Predictive value of postwashed total progressively motile sperm count using CASA estimates in 6871 non-donor intrauterine insemination cycles

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Abstract

Purpose To determine whether postwashed total progressively motile sperm count (TPMSC) obtained by CASA estimates could predict positive pregnancy test result in non-donor IUI cycles.

Methods Six thousand eight hundred and seventy one (6,871) IUI cycles with non-donor semen were retrospectively analyzed. Patient, cycle characteristics and prewashed and postwashed semen parameters were included in analysis. The main outcome measure was the positive pregnancy test result.

Results The pregnancy rate per cycle (PR/cycle) when postwashed TPMSC is between 0–0.5 million, 0.51–1 million, 1.01–5 million, 5.01–10 million and greater than 10 million were 8.1 % (42/520), 14.4 % (41/285), 16.1 % (237/1,469), 18.4 % (193/1,046) and 18.8 % (668/3,551) respectively. The predicted odd of positive pregnancy result is statistically significantly higher when TPMSC is >0.51 million compared to the TPMSC of <0.51 million (OR=1.68, 95 %

CI: 1.04–2.71). The predicted odd of positive pregnancy result is greatest when TPMSC is at least 5 million (OR=2, 95 % CI: 1.38 to 2.9).

Conclusion TPMSC is an independent predictor of pregnancy test result and TPMSC of half million or greater is adequate to achieve statistically similar pregnancy test results after non-donor IUI cycles.

Keywords Intrauterine insemination · Computer assisted sperm analysis · Pregnancy · Semen analysis

Capsule Postwashed total progressively motile sperm count is a predictor of pregnancy test result in nondonor IUI cycles.

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Introduction

Intrauterine insemination (IUI) is one of the most frequently used fertility treatments for infertile couples [1]. However it is still debatable which semen parameters and corresponding cut-off levels successfully predict pregnancy after IUI cycles [2–5]. The utility of postwashed total motile sperm count (TMSC) in predicting pregnancy in IUI cycles has been investigated in several studies; however, there is not a consensus on a reliable semen parameter cutoff to predict IUI outcome [6]. The minimum postwashed TMSC to achieve pregnancy may vary from 0.8 million to 10 million [6, 7]. Thus, postwashed total progressively motile sperm count (TPMSC) could be a clinically more useful parameter instead of TMSC as it may predict treatment outcome better than TMSC following IUI.

Variability in results from prior studies investigating predictors of pregnancy in IUI cycles may be attributed to methodological issues (i.e. small number of patients or cycles) among studies and the inability to adjust for the impact of confounding variables on IUI outcomes [5, 8].

Additionally, assessment of sperm parameters by microscopic versus computer assisted sperm analysis (CASA) may also explain some of the differences related to the predictive role of sperm parameters in IUI cycles [9]. CASA is

advantageous over standard microscopic evaluation, which has large inter-laboratory variation in estimating respective percentages of progressive and non-progressive motile and immotile spermatozoa, making it difficult to predict fertility [10, 11].

Because there are limited data regarding the association between postwashed TPMSC and the pregnancy rates in non-donor IUI cycles, our main purpose was to first determine if an association exists between postwashed TPMSC using CASA estimates and pregnancy rates in non-donor IUI cycles after adjusting for known confounders affecting likelihood of pregnancy. Our second aim was to determine pregnancy rates comparing patient, cycle characteristics and pre- and postwashed TPMSC in positive and negative pregnancy groups.

Materials and methods

Subjects

We reviewed the medical records of all women who underwent intrauterine insemination with their husband or partners' sperm (non-donor IUI) at the Center for Assisted Reproduction in Dallas, Texas from January 1999 through December 2011. The cycle characteristics are summarized in Table 1. All electronic and paper charts of the female patients were reviewed for age, etiology of infertility, type of ovarian stimulation regimens, prewashed and postwashed semen parameters, number of IUI during the same cycle and blood pregnancy test result. Institutional Review Board of the University of Texas Southwestern Medical Center approved this study.

Procedures

Semen analysis using CASA

Both pre- and post-processing of ejaculate for insemination, the semen analysis was performed using the CASA system (Hamilton Thorne Research, Beverly, MA, USA). The prewashed and postwashed total progressively motile sperm count was defined as progressively moving sperm as $>25 \mu\text{m/s}$ as per World Health Organization's 4th laboratory manual version). The prewashed semen parameters recorded were: semen volume, total sperm concentration (total number of spermatozoa in the ejaculate), total motile sperm count, total sperm motility percentile (total motile sperm count divided by the total sperm count multiplied by 100), total sperm progressive motility percentile (total progressive sperm count divided by the total sperm count multiplied by 100). The postwashed semen parameters recorded were: total motile sperm count, TPMSC and progressive motility percentile. Normal semen analyses were defined by the threshold values of the World Health Organization (WHO) 1999 criteria (concentration $\geq 20 \times 10^6/\text{ml}$, total count $\geq 40 \times 10^6$, progressive motility $\geq 50\%$). Male factor was diagnosed if any of the semen parameters is out of the reference range as per WHO 1999 criteria.

Procedure of sperm preparation

The selective concentration of progressively motile sperm for IUI was carried out using a density gradient centrifugation. Two 5 μl aliquots were used for CASA analysis and the rest of

Table 1 Characteristics of non-donor IUI cycles by pregnancy outcome

Characteristic	Pregnancy	No pregnancy	P value
Age (mean $\pm$ SD) (range)	32.1 $\pm$ 4.4 (19–44)	32.4 $\pm$ 4.3 (19–48)	$P=0.01$
CC (%)	460/2,606 (17.7)	2,146/2,606 (82.3)	$P^a<0.0001$
FSH (%)	481/1,855 (25.9)	1,374/1,855 (74.1)	$P^a<0.0001$
Timed IUI (%)	240/2,410 (10)	2,170/2,410 (90)	Reference group
Double IUI ⁺ (%)	468/3,113 (15)	2,652/3,113 (85)	$P^b<0.0001$
Single IUI (%)	713/3,758 (19)	3,050/3,758 (81)	
Male factor*			
Present (%)	463/3,018 (15.3)	2,555/3,018 (84.8)	$P^c<0.0001$
Pregnancy rate per cycle (%)	1,181/6,871 (17.2)		
Pregnancy rate per patient (%)	1,181/3,421 (34.5)		

The values are expressed as mean $\pm$ SD

⁺ Double IUI refers to back to back IUI that was 24 h apart during the same treatment cycle

* Based on 1999 World Health Organization's normal sperm parameters' criteria

^a $p<0.0001$ CC and FSH were compared to the Timed IUI (reference group) within each of the two groups (pregnancy and no pregnancy)

^b $p<0.0001$ based on comparison between Pregnancy vs. No Pregnancy groups

^c $p<0.0001$ based on comparison between Pregnancy vs. No Pregnancy group

$N=6,871$ non-donor IUI cycles. CC: clomiphene citrate; FSH: follicle stimulating hormone; IUI: intrauterine insemination

the suspension was used for IUI. At least 200 sperm were counted with CASA to evaluate the postwashed TPMSC.

Our database included patients who had undergone IUI after ovarian stimulation with clomiphene citrate (CC) or gonadotropin alone [FSH (follicle stimulating hormone) or hMG (human menopausal gonadotropins)] but also patients who underwent IUI without ovarian stimulation (Timed IUI). Typically single IUI was performed in the absence of an LH surge if ovulation was triggered with the hCG injection. Typically if the patient had a spontaneous LH surge, double IUI was performed. If four or more mature follicles (>17 mm) developed, the cycle was cancelled and the couples were advised to avoid intercourse for the next 2 weeks.

Statistical analysis

To address whether there were differences between the two pregnancy outcome groups (positive cases vs. negative cases) on the demographics/clinical characteristics, we used the two-independent sample *t*-test with equal variances (for continuous outcomes) and the Chi-square test or, when appropriate, Fisher's Exact test (for categorical variables). The Chi-square test was also used to test for an association between postwashed TPMSC (<0.50 million, 0.51–1 million, 1.01–5 million, 5.01–10 million, >10 million; coded as five binary indicators with "<0.50 million" as the reference group) and pregnancy rates per cycle.

Multiple logistic regression was used to estimate the adjusted odds of a positive pregnancy test with all predictors (risk factors) included in the model, while adjusting for the covariates. The 95 % Wald confidence intervals (CI) were calculated for the Odds Ratios (OR), and the Wald Chi-square statistic was used to test for a significant association between each predictor and positive pregnancy test.

The statistical analyses were performed using the Statistical Package for Social Science (SPSS) for personal computers, version 19.0 for Windows (SPSS Institute Inc., Chicago, IL, USA) and SAS software, version 9.2 (SAS Institute, Inc., Cary, NC). The level of significance for all tests was set at $\alpha=.05$ (two-tailed) and all *p*-values were adjusted for multiple testing using the Bonferroni's correction.

Results

Comparison of positive and negative pregnancy groups

There were 3,421 patients who underwent a total of 6,871 IUI cycles with known pregnancy test result at the end of the treatment cycle (Table 1). The mean $\pm$ SD age of women were 32.1 ± 4.4 years (range 19–44) and 32.4 ± 4.3 years (19–48) in positive and negative pregnancy groups respectively. The

pregnancy rate per cycle in CC, gonadotropin or timed IUI groups were 17.7 % (460/2,606), 25.9 % (481/1,855) and 10 % (240/2,410) respectively when all age groups were combined. The pregnancy rates per cycle comparing the single IUI with the double IUI cycles were 19 % (713/3,758) and 15 % (468/3,113) respectively. In cycles with known male factor, the pregnancy rate was 15.3 % (463/3,018). Of those 6,871 cycles from 3,421 patients, 1,181 cycles resulted in pregnancy, giving an overall pregnancy rate per cycle of 17.2 % and pregnancy rate per patient of 34.5 %.

We next compared the prewashed and postwashed TPMSC in the positive and negative pregnancy groups (Table 2). There was no statistically significant difference in prewashed TPMSC in between the two groups (53 vs. 49.4 million respectively, $p=0.07$, 95 % CI -7.7 , 0.3). The postwashed TPMSC in the positive pregnancy group was statistically significantly higher than that of the negative pregnancy group (23.4 vs. 21.4 million respectively, $p=0.018$, 95 % CI -4.1 to -0.38).

We next calculated PR/cycle categorized by the postwashed TPMSC (Fig. 1). When the TPMSC was <0.5 million, the PR/cycle was 8.1 % (42/520 cycles) as compared to that of the 14.4 % (41/285 cycles) when TPMSC was between 0.51 million and 1 million ($p<0.05$). The PR/cycle when postwashed TPMSC is between 1.01–5 million, 5.01–10 million and greater than 10 million were 16.1 % (237/1,469), 18.4 % (193/1,046) and 18.8 % (668/3,551) respectively. There was no statistically significant difference among any TPMSC groups once the TPMSC is greater than 0.5 million ($p>0.05$, with Bonferroni's correction).

As shown in Table 3, the logistic regression revealed three significant predictors of a positive pregnancy test: female age, type of ovarian stimulation, and postwashed TPMSC.

Postwashed TPMSC was significantly associated with the positive pregnancy test result when adjusted for the other covariates. Patients with TPMSC between 0.51–1 million had 1.68 times greater predicted odds of a positive pregnancy test (OR=1.68, 95 % CI: 1.04 to 2.71, $p=0.03$) than those whose TPMSC was <0.51 million. When TPMSC was between 1.01–5 million, the predicted odds of a positive pregnancy test result was 1.79 times greater (OR=1.79, 95 % CI: 1.24 to 2.59) than TPMSC of <0.51 million. Patients with TPMSC between 5.01–10 million had 2 times greater predicted odds of a positive pregnancy test (OR=2, 95 % CI: 1.38 to 2.9, $p<0.0001$) than those whose TPMSC was <0.51 million. Similarly, patients with TPMSC >10 million had 2 times greater predicted odds of a positive pregnancy test (OR=2, 95 % CI: 1.43 to 2.87, $p<0.0001$) than those whose TPMSC was <0.51 million (Table 3). The receiver operating characteristic (ROC) curve analysis determined that a threshold or cutoff of >0.51 million on postwashed TPMSC discriminated the presence of a positive pregnancy test, with 96.3 % sensitivity and 8.3 % specificity along with a positive predictive

Table 2 Prewashed and postwashed total progressively motile sperm count by pregnancy outcome

Semen parameters	Pregnancy (mean±SD)	No pregnancy (mean±SD)	<i>P</i> value	95 % CI
Prewashed				
Total progressively motile sperm count (million)	53±61.8	49.4±64.9	0.07	−7.7, 0.3
Postwashed				
Total progressively motile sperm count (million)	23.4±30.9	21.4±29.5	0.018*	−4.1, −0.38

The values are expressed as mean ± SD

* The *p* value was set at 0.05

value (PPV) of 17.9 % and negative predictive value (NPV) of 91.7 %.

For the age variable, women who were ≥40 years old at the time of IUI had a 31 % decrease in the predicted odds of pregnancy compared to that of the women ≤35 years old (OR=0.69, 95 % CI=0.52–0.93) (Table 3). There was no statistically significant difference in the odds of pregnancy when women between 36–39 years old were compared to the women ≤35 years old. The logistic regression analysis revealed that patients who received CC ovarian stimulation had 1.89 times greater predicted odds of a positive pregnancy test (OR=1.89, 95 % CI: 1.6 to 2.24, *p*<0.0001) than those who were in the timed IUI group. The patients who received gonadotropin ovarian stimulation had 3.08 times greater predicted odds of a positive pregnancy test (OR=3.08, 95 % CI: 2.59 to 3.66, *p*<0.0001) than those who are in timed IUI group (Table 3).

Discussion

Several studies have reported different sperm variables, such as TMSC, and thresholds predictive of pregnancy in IUI cycles [5, 12, 13]. The minimum TMSC after preparation recommended for IUI varies from 0.8 to 10 million [6, 7, 12–18]. Most authors agree on this minimum threshold of 1

million for the TMSC, and recommend IVF when TMSC is lower than 1 million [14–16, 19–24]. The TMSC appears to have a consistent and direct relationship with pregnancy test result. However, like other sperm parameters there is no definite threshold (level) at which it could ‘powerfully’ predict treatment outcome [5].

For those aforementioned reasons, we focused on postwashed TPMSC instead of postwashed TMSC as a potential predictor of pregnancy with the hope to determine a definite threshold, which could powerfully predict positive pregnancy test result after non-donor IUI. We found that postwashed TPMSC is a predictor of pregnancy test result.

The odds of a positive pregnancy test result is greater when TPMSC is >0.51 million compared to TPMSC of 0–0.51 million; however, once the TPMSC is greater than 0.51 million, there was no statistically significant difference in pregnancy rates among different levels of TPMSC (Fig. 1). The odds of positive pregnancy test result is greatest when TPMSC is at least 5 million and it does not change whether TPMSC is between 5–10 million or greater than 10 million (Table 3). TPMSC of equal to or greater than half million is associated with a PR/cycle anywhere between 14.4 to 18.8 % (Fig. 1). Interestingly, there were 42 pregnancies out of 520 cycles with PR/cycle of 8.1 % when the TPMSC is less than half million. This is an interesting finding in that TPMSC of half million is adequate to achieve pregnancy in non-donor IUI

Fig. 1 Pregnancy rate per cycle by postwashed total progressively motile sperm count (TPMSC).

* *p*<0.05, each motile sperm count group was compared to the TPMSC of <0.5 million (the reference group).

n=number of cycles that resulted in pregnancy divided by the total number of cycles after non-donor IUI

Table 3 Odds ratios with 95 % confidence intervals for each risk factor and positive pregnancy test

Predictor (Risk Factor)	<i>B</i>	<i>P</i> Value	OR ^{a,b}	95 % CI of OR
Age $\geq$ 40 (compared to $\leq$ 35)	−0.36	0.014	0.69	0.52–0.93
CC ovarian stimulation (compared to Timed IUI)	0.64	<0.0001	1.89	1.6–2.24
Gonadotropin ovarian stimulation (compared to Timed IUI)	1.12	<0.0001	3.08	2.59–3.66
Postwashed TPMSC 0.51–1 million (compared to <0.51 million)	0.52	0.03	1.68	1.04–2.71
Postwashed TPMSC 1.01–5 million (compared to <0.51 million)	0.58	0.002	1.79	1.24–2.59
Postwashed TPMSC 5.01–10 million (compared to <0.51 million)	0.69	<0.0001	2	1.38–2.9
Postwashed TPMSC >10 million (compared to <0.51 million)	0.71	<0.0001	2	1.43–2.87

^a Adjusted odds ratios were estimated for each risk factor and positive pregnancy test (while adjusting for the below mentioned covariates) in the multiple logistic regression model

^b The model adjusted for the following covariates: Single vs. double insemination during the same cycle, semen volume, prewashed total sperm concentration, prewashed total motile sperm count, prewashed total sperm motility percentile, total sperm progressive motility percentile, postwashed total motile sperm count, postwashed progressive motility percentile and male factor (binary indicator–absence/presence, with “presence of male factor infertility” as the reference group). OR: odds ratio, *B*: regression coefficient, 95 % CI: Wald confidence interval for OR. TPMSC: total progressively motile sperm count. *P* <0.05 was considered as statistically significant

cycles bearing in mind that pregnancy can still occur for TPMSC of less than half million. ROC curve analysis determined that a threshold or cutoff of >0.51 million on postwashed TPMSC has a high sensitivity (96.3 %) and high NPV (91.7 %) but low specificity (8.3 %) and low PPV (17.9 %) to discriminate the presence of a positive pregnancy test result.

There are several predictors of pregnancy which are also taken into account in our study such as female age and type of ovarian stimulation. TPMSC is an important predictor of positive pregnancy test result when the data were adjusted for these potential confounders.

Several studies [6, 7, 12–18] have shown that the pregnancy rate significantly varies based on the total motile spermatozoa inseminated however few data are available regarding the progressive nature of the spermatozoa inseminated. In a 2014 study, Dinelli et al. investigated the prognostic factors of pregnancy after IUI [25]. In that study, the pregnancy rate increased when the TPMSC is greater than 1 million as compared to the pregnancy rate when TPMSC is fewer than 1 million. This is consistent with our findings. The important difference between our and Dinelli et al.’s study is that TPMSC was categorized as a binary indicator (TPMSC of <1 million versus >1 million) in their study whereas in our study TPMSC was coded as five binary indicators with “<0.50 million” as the reference group. This enabled us to determine that even 0.5 million or greater TPMSC is associated with a significantly higher chance of pregnancy as compared to TPMSC of <0.5 million. In search for a cutoff level for the predictive value of TPMSC, Bollendorf et al. determined a threshold value of 2 million rapid progressive spermatozoa inseminated to obtain satisfying pregnancy rates [26]. In a small retrospective study, Ok et al. [27] studied a total of 156 cycles to determine the effect of postwashed TPMSC and semen volume on pregnancy outcomes. Their results

showed that an average postwashed TPMSC of 10 million may be a useful threshold value for IUI success. However their study population included a small number of patients and they categorized TPMSC into four groups instead of five and they did not provide any data regarding the pregnancy rate when TPMSC is between 0.5–1 million [27].

The predictive value of postwashed TPMSC was also studied in IVF literature. Rhemrev et al. showed that a postwashed TPMSC of fewer than 1.1 million results in an high risk of total fertilization failure [28]. In a recent study, Nikbakht et al. investigated the prognostic value of sperm morphology, total motile sperm count (TMSC) and the number of motile sperm inseminated (NMSI) on the outcome of 820 IUI cycles [29]. Actually when we read their manuscript carefully, NMSI was actually TPMSC. They showed that NMSI greater than 10 million is one of the prognostic factors of IUI cycles which is consistent with our findings however they did not investigate the pregnancy rate when TPMSC is between 0.5–1 million. In a similar study, Wainer et al. [30] investigated the influence of the number of TMSC inseminated and their morphology on the success of IUI in 889 couples who underwent 2,564 IUI cycles. They did not categorize their data as TPMSC but when methods section was read in detail, TMSC was actually TPMSC. When the number of TPMSC was fewer than 1 million, the pregnancy rate/cycle was significantly lower (3.13 %) than in any of the subgroups with TPMSC greater than 2 million [30]. The highest pregnancy rate was obtained when TPMSC was between 5–10 million [30] which is similar to our findings. However in contrast to our study, Wainer et al. [30] also did not investigate the pregnancy rate when TPMSC is between 0.5–1 million.

Our study is in agreement with similar studies [25, 26, 28–30] in that there is no perfect cutoff for TPMSC to predict positive pregnancy test result. TPMSC of at least 1 million [25], 2 million [26], 5 million [29] and 10 million or greater

[27] were proposed as a cutoff to predict pregnancy. We have shown that the highest odd of pregnancy is achieved when TPMSC is greater than 5 million (Table 3). In addition, our data showed that TPMSC between 0.51–1 million would also provide a reasonable chance of pregnancy and there is no statistically significant difference in pregnancy rates once the TPMSC is greater than 0.51 million. To the best of our knowledge none of the studies have investigated the pregnancy rate when TPMSC is between 0.51–1 million. This is one the main differences between our study and similar studies [25, 26, 28–30], which investigated TPMSC as a predictor of pregnancy.

The statistical analysis of our data showed that TPMSC is one of the independent predictors of pregnancy in addition to female age and type of ovarian stimulation. The other semen parameters as outlined in Table 3's legend have not been found to predict pregnancy and we do not have a clear explanation for it. The value of TPMSC as a predictor of pregnancy may be explained with the fact that TPMSC reflects both sperm concentration and progressive motility. Progressive motility may be a more important variable than the overall motility in the context of the ability of the sperm to reach and fertilize the oocyte. However future studies are needed to determine why TPMSC may be a better predictor of pregnancy compared to the other semen parameters.

Not surprisingly, increasing female age resulted in reduced chances for pregnancy after IUI, confirming the well-known effects of increasing female age on fertility. In our study, as the female age increased, the pregnancy rates decreased for any type of ovarian stimulation cycle. For clomiphene/IUI cycles the pregnancy rates were around 17 % until the age of 39 and started to decrease at and after the age of 40. The same was true for also FSH/IUI and Timed IUI cycles. Our results regarding the impact of advanced maternal age on the likelihood of pregnancy in IUI cycles are consistent with those of the published data [31–33].

Type of ovarian stimulation is also an important factor in predicting pregnancy after IUI cycles. Several studies have shown that ovarian stimulation cycles with gonadotropin use were associated with higher pregnancy rates compared with that of the clomiphene/IUI or Timed/IUI cycles [34–36]. Similar to those results, we found that the type of ovarian stimulation is one of the predictors of pregnancy. We observed the highest pregnancy rates with gonadotropin/IUI cycles compared with that of the clomiphene/IUI or Timed/IUI cycles.

Our study has a few limitations: first, it was a retrospective study with the inherent limitations of a case-controlled study design. Our outcome measure was biochemical evidence of pregnancy rather than clinical pregnancy or live births. Although this may facilitate retrospective investigations, we recognize that the ultimate goal of infertility therapy for both patients and clinicians is live births rather than biochemically

documented conception. Finally, we did not analyze the impact of sperm morphology, which has been reported to have an independent impact on pregnancy rates after IUI [31, 37].

The main strengths of our study are that we addressed certain biases that are commonly associated with case-controlled studies. For example, sampling error, usually related to limited number of samples in case-controlled studies, was not an issue due to large number of non-donor IUI cycles. Secondly, semen parameters were measured objectively via CASA thereby minimizing, if not eliminating, information bias. Thirdly, most studies do not adjust for type of ovarian stimulation, which clearly has an influence in pregnancy rates. Our study was able to importantly account the predictive role of this variable in our analysis.

To the best of our knowledge, this is the largest study from a single center which investigated the presence and strength of association between postwashed TPMSC and pregnancy rates in non-donor IUI cycles and it is the only study that provided the pregnancy rates by CASA estimates when TPMSC is fewer than 0.5 million and between 0.51–1 million.

Conclusion

Postwashed TPMSC of at least 0.5 million by CASA estimates is adequate to achieve statistically similar pregnancy rates above this cutoff in non-donor IUI cycles, and pregnancy can still occur even if TPMSC is less than 0.5 million. TPMSC of at least 5 million is associated with the greatest odds of pregnancy. Female age, type of ovarian stimulation and TPMSC are predictors of pregnancy in non-donor IUI cycles.

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