PREDICTIVE VALUE OF SPERM PARAMETERS FOR PREDICTING SUCCESS AFTER INTRAUTERİNE INSEMINATION: THE EXPERIENCE OF A TERTIARY REFERRAL CENTER

İNTRAUTERİN İNSEMİNASYON SONRASI BAŞARIYI BELİRLEMEDE SPERM PARAMETRELERİNİN PREDİKTİF DEĞERİ: BİR TERSİYER MERKEZ DENEYİMİ

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Abstract

Aim: Intrauterine inseminations (IUI) are commonly used in the treatment of infertile couples. The effectiveness of IUI depends on many factors, including sperm quality. Normal semen quality is usually verified with the use of the World Health Organization (WHO) criteria, but these criteria have little prognostic value in IUI, as pregnancy rates after IUI are acceptable even below the WHO thresholds for normal semen quality.

Materials and Method: In this study we retrospectively evaluated 379 couples with idiopatic or male factor infertility, who had been treated with IUI after controlled ovarian hyperstimulation in infertility department of Dr. Zekai Tahir Burak Hospital during the time period between January 2002 and June 2004.

Results: A total of 379 women underwent 631 cycles of IUI during a 29-months period. Mean age was 27.5 ± 5.37 years and mean infertility duration was 4.28 ± 3.02 years. Fifty nine (93.7%) out of 63 pregnancies were obtained in the first three treatment cycles. Pregnancy rate per cycle was 9.98%, and pregnancy rate per couple was 16.62%. A younger age of the female partner, shorter duration of infertility, and the presence of secondary infertility were significantly associated with enhanced success rates with IUI, but the method of ovulation induction did not have an impact on the likelihood of pregnancy. Patients with total motile sperm count (TMSC) <10x106 had 3 pregnancies in 323 cycles (0.9%), and patients with TMSC ≥10x106 had 60 pregnancies in 308 cycles (19.5%).

Conclusion: Although Kruger's strict criterias were not related with IUI success, TMSC ≥ 10x106 were significantly associated with higher pregnancy rates after IUI.

Keywords: Infertility, intrauterine insemination, total motile sperm count

Giriş

Amaç: İntrauterin inseminasyon (IUI), infertil çiftlerin tedavisinde yıllardır yaygın olarak kullanılan bir yöntemdir. IUI tedavisinin başarısı semen kalitesini de içeren birçok faktöre bağlı olarak değişmektedir. Normal semen kalitesi, Dünya Sağlık Örgütü tarafından belirlenen kriterler kullanılarak tanımlanır, fakat bu kriterlerin IUI'daki başarıyı belirlemedeki prognostik değeri azdı. Çünkü WHO'nun normal olarak önerdiği değerlerin altında bile IUI sonrası elde edilen gebelik oranları kabul edilebilir seviyelerdedir

Gereçler ve Yöntem: Bu çalışmada, Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi İnfertilite Polikliniği'ne Ocak 2002 ve Haziran 2004 tarihleri arasında müracaat eden, açıklanamayan infertilite veya erkek faktörüne bağlı infertilite nedeniyle kontrollü ovaryan hiperstimülasyon sonrasında IUI tedavisi uygulanmış 379 hasta retrospektif olarak incelendi.

Bulgular: Yirmidokuz aylık bir süreçte 379 hastaya toplam 631 IUI siklusu uygulanmıştı. Ortalama hasta yaşı 27.5 ± 5.37 ve ortalama infertilite süresi 4.28 ± 3.02 yıl idi. Gebelikle sonuçlanan 63 IUI işleminin 59'unun (%93,7) üç siklus sonunda elde edildiği saptandı. . Çalışmaya alınan hastalarda siklus başına düşen gebelik oranı %9.98, hasta başına düşen gebelik oranı ise %16.62 idi. Kadının yaşının genç olması, kısa infertilite süresi ve sekonder infertlite nedenlerinden birinin mevcut olması IUI başarısını pozitif etkilemekteydi. Ancak ovulasyon yöntemi gebelik üzerinde anlamlı bir etkiye sahip değildi. Total motil sperm sayısı (TMSS) <10x106 olan grupta hastalara uygulanan 323 IUI siklusu sonrasında toplam 3 gebelik (%0.9), TMSS ≥10x106 olan grupta ise hastalara uygulanan 308 IUI siklusu sonrasında toplam 60 gebelik (%19.5) elde edildiği saptandı.

Sonuç: Her ne kadar Kruger kriterleri IUI başarısı ile alakalı bulunmamış olsa da TMSS ≥10x106 IUI sonrası yüksek gebelik oranı ile ilişkili gibi görünmektedir.

Anahtar Kelimeler: İnfertilite, intrauterine inseminasyon, total motil sperm sayısı

Introduction

For years, intrauterine insemination (IUI) has been a widely used modality for the management of infertility. It has been indicated for the treatment of infertility due to female factors such as cervical mucus abnormalities, as well as for the treatment of unexplained infertility. The role of IUI in the management of male infertility remains controversial (1-3).

The success of IUI is dependent on several factors, including semen quality. Normal semen quality is defined by criteria set by the World Health Organization (WHO), however, the value of these criteria in predicting the success of IUI is quite low (4). This is due to the fact that reasonable pregnancy rates have been reported with IUI in patients with values lower than the normal values recommended by the WHO. Although several studies have reported on a higher chance of success with IUI in couples with a normal sperm morphology rate of >4% according to the Kruger criteria, this has been refuted by other investigators (5, 6).

Although many studies have brought forth the link between sperm morphology and fertilization potential, results on the subject remain contradictory. Nevertheless, the total motile sperm count (TMSC) after washing has been used to distinguish couples who are more likely to benefit from IUI from those expected to benefit from in vitro fertilization (IVF)/intracytoplasmic injection (ICSI) (7,8).

The aim of this retrospective study was to investigate the value of sperm parameters, such as total motile sperm count (TMSC), in predicting success in terms of pregnancy rates in couples with unexplained infertility or infertility due to male factors, undergoing IUI treatment following controlled ovarian hyperstimulation with. Our purpose was to provide information regarding the situation in our country, and in doing so to contribute to the development of more effective treatment protocols.

Materials And Method

The medical records of couples who presented to the Infertility clinic at Zekai Tahir Burak Women's Health Teaching and Research Hospital between January 2002 and June 2004 with the inability to conceive despite regular unprotected intercourse for at least 1 year were systematically reviewed. The complete records of 379 couples with either unexplained infertility or infertility due to male factors, who underwent intrauterine insemination after controlled ovarian hyperstimulation, were retrieved. Relevant data such as age, duration of infertility, gestational history, presence of known cause of infertility, baseline hormone levels, hysterosalpingography results, results of baseline semen analysis, history of laparoscopic surgery, agent used of ovulation induction as well as the number of cycles for which induction was performed, TMSC after semen washing and preparation and pregnancy outcome of IUI treatment, was transcribed onto forms previously prepared for this study.

TMSC was calculated using the formula ((TMSC=(volume) x (sperm concentration) x (motile sperm rate)) taking into account volume, concentration and motility rates of sperm obtained by the swim-up technique from washed semen. A mean sperm volume of 0.4 ml was used for the calculations.

Women with a basal FSH level < 12 IU/L on the 3. day of their menstrual cycle, a normal uterine cavity and bilateral tubal passage on HSG examination, and without a history of oopherectomy or tubal surgery were included in the study.

For patients who received clomiphene citrate for ovarian hyperstimulation, treatment was started on the 5. day of each cycle and was continued for a period of 5 days (50-250 mg/day). On the same day the diameter of the dominant follicle reached 18-20 mm, either 5000 or 10000 IU hCG were administered depending on peak E2

levels. IUI was performed approximately 36 hours later. In patients for whom gonadotropins were used, induction of ovulation was achieved using either a low-dose step-up, step-down or conventional protocol. hCG was administered at a dose of 5000-10000 IU after a dominant follicle diameter of 16-18 mm was achieved, followed by IUI 36 hours later. IUI was performed only once per cycle.

Patients were divided into three groups based on rates of normal sperm morphology as determined by Kruger criteria (≤4%, >4-10%≤ and >10%), with the aim of evaluating the effect of sperm morphology on the success rates of IUI. Pregnancy rates were determined for each of the three groups, which were then compared for age, duration of infertility and TMSC of semen samples prepared for insemination.

Prior to the IUI procedure, semen samples were obtained by masturbation after 3 days of sexual abstinence, and sperms were collected by a standard swim-up technique. Insemination was completed by injecting the sperms into the uterine cavity using an insemination cannula. Patients with delayed menstruation after the procedure were tested for pregnancy by serum βhCG measurement.

Statistical analysis

Data was analyzed using SPSS 10.0 package program for Windows. Comparisons were made using the Chi-square, student-t and one way ANOVA tests. Statistical significance was represented by a p-value of less than 0.05.

Results

The medical records of 379 couples, with a total number of 631 cycles, who underwent IUI treatment following controlled ovarian hyperstimulation for the management of unexplained infertility or infertility due to male factors, were retrospectively analyzed. The demographic characteristics of study subjects are summarized in Table I.

Table I. Characteristics of the study participants

Patient demographics	n
Total number of patients	379
Total number of cycles	631
Number of primary infertile couples	263
Number of secondary infertile couples	116
Mean age (years)	27.5 ± 5.37
Mean infertility time (years)	4.28 ± 3.02

Of the patients included in the study, 263 (69.4%) had primary infertility while the remaining 116 (30.6%) had secondary infertility. Clomiphene citrate was used for ovarian induction in 524 cycles (83%), while for 107 cycles (17%) gonadotropins were preferred (hMG: 52 cycles, uFSH: 17 cycles, rFSH: 38 cycles).

Retrospective analysis of cases in which IUI was performed following ovulation induction revealed a total of 63 successful pregnancies, amassing to a pregnancy rate per cycle of 9.98% and pregnancy rate per patient of 16.62%. The numbers of cycles followed by IUI treatment, as well as the number of attempts preceding a pregnancy were determined for each patient; 93.7% of IUI procedures which resulted in a pregnancy required at least 3 cycles. Pregnancy rates according to the number of cycles in which controlled ovarian hyperstimulation (COH) and IUI were performed are depicted in Table II.

Table II. Pregnancy rates according to the number of cycles in which COH+IUI performed.

Number of cycles	**Pregnancy**				**Total**
	Positive		**Negative**		
	n	**%**	**n**	**%**	
1	36	57.2	185	58.5	221
2	15	23.8	88	27.8	103
3	8	12.7	25	7.9	33
4	0	0	11	3.5	11
5	4	6.3	3	1	7
6	0	0	3	1	3
7	0	0	0	0	0
8	0	0	1	0.3	1
Total	63	100	316	100	379

Out of the 63 pregnancies observed, 28 (44.4%) occurred in couples with an infertility period of less than 3 years, while for 20 couples (32.7%) this period was between 3-5 years. A longer duration of infertility was associated with lower pregnancy rates.

An evaluation of pregnancy rates according to type of infertility after IUI treatment revealed pregnancy rate of 12.9% (34/263) in patient with primary infertility and a rate of 25% (29/116) in those with secondary infertility. The difference between patients with primary and secondary infertility was statistically significant (p=0.01). The difference with regards to pregnancy rates between patients in whom either clomiphene citrate (47/524 cycles; 8.9%) or gonadotropins (16/107 cycles; 14.9%) were used was statistically insignificant (p=0.06).

The pregnancy rate per cycle did not seem to be affected by normal sperm morphology rates, assessed using the Kruger method. Table III depicts the pregnancy rates

per cycle, mean age, TMSC and duration of infertility of the three groups categorized according to the Kruger criteria. When we divided our patients into two groups based on TMSC, with a cut-off point of 10x106, in the group with a TMSC <10x106, 3 out of 323 IUI cycles ended with pregnancy (0.9%), while among patients with TMSC ≥10x106, 60 of 308 IUI cycles resulted in a pregnancy (19.5%). This difference was statistically significant with a p-value of p=0.0001. Stratification of patients with a TMSC ≥10x106 based on sperm morphology as determined by Kruger's criteria did not reveal any correlation between a higher rate of normal sperm morphology and successful pregnancy rate (Table IV). The effect of TMSC values and type of infertility on pregnancy rates per cycle was evaluated. Since only 3 pregnancies occurred from couples with a TMSC <10x106, statistical analysis regarding the effect of primary or secondary infertility on pregnancy outcome could not be performed. On the other hand, in couples in which TMSC was ≥10x106, 32 of 227 IUI cycles (14.1%) in patients with primary infertility resulted in pregnancy, while the pregnancy rate in patients with secondary infertility was 28 out of 81 IUI cycles (34.6%). The difference between patients with primary and secondary infertility was statistically significant (p=0.001) (Table V). Patients were further subdivided into 4 groups based on TMSC values; < 2x106, ≥ 2-5x106, ≥ 5-10x106 and ≥ 10x106 to fully appreciate the relationship between TMSC and pregnancy outcome. Pregnancy rates per cycle were 0%, 1.2%, 1.2% and 19.5%, respectively. This rate was significantly higher in patients with TMSC ≥ 10x106 compared to patients with TMSC < 10x106 (p=0.0001). Distribution of pregnancy rate per cycle according to TMSC value has been summarized in figure I.

Tablo III. Relationship between sperm morphology and pregnancy rates per cycle

Kruger	Number of cycles	Number of pregnancies	%	Mean age (years)	Mean TMSC* number ($x10^6$)	Mean infertilility time (years)
≤4	199	26	13.1	27.15±5.33	9.75±8.08	4.4±3.1
>4-10≤	320	34	10.6	27.14±5.42	13.69±9.66	4.1±2.9
>10	112	3	2.7	28.07±4.56	14.65±9.29	4.5±3.0
Total	631	63	9,9	27.31±5.26	12.62±9.32	4.3±3.0

*TMSC: Total Motile Sperm Count

Table IV. Relationship between TMSC, sperm morphology and pregnancy rates per cycle

TMSC* ($x10^6$)	Kruger	Pregnancy						Mean age (years)
		Yes	%	No	%	Total	%	
<10	≤4	2	1.5	128	98.5	130	100	27.5±5.3
	>4-10≤	1	0.7	144	99.3	145	100	
	>10	0	0	48	100	48	100	
≥10	≤4	24	34.8	45	65.2	69	100	27.0±5.19
	>4-10≤	33	18.9	142	81.1	175	100	
	>10	3	4.7	61	95.3	64	100	

*TMSC: Total Motile Sperm Count

Table V. Effect of TMSC counts and infertility type over pregnancy rates per cycle

TMSC ($x10^6$)	Infertility type	Pregnancy				Total	
		Yes	%	No	%	n	%
<10	Primary	2	0.8	234	99.2	236	100
	Secondary	1	1.1	86	98.9	87	100
	Total	3	0.9	320	99.1	323	100
≥10	Primary	32	14.1	195	85.9	227	100
	Secondary	28	34.6	53	65.4	81	100
	Total	60	19.5	248	80.5	308	100
Total		63	9,98	568	90.02	631	100

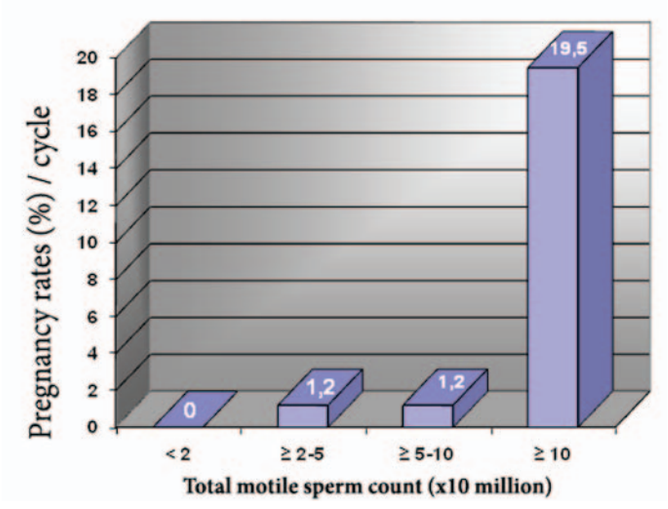

Figure 1. Graphic shows pregnancy rate per cycle according to TMSC values.

Discussion

In this study the predictive value of sperm parameters on the success of pregnancy in patients who underwent IUI treatment for unexplained infertility or with infertility due to male factors was investigated. Although no difference in pregnancy rates was observed based on the Kruger criteria, a TMSC value of more than 10x106 was found to be associated with higher pregnancy rates after IUI treatment.

Compared to other fertility techniques such as IVF/ICSI, IUI offers a simpler, cheaper, safer and less invasive alternative as the first choice for the management of infertility in most couples (1,2). Not only it is beneficial for infertility due to female factors such as cervical mucus abnormalities, it has also been proven to be useful for unexplained fertility as well as for infertility due to immunological causes. On the other hand, the role of IUI in the management of infertility due to male factors remains a source of controversy (9,10). Several factors have been postulated to affect the success of IUI, either directly or indirectly, the most commonly studied being mother's age, duration of infertility, cause of infertility, timing and technique of insemination, number of insemination attempts, concomitant use of ovulation induction, number of sperms used, sperm motility, sperm morphology and TMSC (11,12). It is widely believed that female infertility is affected by age. The quality of ovarian follicles, as well as implantation rates of fertilized ovum decrease with age (13-15). In a study by Stovall et al. (16) on 210 patients with a total of 751 IUI cycles, it was observed that pregnancy rates per cycle in patients older than 35 years were significantly lower than in those younger than 35 years of age. In another study by Sahakyan et al. (13) on 274 patients who underwent COH + IUI, significant decreases in pregnancy rates per cycle along with cumulative pregnancy rates were observed with advanced age. The mean female age in our study was 27.5 ± 5.37 years. We also observed a decrease in pregnancy rates with age in patients who underwent COH + IUI.

Another factor that has an influence on success rates of insemination treatment in infertile couples is duration of infertility. It has been demonstrated that the longer the duration, the lower the pregnancy rates (11). In our study, we also observed lower pregnancy rates associated with a longer duration of infertility. In a similar study by Nuojua-Huttunen et al. on 811 cycles in which COH+IUI treatment was used, it was demonstrated that success rates in couples with duration of infertility of less than 6 years were significantly higher (17). Houmard et al. reported on similar results in couples with less than 3-year duration of infertility after reviewing 658 cycles (18). Our results seem to be consistent with those in the pertinent literature.

Although IUI has been used for the management of infertility due to several male factors, success remains mainly related to semen quality. Worldwide, normal semen quality is determined using WHO criteria, however the prognostic value of these criteria in predicting success after IUI is very poor, and the main reason behind this being the reasonable pregnancy rates reported with IUI with sperm values lower than those recommended by the WHO (19-21). Whereas several studies report on improved success with IUI in infertile couples with a normal sperm morphology rate of >4%, determined by the Kruger criteria (22,23), others have reported on the contrary (24,25). In a metaanalysis by van Waart et al .(23) were the results of 6 different studies were reviewed, it was reported that a normal sperm morphology rate of >4% according to the Kruger strict criteria was associated with higher pregnancy rates after IUI, while also claiming that this value could be used as a cut-off point when making a decision regarding IUI in infertile couples. Other studies in which patients were divided into three groups according to sperm morphology determined using the Kruger criteria (<4%, 4-14% and >14%) have also demonstrated improved pregnancy rates after IUI associated with higher rates of normal sperm morphology (12,26). We divided the couples in our study who underwent IUI treatment into three groups based on the Kruger criteria; ≤4%, >4-10% and >%10. In patients with a normal morphology rate of ≤4%, 199 IUI cycles resulted in 26 pregnancies, while in those with a rate of between 4-10%, 34 out of 320 IUI cycles concluded in successful pregnancies. In patients with a morphology rate of >10 %, 112 IUI cycles resulted in 3 pregnancies. Overall, pregnancy rates per cycle for each group were 13.1%, 10.6% and 2.7%, respectively, and sperm morphology did not seem to have a statistically significant effect on pregnancy rates. With the belief that the inconsistency of our findings with results

from previous studies may be attributed to a difference in patient characteristics, we performed a subgroup analysis taking into account other factors such as age, duration of infertility and TMSC values. However, again no difference could be ascertained which led to the conclusion that an as yet unidentified idiopathic factor may have had an influence on sperm-oocyte interaction. Nevertheless, it is worth noting that other studies also reported results similar to ours. In one such study by Karabunis et al. (24) where patients were divided into 5 different groups based on normal sperm morphology rates determined by the Kruger criteria (<%5, %5-9, %10-19, %20-29 and >%30), it was observed that sperm morphology did not have a significant effect on pregnancy rates after IUI, with reported pregnancy rates per cycle of %6.5±3.9, %13.6±3.2, %8.8±2.4, %7.1±2.5 and %9.7±3.3, respectively. In their report, they suggested that the rate of normal sperm morphology should not be taken intro consideration when deciding on IUI treatment. The results of these findings prompted the use TMSC in distinguishing patients who are expected to benefit from IUI from couples who would benefit better from IVF/ICSI treatment (20).

Many studies report on better conception rates with IUI associated with higher TMSC values, although suggested cut-off values have ranged from 0.3x106 – 20x106 (8,10,27-30). In a study by Miller et al. (28) involving 1114 cycles in 438 patients, subjects were divided into three groups based on TMSC values (<10x106, 10-20x106 and >20x106). The pregnancy rate per cycle for patients with TMSC ≥10x106 was significantly higher than in those with TMSC <10x106. In another study by Brasch et al. (8), 1205 cycles in which IUI was performed were reviewed. It was observed that an increase in TMSC was associated with higher pregnancy rates, but statistical significance was only demonstrated in the group with a TMSC value ≥ 20x106, the highest cut-off value reported in the literature. Other studies have reported on lower cut-off values. For example, Dickey et al. (21) studied 4056 cycles in which IUI was performed where they observed better success rates in patients with TMSC ≥5x106. Centola et al. (31) and Berg et al. (32) reported on similar improvements with TMSC values of ≥1x106 and ≥0.8x106, respectively.

After dividing our patients into 4 groups based on TMSC value (<2x106, ≥2-5x106, ≥5-10x106 and ≥10x106), we observed pregnancy rates per cycle of %0, %1.2, %1.2 and %19.5, respectively. Since the highest level of significance was seen when a comparison was made between patients with TMSC ≥10x106 and those with TMSC <10x106, we decided to use 10x106 as a cut-off point. While patients with TMSC <10x106 had 3 pregnancies out of 323 IUI cycles (0.9%), out of 308 IUI cycles with a TMSC ≥10x106, 60 resulted in successful pregnancies (19.5%). There was no difference between these two groups with regards to age. When we further subdivided patients with TMSC ≥ 10x106 into subgroups based on sperm morphology according to the Kruger criteria, we did not observed any difference in pregnancy rates. The results of our study led us to recommend a TMSC ≥10x106 as a reasonable cut-off value when making a decision on IUI treatment in infertile couples.

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