps were performed using the R statistical computing system (version 3.6.3), and the add-on R packages tableone (v. 0.11.1), gee (v. 4.13-20), geepack (v. 1.3-1), csv (v. 0.5.5), and tidyverse (v. 1.0.3).

RESULTS

In our series, 92,471 cycles were available from 37,553 unique patients. The median TMSC in the overall cohort was 16×10^6 (interquartile range, 17.3×10^6). Supplemental Figure 1 (available online) demonstrates the number of IUI cycles performed for a range of TMSC, and Table 1 and Supplemental Figure 2 (available online) depict the clinical pregnancy rates per IUI cycle according to postwash TMSC. This is further broken down as a function of age in Supplemental Figure 3 (available online). As a validation method, a subanalysis was performed comparing pregnancy rates per TMSC in the first cycle of all women aged <35 years undergoing stimulation with CC only (n = 16,563 cycles). The results are in concordance with the overall cohort with peak pregnancy

TABLE 1

Clinical pregnancy rates per intrauterine insemination cycle according to postwash total mobile sperm count.

Total motile sperm count ($\times 10^6$)	No. of insemination cycles	No. of clinical pregnancies	Clinical pregnancy per cycle
<0.25	263	11	4.18%
0.25–0.49	341	14	4.11%
0.50–0.99	627	23	3.67%
1.00–1.99	1,611	120	7.45%
2.00–3.99	4,561	462	10.13%
4.00–4.99	2,845	331	11.63%
5.00–5.99	3,109	400	12.87%
6.00–6.99	3,474	484	13.93%
7.00–8.99	6,810	976	14.33%
≥9	68,830	11,496	16.70%

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rates found after TMSC of 9×10^6 (Supplemental Fig. 4, available online).

Complete data for the adjusted GEE analysis were available for 62,758 cycles in 26,995 patients. Demographics for the GEE modeling cohort are displayed in Table 2. The mean age of the female partner was 34.5 ± 4.5 years, and the average BMI of the female partner was 26.2 ± 6.1. The average cycle number for each couple was 2.8 ± 2.0. For the stimulation protocol, 12,495 (19.9%) cycles were performed with FSH only, 22,756 (36.2%) were performed with CC only, and 27,537 (43.9%) were performed with a combination of FSH and CC. The median number of IUI cycles performed per couple was 3 (range, 1–25). Clinical pregnancy per cycle remained consistent up to 6 total cycles (range, cycle 1–cycle 6: 15.5%–17.5%).

In the GEE analysis (Fig. 1), clinical pregnancy per cycle by maternal age ranged from 11.9% (>40 years) to 18.5% (<35 years), with patients ≥35 years of age having a statistically significant lower pregnancy rate per cycle ($P<.001$). Clinical pregnancy per cycle by BMI ranged from 15.9% (BMI 25.1–30) to 16.7% (BMI < 18.5), with all subgroups with BMI of ≥18.5 having a statistically significant lower clinical pregnancy per cycle ($P<.001$). Clinical pregnancy per cycle differed according to stimulation protocol. Compared with the reference cohort of patients undergoing stimulation with FSH only (clinical pregnancy per cycle, 19.0%), patients receiving CC or a combination of FSH and CC had lower clinical pregnancy rates of 16% ($P<.001$) and 15.2% ($P<.001$), respectively. Clinical pregnancies per cycle for first, second, and third cycles were 15.5%, 15.9% ($P<.001$ vs. first cycle), and 16.5% ($P<.001$ vs. first cycle), respectively. Of note, clinical pregnancy per cycle remained consistent up to 6 total cycles (cycle 6: n = 2387 cycles; clinical pregnancy per cycle, 17.5%). In the GEE model, age (Wald $\chi^2= 416.75$), cycle number (Wald $\chi^2= 12.59$), and protocol-FSH only (Wald $\chi^2= 64.23$) independently predicted clinical pregnancy in a statistically significant manner ($P<.05$) (Table 3).

Adjusted GEE analysis among cycles with TMSC of $\geq 9 \times 10^6$ (n = 46,557) confirmed that TMSC in this range was not associated with pregnancy outcome ($P=.46$). Conversely, TMSC was highly predictive of pregnancy (Wald $\chi^2 = 39.85$) in the adjusted GEE analysis among cycles with TMSC of $<9 \times 10^6$ (n = 16,201), with a statistically significant decline ($P<.001$). A gradual linear decline in clinical pregnancy rate was observed as TMSC approached $<0.25 \times 10^6$ (4.18%).

TABLE 2

Demographics for generalized estimating equations modeling cohort.

Variable	N
N (cycles)	62,758
Age	
<35, n (%)	31,929 (50.9)
35–37, n (%)	14,180 (22.6)
38–40, n (%)	10,430 (16.6)
>40, n (%)	6,219 (9.9)
BMI	
<18.5, n (%)	1,791 (2.9)
18.5–25, n (%)	31,923 (50.7)
25.1–30, n (%)	15,203 (24.2)
>30, n (%)	13,841 (22.1)
Cycle number	
First, n (%)	19,608 (31.2)
Second, n (%)	15,655 (24.9)
Third, n (%)	11,398 (18.2)
Stimulation protocol	
FSH only, n (%)	12,495 (19.9)
CC only, n (%)	22,756 (36.3)
FSH and CC, n (%)	27,537 (43.9)

Note: BMI = body mass index; CC = clomiphene citrate; FSH = follicle-stimulating hormone.

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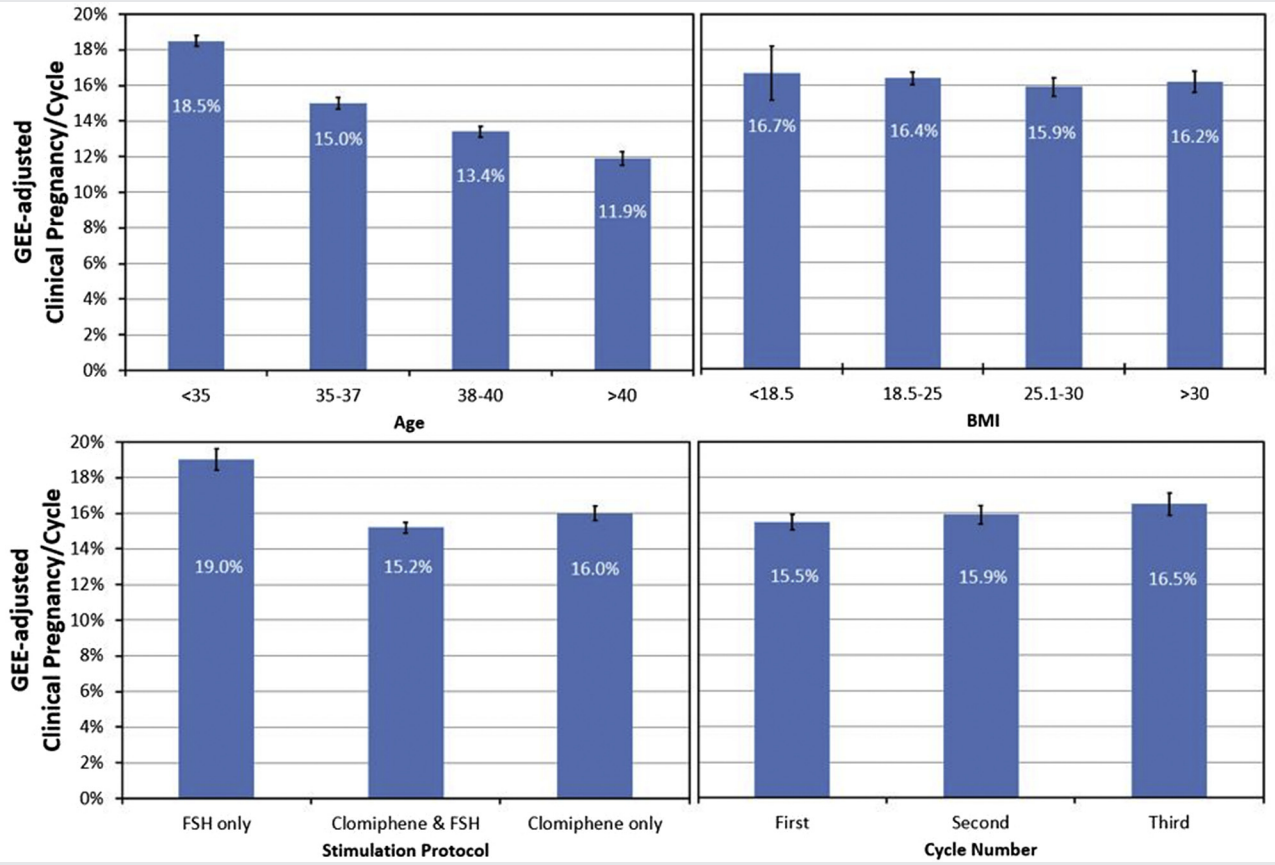
DISCUSSION

The determination of the most appropriate initial assisted reproductive treatment for an individual couple is often a nuanced and difficult one. The primary goal remains efficiently achieving a successful live birth via the least invasive method available. Accordingly, a treatment plan involving IUI is often proposed as a viable option in certain patient populations. Past studies have aimed at delineating the clinical variables that can potentially predict successful IUI outcome. The postwash TMSC may have unique value as a tool for improved patient selection and counseling because it reflects both sperm count and motility after sperm processing.

FIGURE 1



Generalized estimating equations -adjusted clinical pregnancy per cycle according to age, body mass index, stimulation protocol, and cycle number.

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The correlation between clinical pregnancy and postwash TMSC has been highly variable in the literature. In a retrospective study of 526 IUI cycles in 294 couples, Madbouly et al. (9) found postwash TMSC to be an independent predictor of successful pregnancy after IUI with a TMSC of 5×10^6 sperm or more associated with a higher pregnancy rate. Ok et al. (10) in their study of 156 cycles in 141 couples reported a linear-by-linear association between postwash TMSC and pregnancy rate, and their results suggested that TMSC of 10×10^6 or more may be a useful threshold value of IUI success. However, a meta-analysis of 16 studies by van Weert et al. (11) demonstrated that at lower cutoff levels, between 0.8 to 5×10^6 motile spermatozoa, the postwash TMSC provided a substantial discriminative performance for IUI outcome. Nevertheless, Lemmens et al. (7) examined multiple semen parameters and found that postwash TMSC had no predictive value for pregnancy outcome in IUI in their multivariable model with 4,251 IUI cycles. Due to high variability in study design and small sample sizes, drawing definitive conclusions regarding postwash TMSC and IUI success rates remains challenging.

TABLE 3

Generalized estimating equations analysis to model predictors for successful clinical pregnancy.

Variable	Adjusted odds ratio (95% CI)	Wald	*P* value
Cycle number	1.02 (0.01 to 0.03)	12.59	<.001[a]
Age	0.95 (−0.06 to −0.05)	416.75	<.001[a]
Body mass index	1.00 (-1.18×10^{-4} to 1.61×10^{-4})	0.09	.761
Protocol: clomiphene citrate only[a]	0.96 (−0.09 to 0.01)	2.15	.143
Protocol: follicle-stimulating hormone only[a]	1.27 (0.18 to 0.30)	64.23	<.001[a]

[a] Protocol-Clomiphene citrate and follicle-stimulating hormone as reference variable.

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To our knowledge, this study represents the largest series examining the relationship between postwash TMSC and IUI pregnancy rates. Our series demonstrated that clinical pregnancy is optimized with a TMSC of $\geq 9 \times 10^6$. However, we did not detect a steep decline in clinical pregnancy below the 9×10^6 threshold but rather saw a gradual and continuous decline in a linear fashion. Interestingly, clinical pregnancy was achieved in cycles with TMSC of $<0.25 \times 10^6$ at a rate of 4.18%. Therefore, we propose that a specific cutoff threshold should not be utilized as an absolute contraindication for performing IUI, but rather the postwash TMSC value should be employed as a valuable data point along with other variables in counseling and decision making before treatment.

In our GEE model, lower age of female partner (<35 years), stimulation protocol with FSH only, and increased cycle number per couple predicted successful clinical pregnancy in an independent fashion. This corroborates work from prior studies. In their series of 1,038 cycles from 353 couples, Merviel et al. (3) found female age as the strongest predictor of success, with an ongoing pregnancy rate per couple of 38.5% for women <30 years old and 12.5% for those >40 years old ($P<.000001$). In our series, we demonstrate that with increased female partner age, clinical pregnancy rates for a given postwash TMSC were lower relative to the cohort of women immediately younger (Supplemental Fig. 3). This suggests that a younger patient undergoing IUI with a poorer sample (lower postwash TMSC) may have better clinical pregnancy outcomes relative to an older patient undergoing IUI with a better sample (higher postwash TMSC).

With respect to stimulation protocol, a Cochrane review pooling the results of 7 randomized controlled trials among 556 patients found significantly increased pregnancy rates per couple in IUI with ovarian stimulation with FSH compared with CC. The pregnancy rate per couple was 28% when using FSH and 19% when using CC (odds ratio, 1.8; 95% CI, 1.2–2.7) (17).

There is a paucity of published data examining the relationship of female partner BMI to IUI success rates. Souter et al. (18) in their study of 477 women undergoing 1,189 ovulation induction IUI cycles stratified pregnancy outcomes by BMI and found an inverse relationship between BMI and both estradiol level per produced preovulatory follicle and the number of medium-size follicles. Consequently, obese women required higher doses of medication and produced fewer follicles for a given dose; however, with medication adjustments to account for the weight effect, there was no significant difference among the different BMI categories in mean number of cycles to conceive, clinical pregnancy, or spontaneous abortion rates.

Interestingly, clinical pregnancy per cycle remained consistent up to 6 total cycles (range, cycle 1–cycle 6: 15.5%–17.5%). This data can serve to reassure couples on pursuing multiple IUI cycles before in vitro fertilization; however, further work is necessary to delineate the optimal number of cycles individualized to a specific couple.

The strengths of this study include a large sample size with a diverse patient population undergoing treatment at a single institution. Standardized sperm processing and IUI protocols were used across all sites. In addition, a thorough database was generated via automated extraction from the electronic medical record and rigorous statistical methods were used.

There are, however, study limitations to consider as well. First, this study was retrospective in nature and therefore subject to biases, including the inability to identify and control for all confounding variables. The final dataset for the GEE analysis was selected on the basis of completeness and reliability of data, and therefore certain variables linked to IUI success in prior studies could not be included in the final analysis. This includes data on endometrial lining thickness, number of follicles at the time of IUI, ethnicity, and primary infertility diagnosis. In addition, other semen parameters, such as fresh vs. frozen sperm and sperm morphology, were not analyzed in this study.

This study provides an insight for future investigations, such as the inclusion of postwash TMSC with other clinically relevant variables in the development of a nomogram to help predict the likelihood of IUI success. Furthermore, we demonstrated that clinical pregnancy was possible even in couples with a postwash TMSC of $<1 \times 10^6$. Further studies are needed to determine if other factors play a major role in predicting successful clinical pregnancy in this specific cohort of patients with low postwash TSMC.

In conclusion, IUI pregnancy is optimized with postwash TMSC of $\geq 9 \times 10^6$, below which the rates gradually decline. Although rare, pregnancies were achieved even with TMSC of $<0.25 \times 10^6$. Because the decline in pregnancy is gradual and continuous, there is no specific postwash TMSC threshold above which IUI should be recommended. Rather, these more specific quantitative predictions can be used to provide personalized counseling and clinical decision making.

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Aclaración de la relación entre el recuento total de espermatozoides móviles y las tasas de gestación por inseminación intrauterina.

Objetivo: Estudiar la relación entre el recuento total de espermatozoides móviles (TMSC) después del lavado y los resultados de la inseminación intrauterina (IIU).

Diseño: Estudio retrospectivo.

Escenario: Clínica de reproducción asistida.

Paciente(s): En este estudio se incluyeron un total de 92,471 ciclos de inseminación procedentes de 37,553 pacientes.

Intervenciones: Se revisaron todos los ciclos de IIU estimulados con citrato de clomifeno, letrozol y/o gonadotropina inyectable realizados en una única institución desde 2002 hasta 2018. Se utilizó el análisis de ecuaciones de estimación generalizada (GEE) para tener en cuenta los ciclos múltiples realizados en pacientes individuales, y para ajustar la edad de la pareja femenina, el índice de masa corporal y el protocolo de estimulación.

Principal medida de resultado: El embarazo clínico con éxito se definió como aquel que presentó un saco gestacional intrauterino con actividad cardíaca fetal, mediante confirmación ecográfica.

Resultados: Se dispuso de un total de 92,471 ciclos de inseminación para evaluar la relación entre el TMSC y la gestación clínica. Las tasas de gestación fueron mayores con valores de TMSC $\geq 9 \times 10^6$, reduciéndose gradualmente a medida que el TMSC disminuía. Se obtuvieron un total de 62,758 ciclos con datos completos para el análisis ajustado de GEE. El análisis ajustado de GEE entre ciclos con un TMSC $\geq 9 \times 10^6$ (n = 46,557), confirmó que el TMSC en este rango carecía de relación con la gestación. Por el contrario, el análisis ajustado de GEE para ciclos con valores de TMSC $<9 \times 10^6$ (n = 16,201) resultó ser altamente predictivo para la gestación, observando un descenso estadísticamente significativo.

Conclusiones: La gestación a través de la IIU se optimiza con valores de TMSC $\geq 9 \times 10^6$, disminuyendo las tasas gradualmente por debajo de dicho valor. Pese a ser poco común, se lograron gestaciones con un TMSC $<0.25 \times 10^6$. Dado que la probabilidad de lograr una gestación disminuye de forma gradual y continua, no existe un punto de corte específico por encima del cual se deba recomendar la IIU. Más bien, estas predicciones cuantitativas más específicas pueden utilizarse para proporcionar asesoramiento personalizado y servir como guía en la toma de decisiones clínicas.

Palabras clave: Inseminación intrauterina, infertilidad masculina, recuento de espermatozoides