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Pregnancy rates after ovulation induction and affecting factors in unexplained infertile and male factor infertility

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Abstract
Objective: To assess the influence of sperm parameters on pregnancy outcomes in cases which had ovulation induction (OI) with clomiphene citrate (CC) or recombinant gonadotropin and underwent intrauterine insemination (IUI) for unexplained infertility and male factor indications.
Materials and Methods: 183 patients with diagnosed male infertility and 196 patients with unexplained infertility who presented to the infertility outpatient clinic of our hospital between June 2015 and June 2018 underwent OI with CC or gonadotropin and IUI, and the pregnancy outcomes of the patients were retrospectively analyzed. The criteria for female partners in both groups were to be younger than 38 years, to have an ovulatory cycle, and to have at least one open tube. Semen parameters of male partners were assessed according to the thresholds of the 2010 World Health Organization criteria (WHO).
Results: 377 cycles were analyzed, 181 in the male infertility group (Group 1) and 196 in the unexplained infertility group (Group 2) were examined. There were 17 (9.4%) pregnancies in Group 1 and 22 (11.2%) in Group 2 (p:0.559). Clinical pregnancy was found in 7.7% (14 subjects) of group 1 and 11.2% (22 subjects) of group 2. Before washing, the sperm count of 39 pregnant patients was 61±30.6 million/ml. Due to the absence of data from two patients after washing, the sperm count of 37 patients analyzed after washing was 58.7±34.8 million/ml, and the difference between pregnancy and sperm count before and after washing was statistically significant (p:0,001). The percentage of progressive sperm motility of 39 pregnant patients was 43.5%±11.5% before washing. Since the data of 2 patients were not collected after washing, the percentage of progressive sperm motility of 37 patients evaluated after washing was 64.4±13.5%, and it was statistically significant that sperm motility after washing had a positive effect on pregnancy (p:0.001).
Conclusion: Pregnancy rates after OI and IUI are similar in male infertility and unexplained infertility, regardless of treatment option. However, to determine the fertilization potential of a semen sample, more powerful tests than standard semen analysis are required.

Keywords: Unexplained infertility, male factor; ovulation induction, intrauterine insemination; clomiphene citrate, gonadotropin

Introduction

The American Society for Reproductive Medicine (ASRM) Practice Committee defines infertility as the inability to become pregnant within 12 months despite regular unprotected intercourse in women younger than 35 years and within 6 months in women older than 35 years despite regular unprotected intercourse [1]. Male factor, decreased ovarian reserve, ovulatory disorders, tubal damage, endometriosis, pelvic infections, uterine factors, chronic renal failure, and chronic diseases such as autoimmune, cervical, and immunological factors are causes of infertility [2]. Male infertility refers to a fertile woman's inability to conceive pregnant due to a male factor. Problems with sperm concentration, motility, and morphology in at least one of the two sperm analyses performed between 1-4 weeks indicate male factor infertility. According to data given by the World Health Organization (WHO) in 2010, a "normal range sperm test" should have 39 million (15 million per milliliter) sperms, 32% forward motility, pH> 7.2, volume>2 ml, and a normal shaped sperm ratio (morphology) of more than 4% [3]. Defects in sperm analysis are observed in 40-50% of infertility cases and 7% of all men [4, 5]. Environmental factors, daily stress, medications, and genetic factors affect male fertility by reducing sperm quality and fertilization ability [6].
Up to 30% of couples with infertility problems are diagnosed with unexplained infertility. This evaluation contains demonstrating the patent of at least one fallopian tube, documenting the

female partner's ovulation, and a semen analysis containing enough motile sperm for the male partner [7]. For such couples, IUI has usually considered the first-line treatment because it is less invasive and costly.

In case of infertility due to male factor, the pregnancy rate per cycle due to stimulation with clomiphene citrate is between 6-8%. When stimulation is done with gonadotropins, the pregnancy rate per cycle is 10-15%. IUI is a popular method for unexplained infertility, mild to moderate male factor infertility, ovulation disorders, mild endometriosis, and cervical infertility [8, 9, 10].

In light of recent publications, this study is aimed to discuss pregnancy outcomes after ovulation induction with clomiphene citrate and gonadotropins and the influence of sperm parameters on pregnancy rates in cases with diagnosed infertility due to a male factor and unexplained infertility.

Materials and Methods

Patients' records who underwent OI and IUI in our infertility outpatient clinic between June 2015 and June 2018 were retrospectively reviewed. Approval of our study by the Ethics Committee was granted on 28.02.2019 with decision number 7/18. Patients with primary and secondary infertility were included in the study. The pregnancy results of patients undergoing OI and IUI for unexplained infertility and male factor infertility were compared. To distinguish between normal and abnormal sperm, WHO 2010 criteria were used [3]. The criteria for inclusion in the study were as follows: failure to conceive despite at least one year of regular sexual intercourse and without protection, female age less than 38 years, normal ovarian reserve (basal FSH<15 IU/ml), at least one intact fallopian tube, semen analysis results above the WHO 2010 reference values for unexplained infertility and below the WHO 2010 reference values for male infertility. Exclusion criteria for the study were women older than 38 years, polycystic ovary syndrome, untreated hypothyroidism or hyperthyroidism, diabetes, hyperprolactinemia, hypogonadotropic hypogonadism, confirmed endometriosis implants, sperm concentration less than 1 million on semen analysis, and sperm motility of 0%. Clomiphene citrate was administered to 54 of 196 patients diagnosed with unexplained infertility; out of a total of 377 patients who met study criteria, gonadotropin was administered to 142 patients, clomiphene citrate was administered to 44 of 181 patients diagnosed with male factor, and gonadotropin was administered to 137 patients.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) 25 software was used in the analysis of the data. The suitability of the data for normal distribution was examined using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. Parametric methods were used to analyze normally distributed variables, and non-parametric methods were used to analyze variables not normally distributed. The Independent-Samples T-test and Mann-Whitney U test were used to compare two independent groups. The comparison of the categorical data was tested by the Pearson Chi-Square and Fisher's exact test. Normally distributed data are reported as mean ± standard deviation, while non-normally distributed data are reported as median (minimum-maximum). The categorical data were expressed as n (number) and percentages (%). Data were analyzed within the 95% confidence interval, and a p-value of less than 0.05 was considered significant.

Results

377 cycles were studied, 181 in the male infertility group (Group 1) and 196 in the unexplained infertility group (Group 2). Women in Group 1 in the study had a mean age of 28.9±3.9 years and a mean body mass index (BMI) of 24.4±4.0. The women in group 2 were statistically similar, with a mean age of 28.7±3.5 years and a mean BMI of 24.8±4.8 (p:0.490, p:0.759). In group 1, 130 were primarily infertile (71.8%), and 51 were secondarily infertile (28.2%); in group 2, 129 were primarily infertile (65.8%), and 67 were secondarily infertile (34.2%). No significant difference was found in both groups in the distribution of primary and secondary infertility (p: 0.32). The duration of infertility was 3.1±2.3 years in group 1 and 2.8±2.1 years in group 2, and no significant difference was found (p:0.122). Mean gravida of group 1 was 0 (0-5), mean parity was 0 (0-2), mean survival was 0 (0-2), mean abortion rate was 0 (0-4). In group 2, the same parameters were 0 (0-4), 0 (0-2), 0 (0-2), 0 (0-4), respectively, and there was no significant difference between the two groups (p:0.196, p:0.866, p:0.992, p:0.103). There were 7 (3.9%) people with a known disease in group 1 and 5 (2.6%) in group 2, and both groups were similar. There were 16 (8.8%) patients in group 1 and 29 (14.8%) in group 2 who underwent laparoscopy, hysteroscopy, or laparotomy, and no statistically significant difference was found (p:0.094). Of the patients included in the study, hysterosalpingography (HSG) was performed in 49.2% of the patients in group 1 and 51.5% in group 2. In group 1 patients, the tubes were intact bilaterally in 41.4% (75 subjects), and one tube was intact in 9.4% (17 subjects). In group 2 patients, the tubes were intact bilaterally in 36.7% (72 subjects), and one tube was intact in 11.7% (23 subjects), with no statistically significant difference noted between the two groups. As uterine anomaly, arcuate uterus was observed in 7 (3.9%) patients in the 1st group and uterine septum was observed in 2 (1.1%) patients; In group 2, unicornuate uterus was observed in 1 (0.5%) patient, and the septum was operated in 1 (0.5%) patient. No uterine abnormality was determined in 172 (95%) patients in group 1 and 191 (97.4%) patients in group 2, and there was no statistically significant difference (p:0.199) (Table 1).

During IUI, the mean thickness of the endometrium was 9.1±1.7 mm, the number of follicles was 2 (1-4), and the number of treatment days was 7 (3-19) days in group 1 patients. The mean endometrial thickness in group 2 was 9.32 mm, the number of follicles was 2 (1-4), and the number of treatment days was 7 (4-14), with no statistically significant difference between the two groups (p:0.426, p: 0.917, p:0.059). The number of those who underwent CC in group 1 was 44 (24.3%), the number of those who received gonadotropin was 137 (75.7%), the number of those who underwent CC in group 2 was 54 (27.6%), the number of those who received gonadotropin was 142 (72.4%), and there was no statistically significant difference between the groups in terms of the type of treatment (p:0.473) (Table 2).

The mean age of men was 32.8±5.9 years in group 1 and 32.3±5.2 years in group 2, which was statistically similar (p:0.677). According to the results of semen analysis, sperm concentration in group 1 was 43.1±30.76x106/ml, sperm concentration after washing was 25±21.3x106/ml, sperm volume was 2.3±1.23 m, percentage of total motility was 38.6±13.79, percentage of total motility after washing was 53.9±17.79, total motile sperm count was 28.6±28x106/ml. In group 2, sperm concentration was 73.6±31x106/ml, sperm concentration after washing was 48.4±22.38x106/ml, sperm volume was 2.8±1.28 ml, percentage of total motility was 43.5±11.27, percentage of total motility after washing was 65.15±12.67, total motile sperm

count was 91.9±68x106/ml. Sperm concentration before and after washing, sperm volume, percentage of total motility before and after washing, and total motile sperm count were all significantly lower in group 1, and the difference between the two groups was statistically significant (p:0.001). When the semen was analyzed, the number of leukocytes in group 1 was 0.6±3.1, while the number of leukocytes in group 2 was 0.4±2.5, and there was no statistically significant difference (p:0.676) (Table 3).

There were 17 (9.4%) pregnancies in Group 1 and 22 (11.2%) in Group 2 (p:0.559). Clinical pregnancy was found in 7.7% (14 subjects) of group 1 and 11.2% (22 subjects) of group 2. In terms of pregnancy rate, there was no significant difference between the two groups (p:0.249). Group 1's pregnancies included 2 multiple pregnancies, 2 ectopic pregnancies, 10 singleton pregnancies, and 3 chemical pregnancies. 1 of the clinical pregnancies in group 2 was multiple, 1 was ectopic, and the remaining 20 were singleton pregnancies. In terms of pregnancy status, there was no statistically significant difference between the two groups (p:0.152) (Table 4).

Female age was 27.5±4.3 years for those who became pregnant and 28.9±3.6 years for those who did not. Male age was 31.5±4.6 years for couples who became pregnant and 32.7±5.6 years for couples who did not become pregnant. The duration of infertility was 2.5±2 years in couples who became pregnant and 3±2.2 years in couples who did not. There was no statistically significant difference between them in female age (p:0.068), male age (p:0.195), and duration of infertility (p:0.106), and pregnancy outcomes. On the day of HCG treatment after ovulation induction, the mean number of dominant follicles was 2 (min:1, max: 3) in pregnant women and 2 (min:1, max: 4) in non-pregnant women, which was not statistically significant (p:0.600). When patients were divided into three groups according to sperm concentration (below 5 million/ml, 5-15 million/ml, and above 15 million/ml), no pregnancy was observed in 5 patients below 5 million/ml, whereas no pregnancy was observed in 19 patients (5.6%) in the 5-15 million/ml group. In 39 (100%) of 353 patients with more than 15 million/ml, pregnancy was not detected in 314 (92.9%) patients. In terms of the influence of sperm count on pregnancy, there was no statistically significant difference between the two groups (p:0.369). When patients were divided into three groups according to their total motile sperm count (TMSC) (below 5 million, 5-15 million, and more than 15 million), no pregnancy was observed in 19 patients (5.9%) with a TMSC less than 5 million, whereas pregnancy was observed in 1 patient (2.7%). There were five pregnancies (13.5%) in 57 patients between 5-15 million and 31 pregnancies (83.8%) in 284 patients over 15 million. There was no statistically significant difference between groups concerning TMSC on pregnancy outcome (p:0.647). Because the number of washed sperm could not be obtained in 12 patients and the morphology of washed sperm could not be obtained in 4 patients, 16 patients could not be included in the statistics.

According to the Kruger strict method, pregnancy was detected in 12 (30.8%) of 118 patients with a normal sperm percentage of less than 4 and 27 (69.2%) of 259 patients with more than 4. These findings were not statistically significant (p:0.940). Pregnancy was observed in 4 (10.3%) of 61 patients with a sperm volume of fewer than 1.5 ml and 35 (89.7%) of 316 patients with a sperm volume of more than 1.5 ml. These findings were not statistically significant (p:0.289). Before washing, the sperm count of 39 pregnant patients was 61±30.6 million/ml. Because the data of 2 patients were not collected after washing, the sperm count of 37 patients evaluated after washing was 58.7±34.8 million/ml after washing, and there was a statistically significant difference between pregnancy and sperm count before and after washing (p:0.001). The percentage of progressive sperm motility of 39 pregnant patients was 43.5%±11.5 before washing. Since the data of 2 patients were not recorded after washing, the percentage of progressive sperm motility of 37 patients evaluated after washing was 64.4%±13.5, and it was statistically significant that sperm motility after washing had a positive effect on pregnancy (p:0.001) (Table 5).

Table 1: Demographic characteristics of patients who underwent OI+IUI for male infertility and unexplained infertility.

		Male Factor infertility (n:181)	Unexplained infertility (n:196)	P-Value
Female Age (yıl)		28,9±3,9	28,7±3,5	0,490
BMI (kg/m^2)		24,4±4	24,8±4,8	0,759
Infertility type	primary	130 (%71,8)	129 (%65,8)	0,209
	secondary	51 (%28,2)	67 (%34,2)	
Infertility duration (years)		3,1±2,3	2,8±2,1	0,122
Gravida		0 (0-5)	0(0-4)	0,196
Parity		0(0-2)	0(2-2)	0,866
Abortion		0(0-4)	0(0-4)	0,103
Alive		0(0-2)	0(0-2)	0,992
Presence of disease	no	174 (%96,1)	191 (%97,4)	0,467
	yes	7 (%3,9)	5 (%2,6)	
Operation	no	165 (%91,2)	167 (%85,2)	0,094
	laparotomy	8 (%4,4)	21 (%10,7)	
	laparoscopy (LS)	(4 (%2,2)	4 (%2)	
	hysteroscopy(HS)	4 (%2,2)	2 (%1)	
	LS+HS	0	2 (%1)	
HSG	normal	75 (%41,4)	72 (%36,7)	0,570
	One tube intact	17 (%9,4)	23 (%11,79	
Uterine anomaly	no	172 (%95)	191 (%97,4)	0,199
	arcuate uterus	7 (%3,9)	-	
	uterine septum	2 (%1,1)	-	
	operated septum	-	1 (%0,5)	0,199
	unicornuate uterus	-	1 (%0,5)	

Table 2: Findings during IUI application after ovulation induction

		Male Factor Infertility (n:181)	Unexplained Infertility (n: 196)	P-value
Endometrial thickness (mm)		9,1±1,7	9,3±2	0,426
Number of follicles		2(1-4)	2(1-4)	0,917
Number of treatment days		7(3-19)	7(4-14)	0,059
Treatment	CC	44 (%24,3)	54 (%27,6)	0,473
	COH (Gnrh)	137 (%75,7)	142 (%72,4)	

Table 3: Male semen analysis

	Male factor infertility (n: 181)	Unexplained infertility (n:196)	P-value
Male age (years)	32,8±5,9	32,3±5,2	0,677
Ph	8±0	8±0	0,959
Sperm concentration (x10^6/ml)	43,1±30,76	73,6±31	0,001
Sperm concentration after washing (x10^6/ml)	25±21,3	48,4±22,38	0,001
Sperm volume (ml)	2,3±1,23	2,8±1,28	0,001
Movement a+b (%)	38,6±13,79	43,5±11,27	0,001
Movement after washing a+b (%)	53,9±17,79	65,15±12,67	0,001
TMSS (x10^6/ml)	28,6±28	91,9±68	0,001
Leukocyte (per/ml)	0,6±3,1	0,4±2,5	0,676

Table 4: Pregnancy outcomes after OI+IUI in male infertility and unexplained infertility

		Male Factor Infertility (n:181)	Unexplained Infertility (n:196)	P-value
Pregnancy	yes	17 (%9,4)	22 (%11,2)	0,559
	no	164 (90,6)	174 (%88,8)	
Pregnancy status	single	10 (%5,5)	20 (%10,2)	0,152
	chemical	3 (%1,7)	-	
	multiple	2 (%1,1)	1 (%0,5)	
	ectopic	2 (%1,1)	1 (0,5)	

Table 5: Analysis of sperm parameters affecting pregnancy.

		Pregnancy positive (n:39)	Pregnancy negative (n:338)	P-value
Female age (mean±sd)(years)		27,5±4,3	28,9±3,6	0,068
Male age (mean±sd)(years)		31,5±4,6	32,7±5,6	0,195
Infertility period (mean±sd)(years)		2,5±2,0	3,0±2,2	0,106
Number of follicles per day of hCG (median)(min-max)		2(1-3)	2(1-4)	0,600
Sperm concentration (milyon/ml) n(%)	-<5 -≥5-15 -15 and above	0(%0) 0(%0) 39(%100)	5(%1,5) 19(%5,6) 314(%92,9)	0,369
TMSS (milyon/ml) n(%)	-<5 -≥5-15 -15 and above	1(%2,7) 5(%13,5) 31(%83,8)	19(%5,9) 52(%16) 253(%78,1)	0,647
Kruger strict n(%)	-<4 -≥4	12(%30,8) 27(%69,2)	106(%31,4) 232(%68,6)	0,940
Sperm volüme (ml) n(%)	-<1,5 -≥1,5	4(%10,3) 35(%89,7)	57(%16,9) 281(%83,1)	0,289
Sperm count (milyon/ml)(mean±sd)	-Before washing - After washing	61±30,6 58,7±34,8		**0,001**
Total progressive sperm motility (%)	-Before washing - After washing	43,5±11,5 64,4±13,5		**0,001**

Sd: Standart deviation
HCG: Human chorionic gonadotropin
TMSS: Total progressive motile sperm count

Discussion

If we consider the general results of our study, 17 (9.4%) pregnancies were obtained in group 1 and 22 (11.2%) pregnancies in group 2 (p=0.559). Clinical pregnancy was achieved in 7.7% (14 subjects) of group 1 and 11.2% (22 subjects) of group 2. In terms of clinical and biochemical pregnancies, the results were similar, and no statistically significant difference in the effect of sperm parameters on pregnancy outcomes was identified between the two groups (p:0.249). According to the results of semen analysis, sperm concentration, sperm concentration after washing, sperm volume, percentage of total motile sperm, percentage of total motile sperm after washing, and total motile sperm count were higher in the unexplained infertility group than in the male infertility group, and a statistically significant difference was found between the two groups (p:0.001). When sperm factors were analyzed in the pregnant cases, it was found that the values before washing were higher in terms of sperm count, and a

statistically significant difference was found compared to the sperm after washing (p:0.001). When the percentage of progressive sperm motility was compared before and after washing, the rates were higher after sperm washing, and a statistically significant difference was found between the two groups compared to before washing (p: 0.001).

In 2010, more men could be classified as "normal" because of innovations in the semen analysis guideline by the WHO [11]. Although the number of infertile men increased imperceptibly, more men were classified as fertile with the new guideline. Therefore, the study by Esteve *et al*. published in 2012 advises caution in interpreting these reference values, as the distinction between fertile and infertile men could not be precisely defined with the new reference values from WHO [12]. The WHO guideline recommends that at least 2, preferably 3, semen samples be evaluated together to determine male fertility status. The most important feature of the published reference values for semen analysis is that they were determined using controlled studies of fertile men with known unprotected pregnancies. The purpose of lower reference values is to provide evidence-based values that can help clinicians estimate a patient's relative fertility (3). In our study, the WHO 2010 handbook was used as the reference value for semen analysis, and OI and IUI were performed when the sperm concentration was at least 1 million/ml and above. In 1662 IUI cycles studied by Sakhel *et al*., the pregnancy rate per cycle was 30.3% in patients with sperm concentrations greater than 5 million sperm/mL and 18.8% in those with lower sperm levels [13]. Belaisch-Allart *et al*. reported 12.5% pregnancy per cycle at sperm concentrations less than 10 million/ml and 17% at sperm concentrations greater than 20 million/ml [14].

If we look at the results of our study, in the group with sperm concentration below 5 million/ml, no pregnancy was achieved, in the group with 5-15 million/ml, it was 7.4%, and in the group with 15 million/ml and more it was 10.1%, and if we compare them with different sperm concentration groups in the literature, it is seen that the rates are similar.

When Hughes examined 22 studies involving 5214 cycles, he compared gonadotropin with OI in 15% of cases of unexplained infertility, clomiphene citrate with OI in 7%, and the natural cycle in 6%. Based on the results of this study, he recommended the use of OI and IUI as effective methods for unexplained infertility [15]. Our study obtained 39 pregnancies (12.7%) following ovulation induction with CC and gonadotropins. While male factor infertility resulted in 17 (9.4%) pregnancies, unexplained infertility was 22 (11.2%). About 25% of cases were initiated with clomiphene citrate and about 75% with gonadotropins, followed by IUI. When comparing the two groups, no statistically significant difference was found between pregnancy rates and the method of induction used. The reason for the low results on pregnancy rates in unexplained infertility can be explained with the collection of retrospective data and the lack of a targeted study.

In a study by Guzick *et al*. involving 696 fertile and 765 infertile male patients, it was reported that sperm morphology is a more effective parameter among sperm morphology, sperm motility, and sperm concentration used to distinguish fertile and infertile patients [16]. In a study by Demir *et al*. in which 212 infertile couples were included in the study of factors affecting pregnancy outcomes after IUI and a total of 253 IUI cycles were performed, it was found that pregnancy rates were statistically higher in patients with a percentage of normal sperm morphology less than 4% and greater than 4% [17]. In a study by Hauser *et al*. that included 108 couples without known female infertility and examined the importance of motility and morphology in IUI treatment, pregnancy rates in the patient group with normal sperm morphology of less than 4% were compared with the other group with 4% or more. Accordingly, pregnancy rates in the group with normal morphology were found to be statistically lower than 4% [18]. Our study detected pregnancy in 10 (8.8%) of 114 patients with a normal sperm percentage of less than 4 by Kruger's strict method and 29 (11%) of 234 patients with more than 4. Although these results are not statistically significant, it is possible to conclude that the parameters below and above the 4% reference value alone are insufficient to predict the success of OI and IUI, as pregnancy rates are consistent with the literature. In contrast to these studies, the inadequacy of sperm morphology in OI and pregnancy success of IUI in our study may be because only the male factor and the unexplained factor are not included in the treatment etiologically.

Ombelet *et al*. conducted a review of semen quality and prediction of IUI success in male subfertility that included a total of 55 research; 36 retrospective, 14 prospective, and 5 meta-analyses. As a result of the review of data from previous studies in the literature in this publication, it was found that the sensitivity is low, but the specificity is high when the threshold for normal sperm morphology after washing is set at 4% [19]. Up to 90% of male factor infertility is related to sperm count, and there is a positive correlation between abnormal semen parameters and sperm count. Problems with sperm count, motility, and morphology are caused by irregularities in the control mechanism of pre-testicular, testicular, and post-testicular factors. As a result, with a sensitivity of 89.6%, semen analysis alone is the most useful and fundamental diagnostic method [20, 21].

Although epidemiologic evidence for infertility is limited [22], the influence of the male factor alone is cited in about 20% of cases [23]. IUI is an effective treatment for male factor infertility [24]. Even when other causes of infertility are suspected, paternal factors such as total motility count (TMC), sperm count after washing, and sperm morphology are essential criteria for estimating the IUI success rate.

Male age and body mass index (BMI) may also affect clinical outcomes. However, the ability to predict pregnancy based on sperm parameters alone is limited because results also depend on age and diagnosis of infertility, as well as the day of stimulation regimens and methods used, and a number of female factors [22, 23, 24].

There are conflicting recommendations in the literature regarding the threshold for total motile sperm count to achieve excellent pregnancy outcomes in IUI cycles. Many retrospective studies have evaluated results based on sperm parameters in couples with various ovulation induction (OI) regimens and infertility diagnoses. Considering the retrospective and heterogeneous nature of the studies in general, it was found that a value of 5-10 million could be used as a cut-off value for TMSC in most studies. A 2001 research examined 1039 couples aged 43 and under who had 3.479 IUI cycles using natural cycles, ovulation induction with gonadotropins, or clomiphene citrate (CC) to determine prognostic factors for achieving pregnancy. In this study, they found increased pregnancy rates with TMSC sperm values of 10 million or more. While couples with TMSC values below 10 million achieved 1.5% pregnancy in the first IUI cycle, couples with TMSC values of 10-30 million and > 30 million achieved 10.5% and 12,0% pregnancy respectively [24]. Similar results have been obtained in other studies using IUI after spontaneous cycles or ovulation induction

in couples with infertility due to a single male factor.

In a randomized controlled trial involving 308 spontaneous and post-ovulation induced IUI, the cut-off value of 10 million was reported for the TMSC value. It was also observed that there was no effect on pregnancy rates after ovarian stimulation in couples with a TMSC value below 10 million [25]. Two retrospective studies showed a threshold of 4,056 and 2,062 spontaneous and 5 million, respectively, for high pregnancy outcomes in OI/IUI cycles [26, 27].

If we look at the literature, publications state that even low values such as 0.3 million and 1 million can be considered thresholds for a good pregnancy outcome in TMSC [28, 29]. However, these numerical values could not be confirmed by effective studies.

In a retrospective study of 310 women with unknown causes of infertility in 2019, no viable pregnancy was achieved in couples with a TMSC below 2 million after 655 IUI cycles [30]. Given all these results, couples with a TMSC below 5 million are recommended by some authors and below 10 million by some authors to proceed with IVF treatment [24, 25, 26].

When examining total sperm count after washing as an indicator of IUI success, a threshold of 1 million has been reported in many studies [31, 32, 33].

In another retrospective study, as a result of 9963 cycles performed in 3200 infertile couples, it was found that pregnancy rates decrease when TMSC after sperm washing is below 2 million, so higher thresholds are required. While the lowest TMSC was reached at 0.8 million after sperm washing in pregnancy, pregnancy rates have been reported to increase progressively at 4 million and above [34]. In another study evaluating 1038 IUI cycles, it was found that the best pregnancy rates were obtained when the TMSC value was 5 million and above and the TMSC value of 1 million after sperm washing was accepted as a threshold, and it was found that this situation was more applicable, especially in women with ovulation disorders and cervical factor infertility [31].

Some studies say that washing, centrifuging, swim-up, and concentration determination in preparing sperm for insemination do not affect pregnancy and miscarriage rates [35]. Considering all these results, it can be concluded that it is crucial to evaluate sperm parameters along with female factors to achieve high pregnancy rates in IUI.

Ovulation induction with CC or gonadotropin followed by IUI is an effective treatment often used for infertility. The pregnancy results obtained depend on the clinical, laboratory, and some family factors of the couples. Considering the heterogeneity of all studies and the limited number of randomized controlled trials, it should be noted that the optimal treatment management of infertile couples should apply only to them.

In light of our study's limitations, the negative impacts of its retrospective nature and the small number of patients in both groups should be noted. However, the lack of statistical difference between pregnancies and those with a normal sperm percentage of less than or greater than 4 by the strict Kruger method and the pregnancy rates that were consistent with the literature in our study may suggest that the 4% reference value for sperm morphology alone is not sufficient to predict the success of OI and IUI.

Conclusion

Regarding the male factor and unexplained infertility, it should not be forgotten that in cases with a TMSC below 5 million, assisted reproductive techniques should be used, but these methods are difficult to achieve, especially in developing countries and underdeveloped populations. In this regard, it might be advisable to revise the criteria of WHO 2010 with prospective studies to facilitate their application and make them more effective in terms of fertility.

Author contributions

MS and ET conceived, designed and supervised the study, interpreted the data, prepared the figure with the related legend, and wrote the manuscript; AU analyzed the data; ET and BK performed the literature search. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of the Antalya Training and Research Hospital, date 28.02.2019 and approval number: 7/18.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Fertil Steril by American Society for Reproductive Medicine. 2020;113:305–22.
2. Berek and Novak's Gynecology, 15th Edition. Çeviri editörleri: Doç. Dr. Ahmet Erk, Prof. Dr. Fazlı Demirtürk; 32. Bölüm: İnfertilite ve Yardımcı Üreme Teknikleri, 2012.
3. World Health Organization. WHO Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction. 4th ed. Cambridge: Cambridge University Press, 2010. p. 1 86.
4. Men's Health-Male Factor Infertility. University of Utah Health Sciences Center. 04 January, 2003.
5. Ray A, Shah A, Gudi A, *et al*. Unexplained infertility: an update and review of practice. Reprod Biomed Online. 2012;24:591.
6. Suresh C Sikka, Wayne JG Hellstrom. Current updates on laboratory techniques for the diagnosis of male reproductive failure. Asian Journal of Andrology. 2016;18:392–401.
7. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, *et al*. The International Glossary on Infertility and Fertility Care, Fertil Steril. 2017;108:393–406.
8. Wordsworth S, Buchanan J, Mollison J, Harrild K, Robertson L, Tay C, *et al*. Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: are they cost-effective? Hum Reprod. 2011;26:369–75.
9. Ayaz R, Asoglu MR, Ayas S. Use of clomiphene citrate alone, urinary follicle stimulating hormone alone, or both combined sequentially in patients with unexplained subfertility undergoing intrauterine insemination. A randomized trial. Turk J Obstet Gynecol. 2018;15:243–8.
10. Danhof NA, van Wely M, Repping S, Koks C, Verhoeve HR, de Bruin JP, *et al*. Super study group. Follicle

stimulating hormone vs. clomiphene citrate in intrauterine insemination for unexplained subfertility: a randomized controlled trial. Hum Reprod. 2018;33:1866–74.
11. Bablok L, Dziadecki W, Szymusik I, Wolczynski S, Kurzawa R, Pawelczyk L, *et al*. Patterns of infertility in Poland - multicenter study. Neuro Endocrinol Lett. 2011;32:799–804.
12. Esteves SC, Zini A, Aziz N, Alvarez JG, Sabanegh Jr ES, Agarwal A. Critical appraisal of World Health Organization's new reference values for human semen characteristics and effect on diagnosis and treatment of subfertile men. Urology. 2012;79:16–22.
13. Sakhel K, Schwarck S, Ashraf M, Abuzeid M. Semen parameters as determinants of success in 1662 cycles of intrauterine insemination after controlled ovarian hyperstimulation. Fertil Steril. 2005;84:248–9.
14. Belaisch-Allart J, Mayenga JM, Plachot M. Intrauterine insemination. Contracept Fertil Sex. 1999;27:616–21.
15. Hughes EG. The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a meta-analysis. Hum Reprod. 1997;12:1865–72.
16. Guzick DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C, *et al*. Spermmorphology, motility, and concentration in fertile and infertil men. N Engl J Med. 2001 Nov8;345(19):1388-93.
17. Demir B, Dilbaz B, Cinar O, Karadag B, Tasci Y, Kocak M, *et al*. Factors affecting pregnancy outcome of intrauterine insemination cycles in couples with favourable female characteristics. J Obstet Gynaecol. 2011 Jul;31(5):420-3.
18. Hauser R1, Yogev L, Botchan A, Lessing JB, Paz G, Yavetz H. Intrauterine insemination in male factor subfertility: significance of sperm motility and morphology assessed by strict criteria. Andrologia. 2001 Jan;33(1):13-7.
19. Ombelet W, Deblaere K, Bosmans E, Cox A, Jacobs P, Janssen M, *et al*. Semen quality and intrauterine insemination. RBM Online. 2014;7(4):485–492.
20. Sabra SM, Al Harbi MS. An influential relationship of seminal fluid microbial infections and infertility, Taif Region, KSA. World J Med Sci. 2014;10:327.
21. Wang C, Swerdloff RS. Limitations of semen analysis as a test of male fertility and anticipated needs from newer tests. Fertil Steril. 2014;102:1502–7.
22. Barratt CLR, Björndahl L, De Jonge CJ, Lamb DJ, Osorio Martini F, McLachlan R, *et al*. The diagnosis of male infertility: an analysis of the evidence to support the development of global WHO guidance-challenges and future research opportunities. Hum Reprod Update. 2017;23:660–80.
23. Anderson JE, Farr SL, Jamieson DJ, Warner L, Macaluso M. Infertility services reported by men in the United States: national survey data. Fertil Steril. 2009;91:2466–70.
24. Van Voorhis B. Effect of the total motile sperm count on the efficacy and cost-effectiveness of intrauterine insemination and in vitro fertilization. Fertil Steril. 2001;75:661–8.
25. Cohlen BJ, te Velde ER, van Kooij RJ, Looman CW, Habbema JD. Controlled ovarian hyperstimulation and intrauterine insemination for treating male subfertility: a controlled study. Hum Reprod. 1998;13:1553–8.
26. Dickey RP, Pyrzak R, Lu PY, Taylor SN, Rye PH. Comparison of the sperm quality necessary for successful intrauterine insemination with World Health Organization threshold values for normal sperm. Fertil Steril. 1999;71:684–9.
27. Gubert PG, Pudwell J, Van Vugt D, Reid RL, Velez MP. Number of motile spermatozoa inseminated and pregnancy outcomes in intrauterine insemination. Fertil Res Pract. 2019;5:10.
28. Paulmyer-Lacroix O, Mollé L, Noizet A, Guérin A, Mollar M, Gamerre M, *et al*. [Intrauterine insemination with the husband's sperm: conclusions of five years experience]. Contracept Fertil Sex. 1998;26:300–6.
29. Dinelli L, Courbière B, Achard V, Jouve E, Deveze C, Gnisci A, *et al*. Prognosis factors of pregnancy after intrauterine insemination with the husband's sperm: conclusions of an analysis of 2,019 cycles. Fertil Steril. 2014;101:994–1000.
30. Mankus EB, Holden AE, Seeker PM, Kampschmidt JC, McLaughlin JE, Schenken RS, *et al*. Prewash total motile count is a poor predictor of live birth in intrauterine insemination cycles. Fertil Steril. 2019;111:708–13.
31. Merviel P, Heraud MH, Grenier N, Lourdel E, Sanguinet P, Copin H. Predictive factors for pregnancy after intrauterine insemination (IUI): An analysis of 1038 cycles and a review of the literature. Fertil Steril. 2010;93:79–88.
32. Campana A, Sakkas D, Stalberg A, Bianchi PG, Comte I, Pache T, *et al*. Intrauterine insemination: evaluation of the results according to the woman's age, sperm quality, total sperm count per insemination and life table analysis. Hum Reprod. 1996;11:732–6.
33. Ombelet W, Vandeput H, Van de Putte G, Cox A, Janssen M, Jacobs P, *et al*. Intrauterine insemination after ovarian stimulation with clomiphene citrate: predictive potential of inseminating motile count and sperm morphology. Hum Reprod. 1997;12:1458–63.
34. Stone BA, Vargyas JM, Ringler GE, Stein AL, Marrs RP. Determinants of the outcome of intrauterine insemination: Analysis of outcomes of 9963 consecutive cycles. Am J Obstet Gynecol. 1999;180:1522–34.
35. Boomsma CM, Cohlen BJ, Farquhar C. Semen preparation techniques for intrauterine insemination. Cochrane Database Syst Rev. 2019;10:CD004507.