Intrauterine Insemination Among Filipino Couples with Processed Total Motile Count of 1.0 x 10^6 or Less: Semen Quality Profile and Prognosis for Pregnancy

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Objective: To determine the pregnancy rate after intrauterine insemination using samples with processed total motile count of 1.0 x 10^6 and less and describe the semen quality profile of Filipino males with severe male factor infertility in both the raw and processed semen samples. **Design**: Retrospective descriptive study. **Setting**: Andrology Laboratory, St. Luke's Medical Center. **Patients**: 307 infertile Filipino couples who underwent 426 IUI cycles. **Main Outcome Measures**: Pregnancy rate (PR) after intrauterine insemination. **Results**: A total of 10 pregnancies were obtained out of 426 IUI cycles, for a pregnancy rate per cycle of 2.4%. Seven of these eventually delivered to term, for a live birth rate of 1.6%. Among those who did not get pregnant with IUI, 8 had spontaneous pregnancies within 1 to 5 year period of follow-up for a spontaneous pregnancy rate of 1.9%. As expected, all the semen parameters analysed showed improvement after semen processing in all subjects. However, these improvements failed to result in a more acceptable pregnancy rate. Among the parameters, morphology was notably better among those who had pregnancies. **Conclusion**: The chance of pregnancy with IUI using semen samples with processed total motile count of 1.0 x 10^6 or less is relatively low. For these couples, it may be more prudent to proceed directly to IVF-ICSI than to try several cycles of IUI in futility.

Key words: intrauterine insemination, severe oligospermia

Introduction

In recent years, infertility has become a prevalent global health concern among the reproductive age group and is now considered a disease.[1] At present, approximately 10 to 15 percent of couples are unable to conceive after 1 year of unprotected intercourse.[2] In about 20 percent of these infertile couples, a male factor is solely responsible and in another 30 to 40 percent, it is contributory.[3] The cause of male infertility is oftentimes, unidentifiable, making it difficult to prevent. To this date, most cases are incurable and can only be overcome through various assisted reproductive techniques.[4]

Intrauterine insemination (IUI) has been used to treat infertile couples for almost 200 years. It has been used to overcome oligospermia, asthenospermia, low ejaculate volumes, antisperm antibodies and cervical factors.[2] The likelihood of success with this procedure, depends, to some extent, on the severity of the seminal quality problem. The World Health Organization (WHO) established reference values to define normospermia. However, most often than not, pregnancies achieved with insemination in infertile couples, have been achieved with sperm parameters below the reference values.[5,6] Various studies have already been published on the linear correlation of sperm density, motility and morphology on pregnancy outcome.[5,6,7,8,9] Analysis of parameters using processed semen was found to provide better prognostic information for couples undergoing intrauterine insemination than raw samples. Parameters of raw samples, do not correlate consistently with cycle fecundity.[10] This may be because,

and range of values were used for continous variables, while frequencies and proportions were used for categorical variables. Statistical significance between the means could not be determined due to the very large difference in the sample size between the two groups. Abnormal semen values (Table 1) were defined from World Health Organization (2nd ed, 1987) reference values. Patients who underwent double insemination in one cycle were excluded from the analysis.

Results

Overall Pregnancy Rates

The over-all pregnancy rate was 2.4% per cycle (10/426) for couples who underwent intrauterine insemination with processed total motile count of 1.0 x 10^6. The pregnancy rate per couple was 3.3% (10/307). Out of the 10 documented pregnancies, 3 were chemical pregnancies which ended in spontaneous miscarriages and 7 clinical pregnancies which resulted in livebirths. This gives a livebirth rate of 1.6%.

For those who discontinued treatment after their failed IUI procedures, a review was made to document whether there was occurrence of any spontaneous pregnancy. Out of 297 couples, 8 eventually had spontaneous pregnancies during the follow-up period. This gives a spontaneous pregnancy rate per couple of 2.7%.

Characteristics of the Study Population

There were a total of 307 couples who underwent 426 cycles of sperm washing and intrauterine insemination that were included in this study. The number of insemination cycles per couple, including those cycles wherein the processed total motile count for the subject was above 1.0 x 10^6, was no longer recorded since all of the 10 documented pregnancies were among those who only had 1 or 2 insemination cycles. The distribution of male partners by age is seen in Figure 1 while the distribution of female partners by age is seen in Figure 2. Over-all, the average age of the male partners consulting for infertility with severe oligospermia is 37.93 years (SD = 8.12) with the median at 36 years. One hundred eighty eight subjects (61%) were 35 years old or older. The average age of the female partners, on the other hand, was 34.41 (SD = 5.21) with the median at 34 years. One hundred forty six of these were 35 years or older, which was 48 percent of the study population.

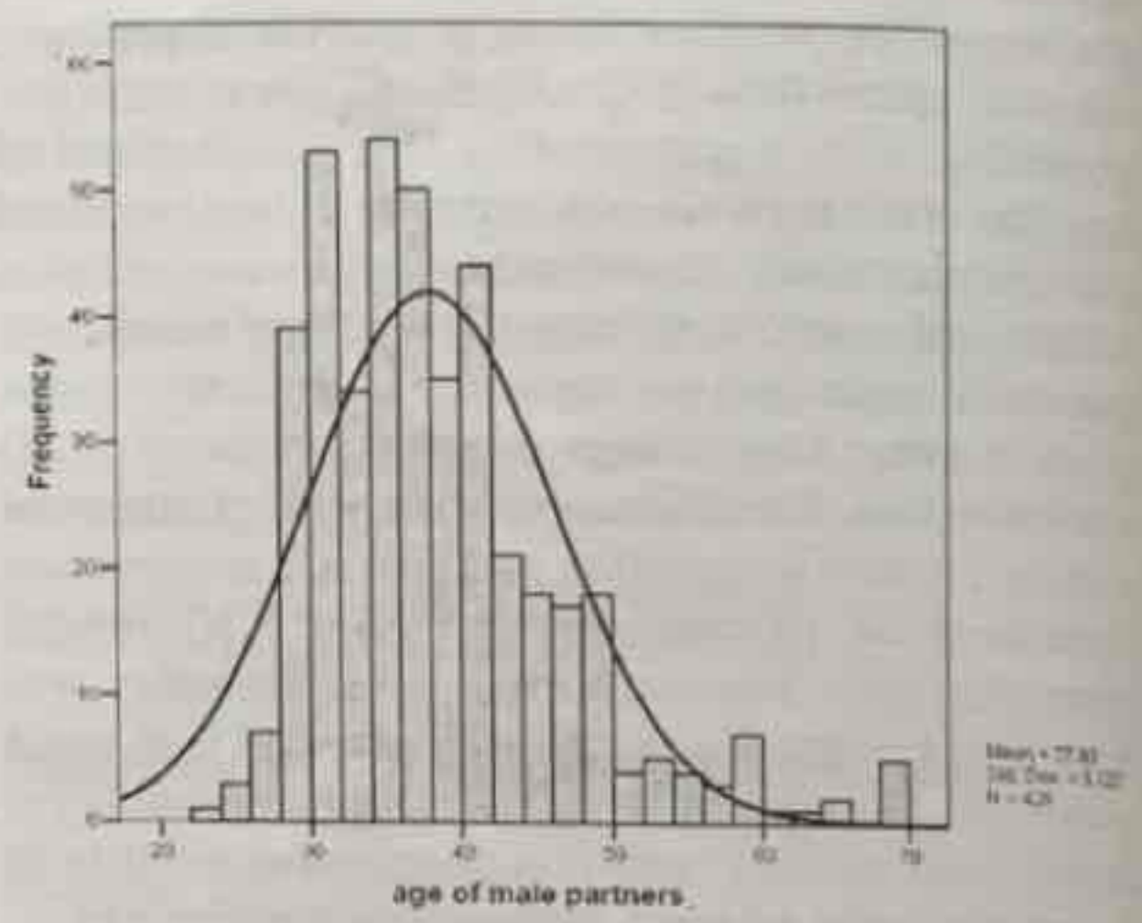

Figure 1. Distribution of male partners by age.

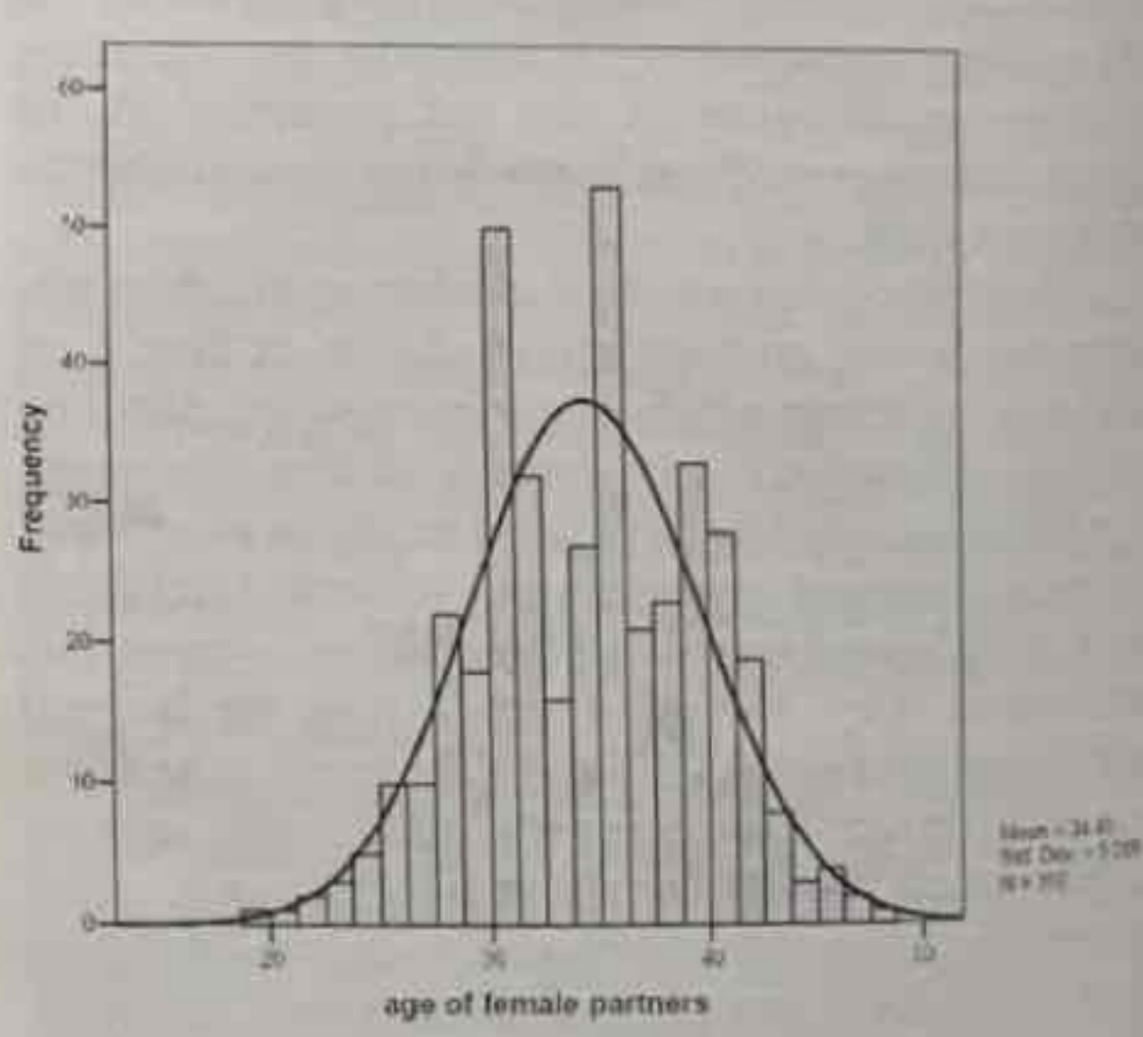

Figure 2. Distribution of female partners by age.

Table 1. Age of male and female partners in relation to pregnancy outcome (Mean, Median and Range of Results).

Variables	With Pregnancy (N=10)			Without Pregnancy (N=416)			Over-all (N=426)
	Mean (SD)	Median	Range of Results	Mean (SD)	Median	Range of Results	
Age, years (SD)							
Husband	36.71 (±5.38)	40.00	29-41	37.58 (±7.80)	36.00	23-69	37.93 (±8.12)
Wife	33.29 (±4.79)	32.00	28-42	34.32 (±5.13)	34.00	19-48	34.41 (±5.21)

Comparisons of the clinical characteristics of the study population and the summary of the semen parameters in pregnancy versus non-pregnancy cycles are described in Tables 1 and 2. The average age of the male partners of couples who had successful pregnancies was 36.71 years (SD = 5.38) with age range from 28 – 41 years while that for the couples who had failed outcomes was 37.58 years (SD = 7.80) with age range from 23-69 years. The average age of the female partners who had pregnancies was 33.29 years (SD = 4.79) with age range from 28-42 years while that without pregnancy was 34.32 years (SD = 5.13) with age range from 19-48 years.

Semen Processing/Sperm Washing Procedures

Semen processing procedures differed among the subjects. Selection of the type of sperm washing procedure was tailored to individual cases and was primarily dependent on the quality of the raw specimen submitted. This was done in order to maximize sperm recovery. Table 3 presents a comparison of the different semen processing procedures used in pregnancy versus non-pregnancy cycles. Over-all, majority of the samples were processed with either gradient processing technique (47.1%) and fiberwool filtration (37%). Six of the seven subjects who had pregnancy outcomes were processed using either technique. As per guidelines set by the Andrology Laboratory, these procedures are reserved for those with moderate oligoasthenospermia and severe oligoasthenoteratozoospermia. This is to achieve the highest possible yield, since majority of the specimens received had very poor semen quality profile. For specimens wherein initial analysis revealed normospermia or only mild oligoasthenospermia and debris > + 4, Swim-

Table 2. Summary of semen parameters (raw and processed samples) and pregnancy outcome (Mean, Median and Range of Results).

Variables	WHO Reference Value	With Pregnancy (N=10)			Without Pregnancy (N=416)			Over-all (N=426)
		Mean (SD)	Median	Range of Results	Mean (SD)	Median	Range of Results	
Raw Sample, X (SD)								
Volume, mL	≥ 2.0	2.6 (±0.84)	2.45	1.6-4-6	2.49 (±1.57)	2.40	0.5-20.8	2.49 (1.55)
Concentration (x10⁶/mL)	≥ 20.0	1.53 (±1.77)	1.12	0 -6.0	3.11 (±4.69)	1.80	0-35.6	3.07 (±4.65)
Total Sperm Count (x 10⁶)	≥ 40.0	4.36 (±5.70)	2.0	0 -19.2	6.84 (±11.9)	3.60	0-115.5	6.78 (±11.82)
Over-all Motility, %	≥ 50%	26.70 (±17.96)	32.0	0- 48.0	29.25 (±17.55)	28.00	0-85.0	29.19 (±17.54)
Total Motile Count (x10⁶)	NA*	1.45 (±2.37)	0.395	0-7.7	2.45 (±6.22)	1.00	0.76.0	2.43 (±6.16)
Forward Progression, %	≥ 30%	18.8 (±10.65)	18.0	0-33.0	22.77 (±16.21)	20.0	0-80.0	22.68 (±16.10)
Viability, %	≥ 75%	55.80 (31.85)	68.0	0-95.0	51.19 (±28.46)	58.0	0-94.0	51.30 (±28.51)
Morphology, %	≥ 50%	20.30 (±11.39)	22.5	2-37.0	14.47 (±14.40)	10.0	0-90	14.61 (±14.35)
Processed Sample, X (SD)								
Volume, mL	NA*	0.51 (±0.03)	0.50	0.5-0.6	0.47 (±0.12)	0.50	0.3-0.5	0.47 (±0.12)
Concentration (x10⁶/mL)	NA*	2.03 (±1.50)	1.55	0.27-4.30	3.26 (±2.85)	2.70	0.02-30.0	3.23 (±2.83)
Total Sperm Count (x 10⁶)	NA*	1.01 (±0.75)	0.78	0.14-2.10	1.45 (±1.25)	1.20	0.008-15.000	1.44 (±1.24)
Over-all Motility, %	NA*	36.50 (±17.62)	35.50	10.0-70.0	33.97 (±17.55)	32.00	2.0-90.0	34.03 (±17.54)
Total Motile Count (x10⁶)	NA*	0.322 (±0.258)	0.238	0.055-0.851	0.431 (±0.279)	0.402	0.004-0.990	0.429 (±0.279)
Forward Progression, %	NA*	38.60 (±20.54)	33.0	17.0-79.0	37.25 (±18.88)	36.0	0-90.0	37.29 (±18.89)

*Not Applicable

up technique can be used. In this study, there were 25 samples processed using this procedure, primarily because of the presence of concomitant pyospermia. Mean total sperm count of the raw specimens under this group was 9.4 x 10^6 with mean over-all motility of 35.4%. One subject who had a successful pregnancy outcome had semen processed using this technique. Straight wash was done on 42 samples with initial sperm counts too low in order to maximize sperm recovery. Mean initial total sperm count for this group was 5.8 x 10^6 with mean initial over-all motility of 20%. This procedure, however, has the great disadvantage of allowing all spermatozoa, including the dead, moribund and abnormal ones present in the original semen to remain in the final sperm population[19]. The presence of these non-functional gametes are detrimental to the pregnancy outcome when injected into the uterine cavity during IUI because of inhibition in sperm capacitation. No pregnancy resulted in this group.

Semen Parameters in Raw and Processed Samples

The characteristics of the semen parameters (mean, standard deviation, median and range of results) of the 'with pregnancy' group (n=10) versus the 'without pregnancy' group (n=416) are described in Table 2. The study population's mean values for sperm concentration, total sperm count, percent over-all motility, percent forward progression, percent viability and percent normal morphology were all below the WHO reference values. This is true for both groups. Analysis of the semen parameters of the raw sample showed that the mean value for sperm concentration (1.53 x 10^6 vs. 3.11 x 10^6), total sperm count (5.35 x 10^6 vs. 6.83 x 10^6), percent over-all motility (26.70 vs. 29.24), total motile count (22.77) were lower among the group with pregnancy versus the group without pregnancy. However, the percent viability (55.80 vs. 51.19) and percent normal morphology (20.30 vs. 14.47) were higher among those with pregnancy than those without pregnancy.

After semen processing, there is significant improvement in both percent over-all motility (36.50 vs. 26.70) and percent forward progression (18.80 vs. 38.60). An improvement in these parameters has been one of the established advantages of doing semen processing prior to intrauterine insemination. On analysis of the semen quality parameters of the processed samples, the mean values for sperm concentration (2.03 x 10^6 vs. 3.26 x 10^6), total sperm count (1.13 x 10^6 vs. 1.45 x 10^6) and total motile count (0.32 x 10^6 vs. 0.43 x 10^6) were still lower in the group with pregnancy compared to the group without pregnancy. However, as mentioned, the percent over-all motility (36.50 vs. 33.97) and percent forward progression (38.60 vs. 37.25) were higher among the former.

The lowest value for which pregnancy was documented was a total sperm count of 0.55 x 10^6, percent over-all motility of 10.00, percent forward progression of 20.00 and processed total motile count of 0.055 x 10^6 (Table 4). A summary of the clinical characteristics and semen quality profile of the subjects with documented pregnancies is presented in Table 4. Out of the ten documented pregnancies, two conceptions occurred with a processed total motile count of < 0.10 x 10^6 with percent normal morphology of 20.00 and 37.00 based on WHO 1992 reference values . The first ended in a miscarriage and the second eventually delivered to term. Three

Table 3. Semen processing/type of washing and outcome cross tabulation.

Semen Processing/Type of Washing	Outcome			Total
	Number of Samples % Within Outcome			
	No Pregnancy	Pregnancy with Miscarriage	With Pregnancy	
Straight Wash	42	–	–	42
	10.3%	–	–	9.9%
Fiber Wool Filtration	154	3	3	160
	37%	100%	42.9%	37.5%
Gradient Processing	196	–	3	199
	47.1%	–	42.9%	46.7%
Swim-up	24	–	1	25
	5.8%	–	14.3%	5.9%
	416	3	7	426
	100.0%	100.0%	100.0%	100.0%

conceptions resulted from IUI of PTMC between 0.10×10^6 and 0.30×10^6, another 4 conceptions with PTMC between 0.30×10^6 and 0.80×10^6 and one with PTMC of 0.85×10^6. Data on percent normal morphology for these pregnancies are illustrated in Table 4.

The distribution of values for each semen parameter is graphically presented in Figure 3 (semen volume), Figure 4 (sperm concentration, raw sample), Figure 5 (total sperm count, raw sample), Figure 6 (percent over-all motility, raw sample), Figure 7 (total motile count, raw sample), Figure 8 (percent forward progression, raw sample), Figure 9 (percent viability, raw sample), Figure 10 (percent normal morphology), Figure 11 (sperm concentration, processed sample), Figure 12 (total sperm count, processed sample), Figure 13 (processed total motile count) and Figure 14 (percent forward progression, processed sample).

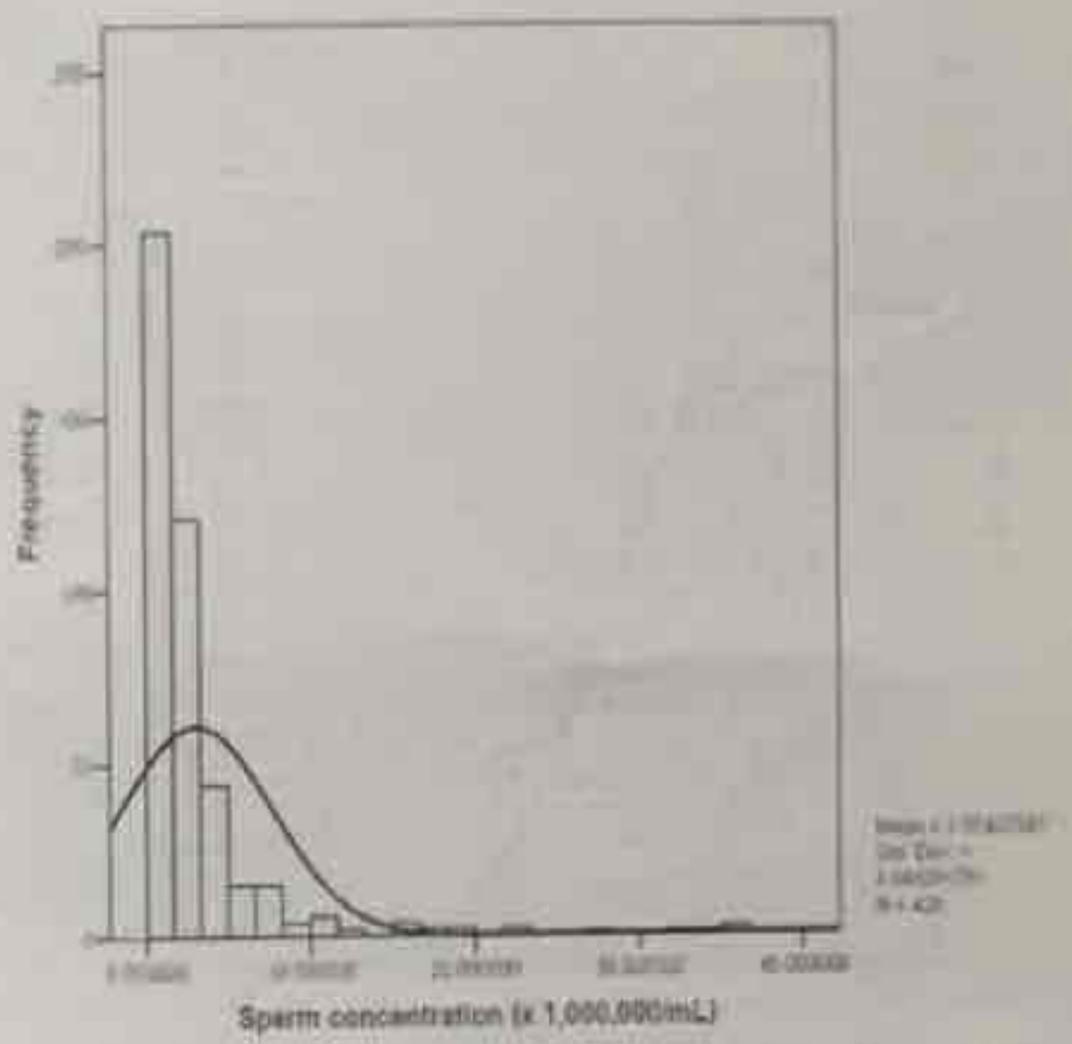

Figure 4. Distribution of sperm concentration (Raw Sample).

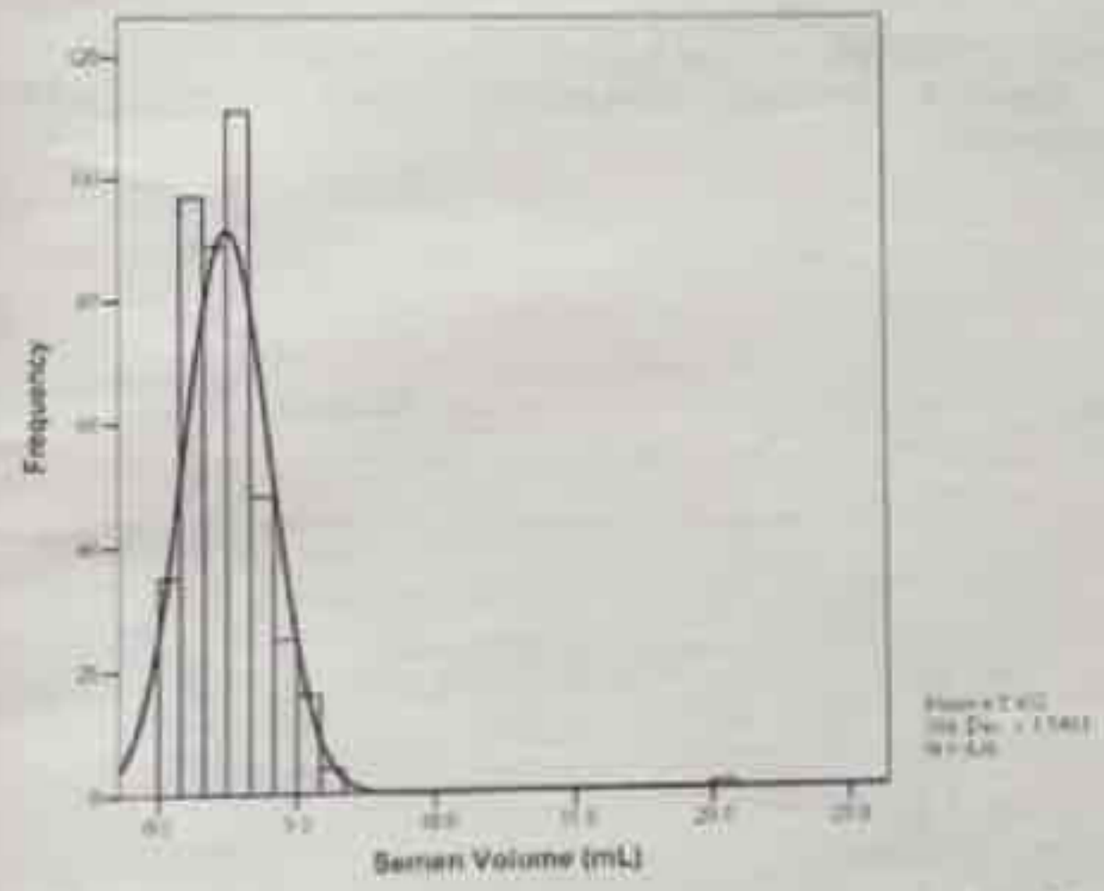

Figure 3. Distribution of semen parameters-volume (Raw Sample).

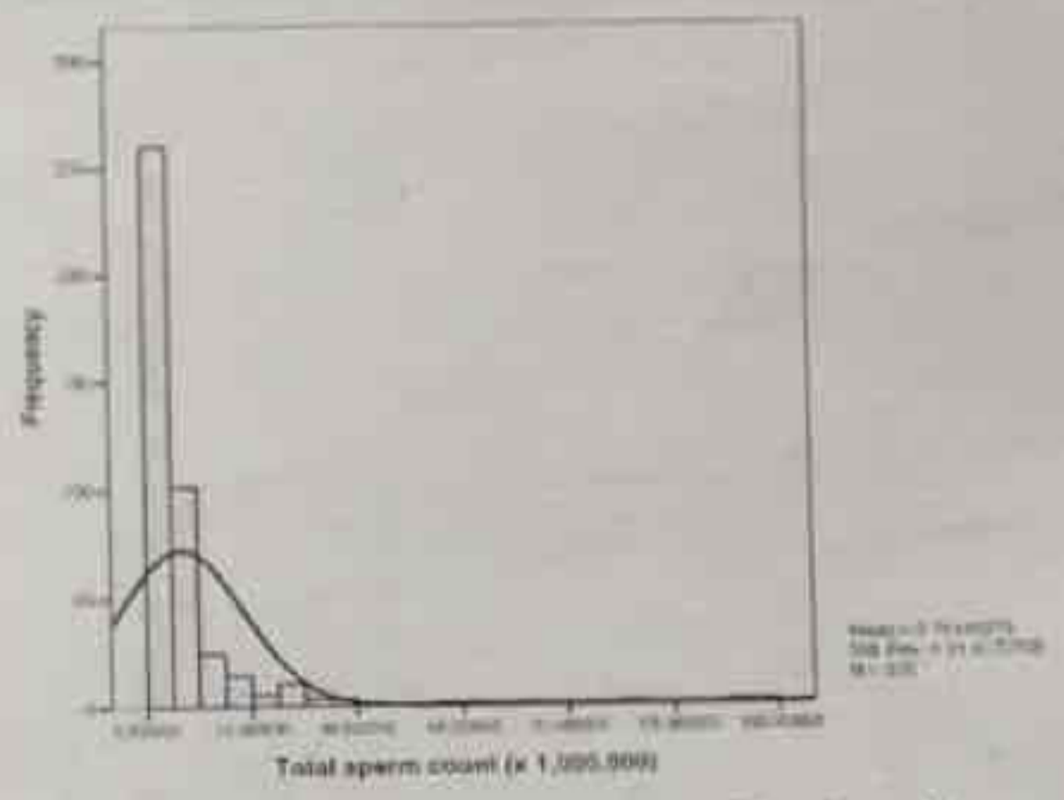

Figure 5. Distribution of total sperm count (Raw Sample).

Table 4. Summary of clinical characteristics and semen quality profile of subjects with documented pregnancies.

Subject	Age (yrs) Male	Age (yrs) Female	Semen Volume (mL)	Sperm concentration (x 1 M/mL)	Total sperm count (x 1 M)	Over-all motility (%)	Total motile count (x 1 M)	Forward progression (%)	Viability (%)	Morphology	(Semen Processing) Type of Washing	Vol	Sperm Concentration 2 (x 1 M/ml)	Total sperm count 2 (x 1 M)	Overall Motility 2 (%)	Total Motile Count 2 (x 1 M)	Forward Progression 2 (%)	Pregnancy
1	41	28	3.2	6.000000	19.200000	40.00%	7.700000	13.00%	57.00%	4.00%	Swim-UP	0.5	3.500000	1.800000	32.00%	0.560000	55.00%	P
2	35	35	2.3	0.290000	0.667000	45.00%	0.300000	9.00%	75.00%	13.00%	Gradient Processing	0.5	1.000000	0.500000	30.00%	0.150000	79.00%	P
3	30	32	2.0	0.950000	1.900000	16.00%	0.304000	20.00%	70.00%	29.00%	Gradient Processing	0.5	4.300000	2.100000	14.00%	0.301000	17.00%	P
4	41	30	2.6	0.550000	1.400000	34.00%	0.486200	26.00%	75.00%	26.00%	Fiber Wool Filtration	0.5	0.500000	0.250000	70.00%	0.175000	43.00%	P
5	29	30	4.6	1.300000	6.000000	41.00%	2.400000	16.00%	66.00%	25.00%	Gradient Processing	0.5	3.700000	1.900000	46.00%	0.851000	41.00%	P
6	41	42	2.3	2.800000	6.400000	10.00%	0.640000	30.00%	48.00%	2.00%	Fiber Wool Filtration	0.5	2.000000	1.000000	36.00%	0.360000	25.00%	P
7	40	36	1.6	1.300000	2.100000	3.00%	0.063480	33.00%	0.00%	29.00%	Fiber Wool Filtration	0.5	2.100000	1.500000	35.00%	0.542500	23.00%	P-M
8	28	28	3.0	1.700000	5.100000	48.00%	2.400000	29.00%	95.00%	17.00%	Fiber Wool Filtration	0.5	0.800000	0.400000	38.00%	0.152000	24.00%	P-M
9	40	37	2.2	0.378000	0.831000	30.00%	0.249000	12.00%	72.00%	30.00%	Fiber Wool Filtration	0.5	0.270000	0.135000	54.00%	0.072900	59.00%	P-M
10	36	36	3.0	0.000000	0.000000	0.00%	0.000000	0.00%	0.00%	37.00%	Fiber Wool Filtration	0.5						

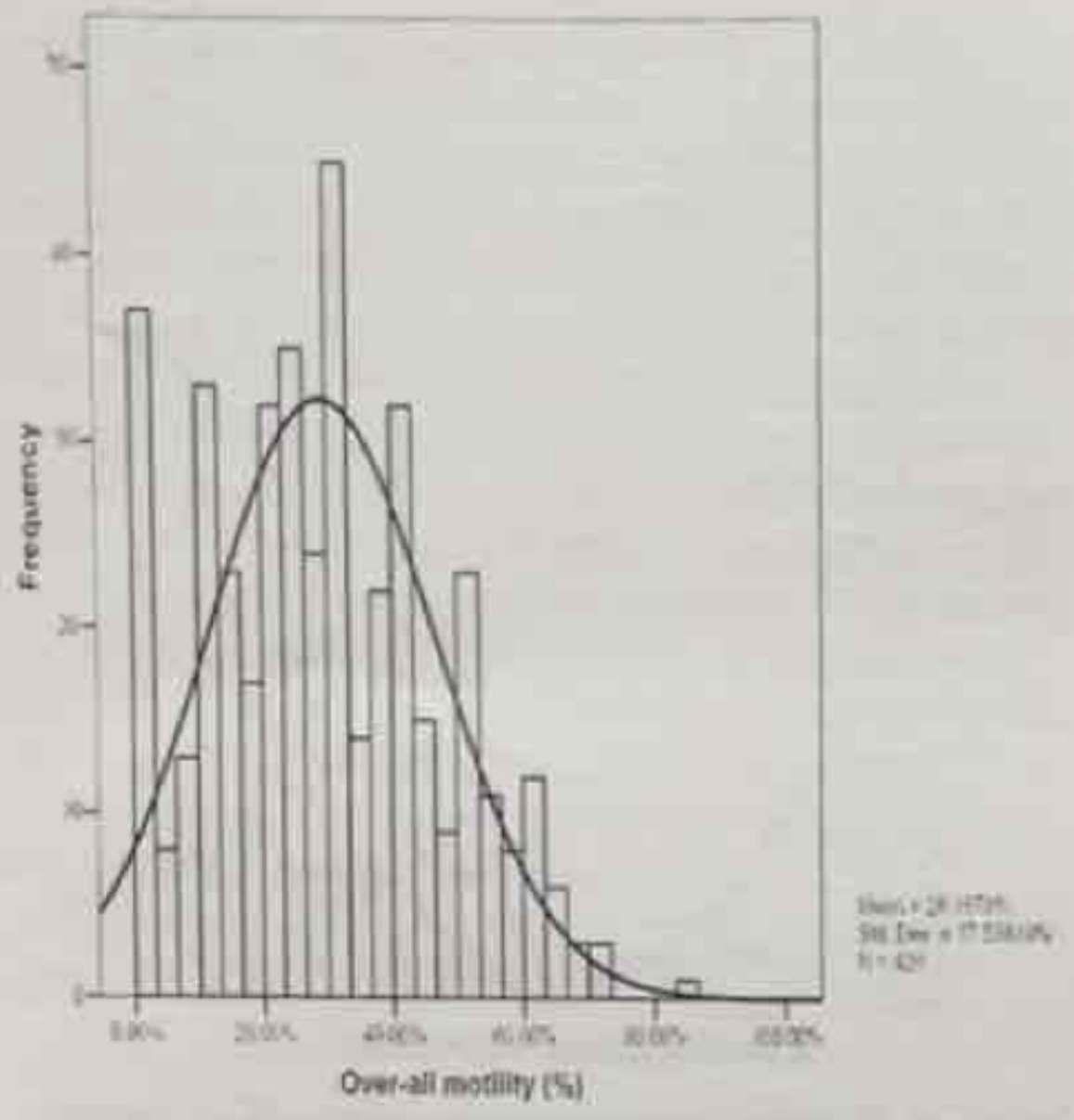

Figure 6. Distribution of percent over-all motility (Raw Sample).

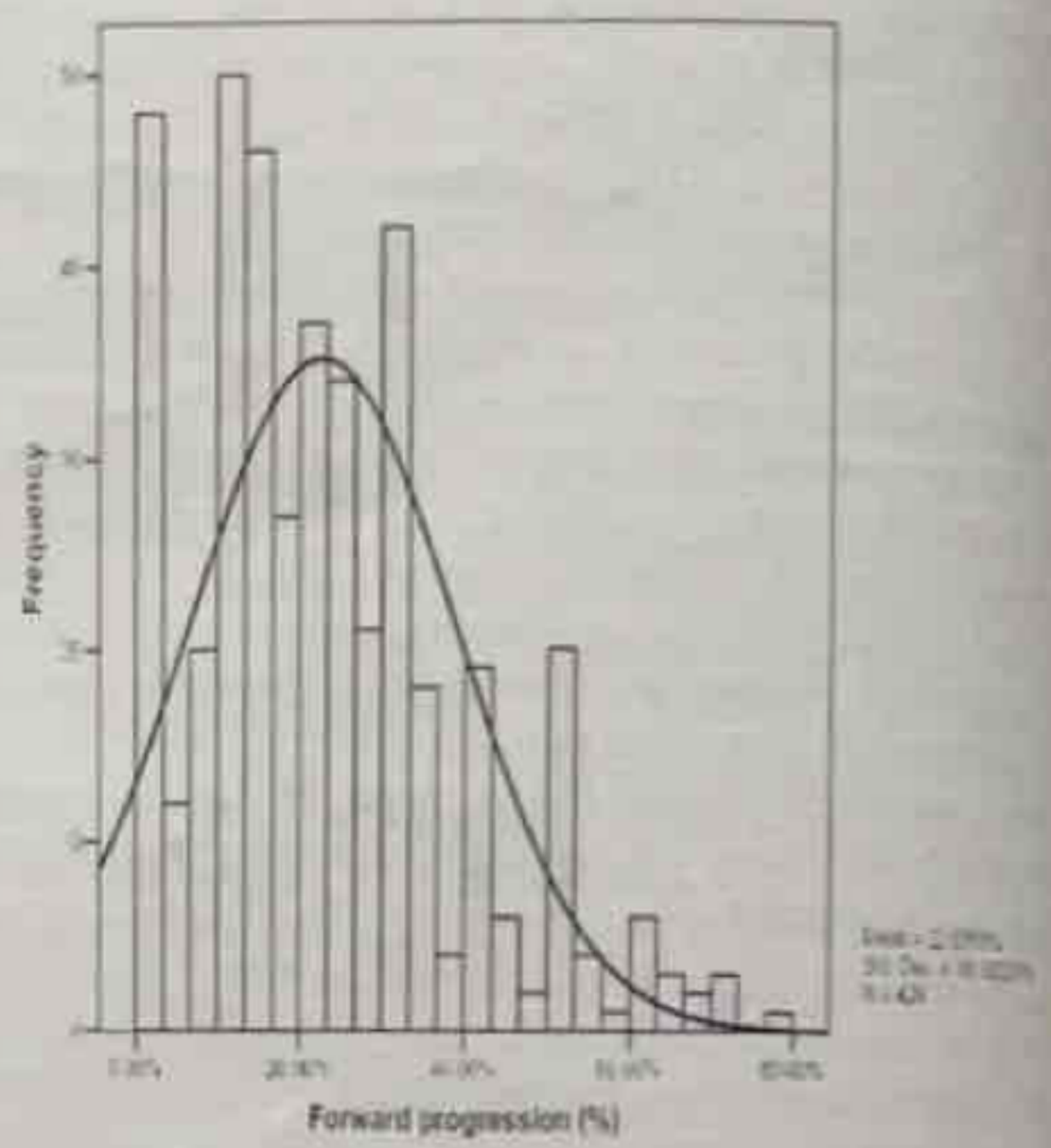

Figure 8. Distribution of percent forward progression (Raw Sample).

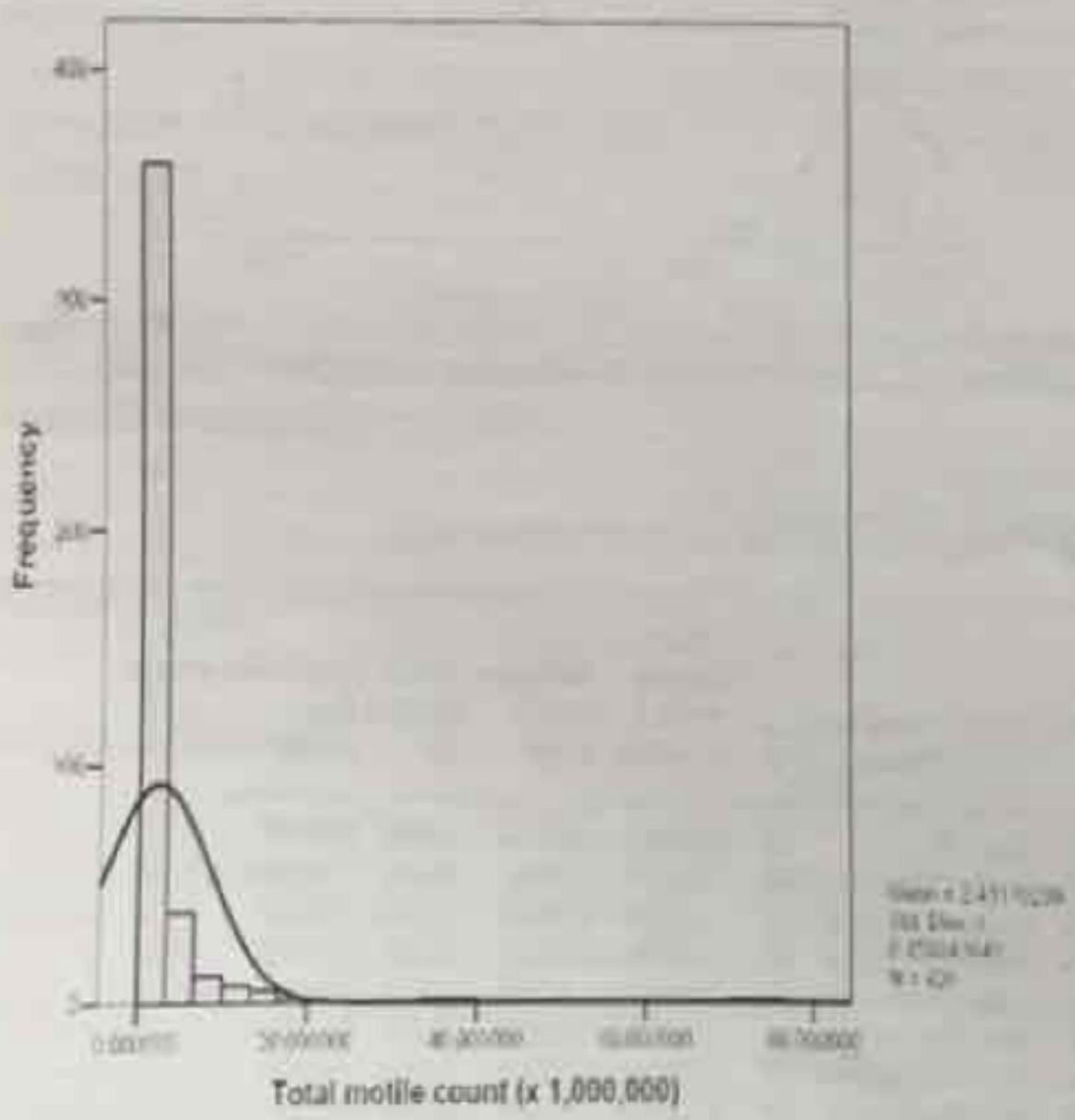

Figure 7. Distribution of total motile count (Raw Sample).

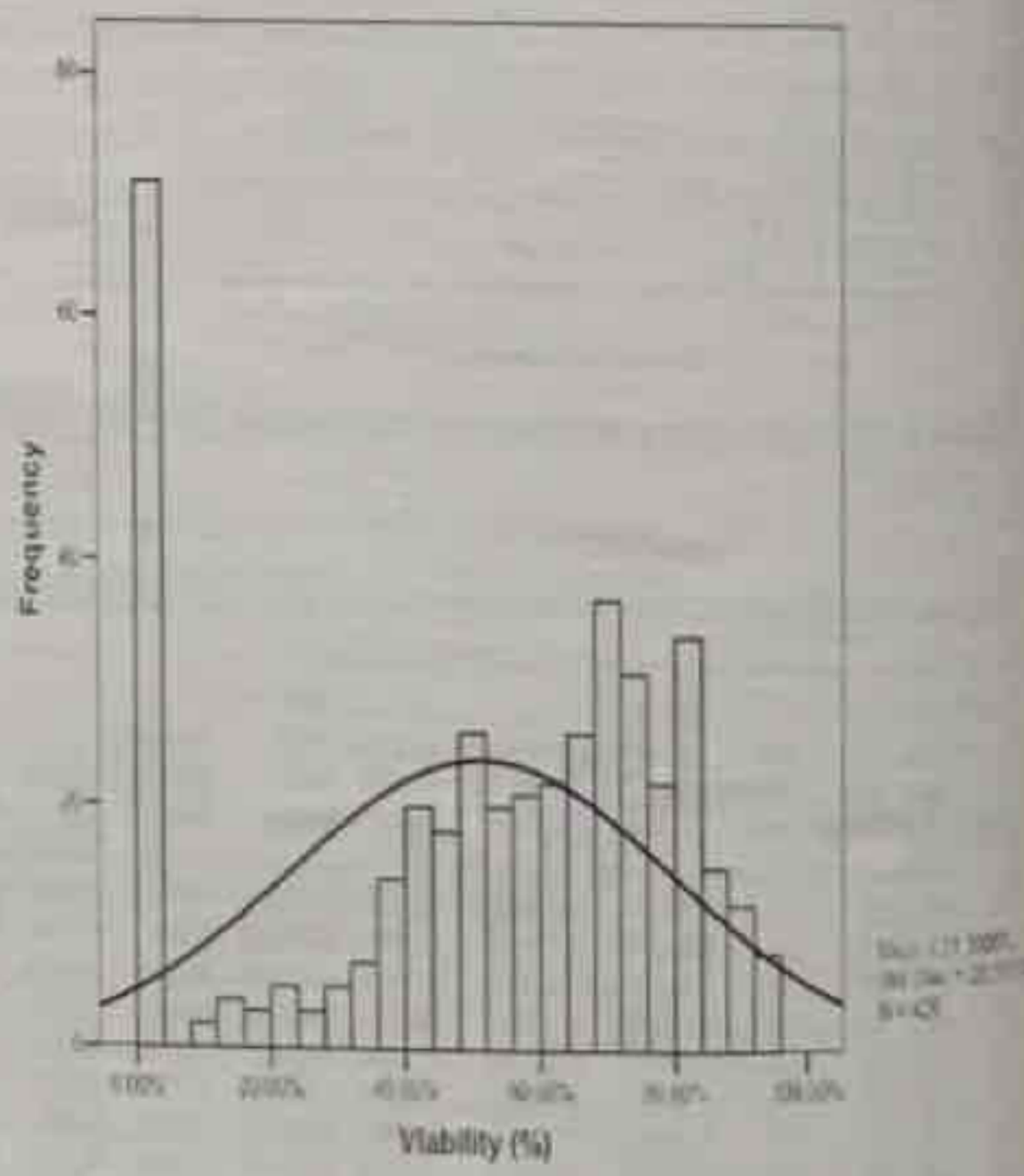

Figure 9. Distribution of percent viability (Raw Sample).

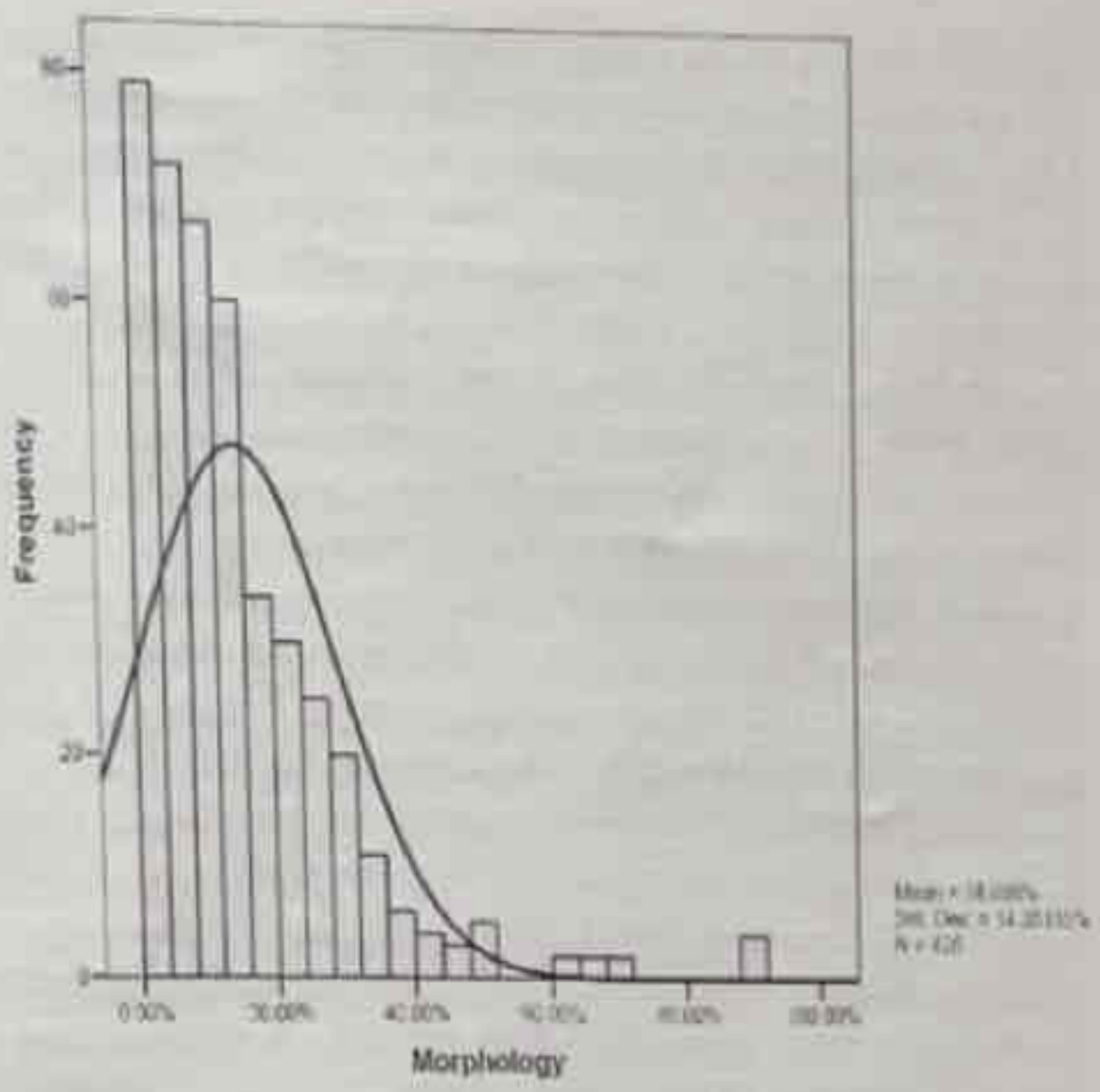

Figure 10. Distribution of percent normal morphology (Raw Sample).

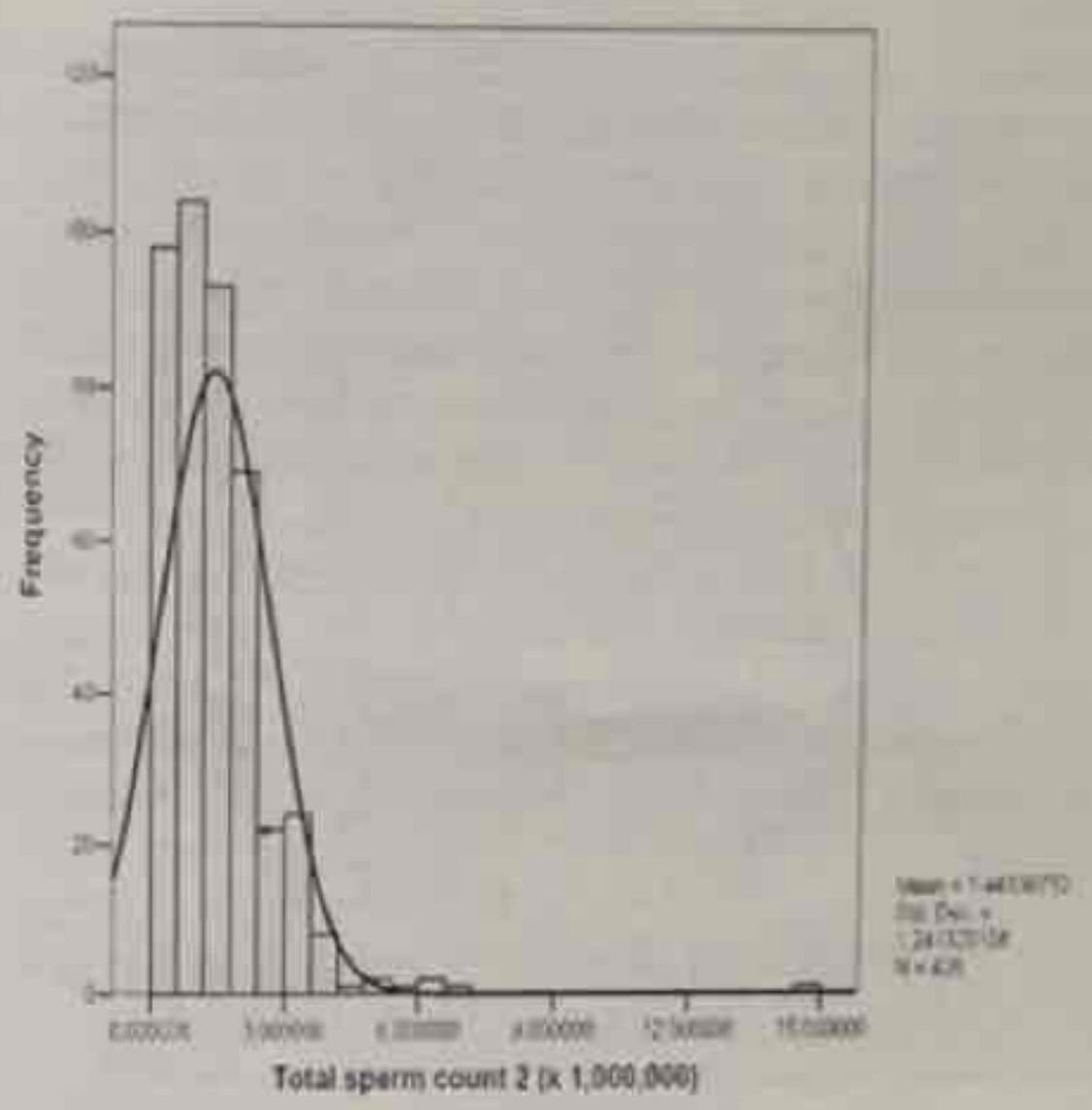

Figure 12. Distribution of total sperm count (Processed Sample).

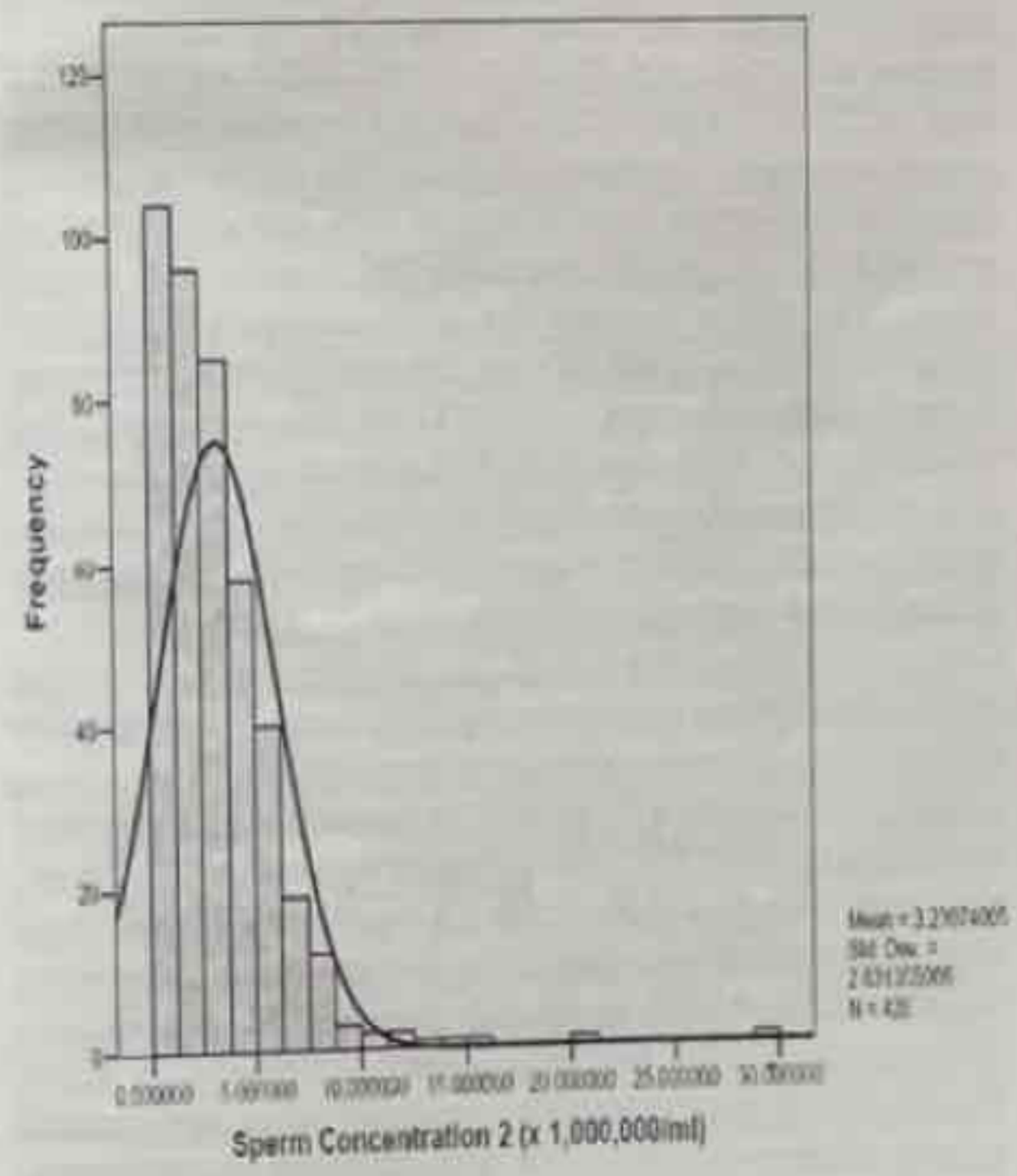

Figure 11. Distribution of sperm concentration (Processed Sample).

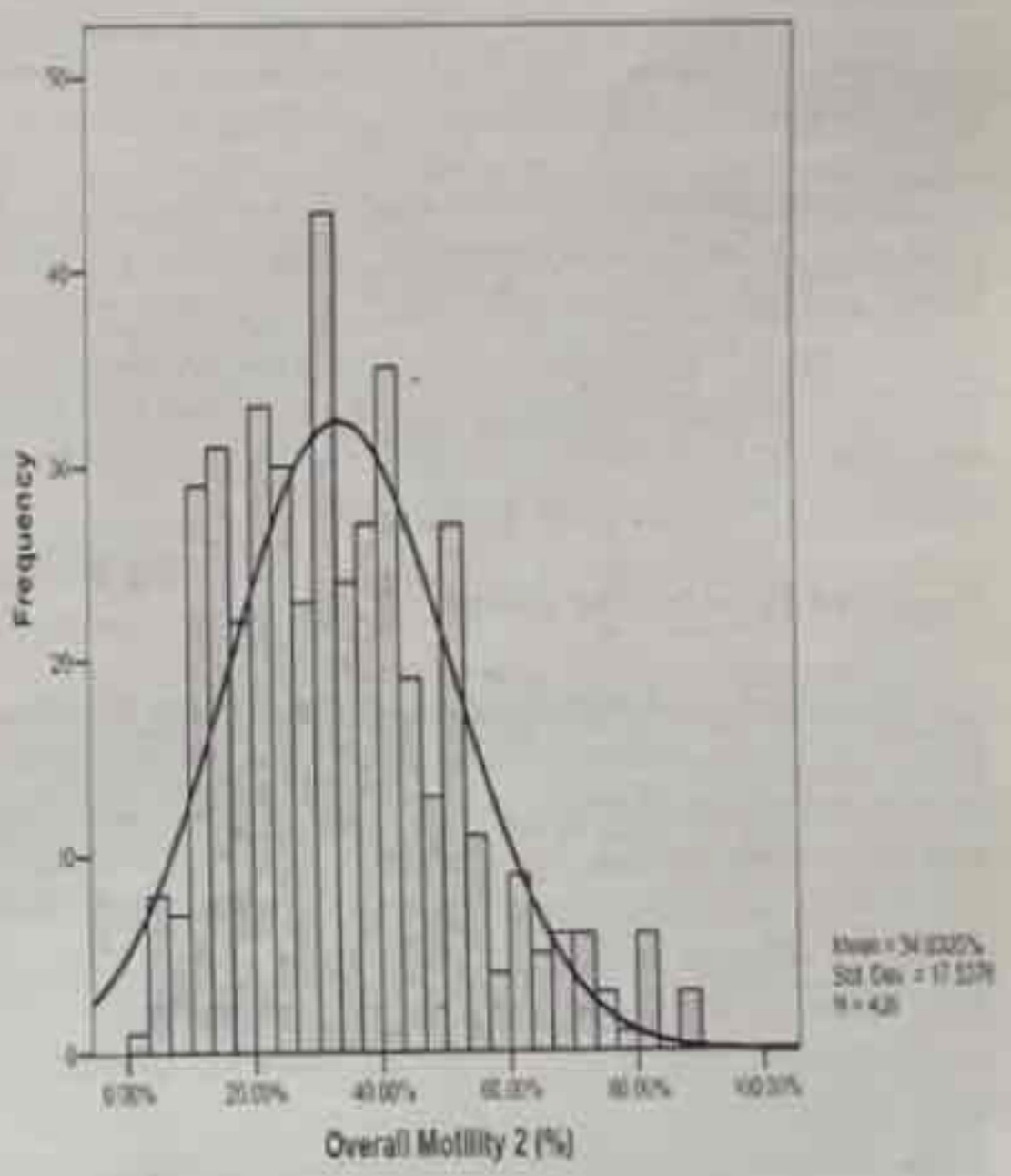

Figure 13. Distribution of processed total motile count (Processed Sample).

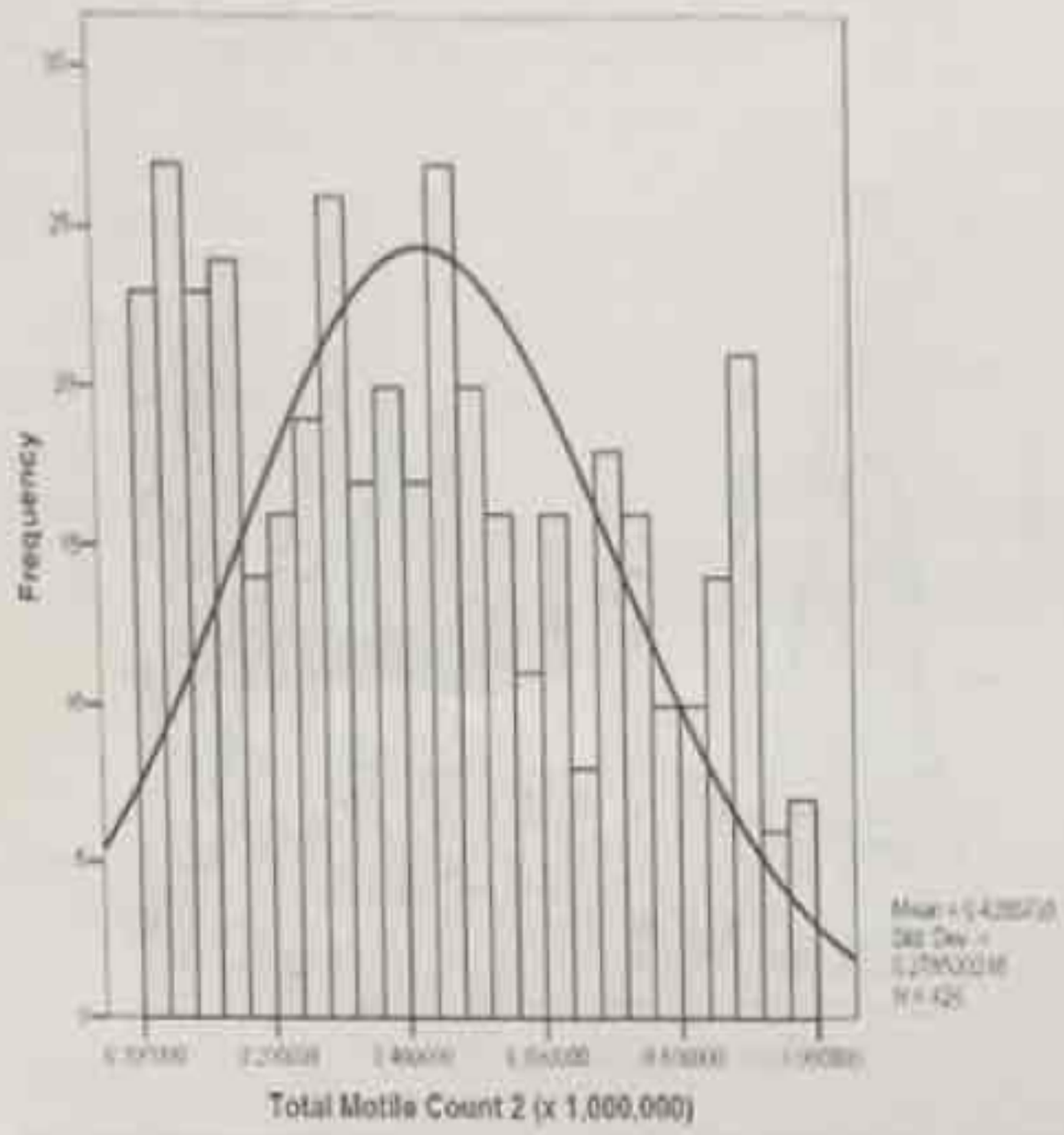

Figure 14. Distribution of percent forward progression (Processed Sample).

Discussion

Over-all Pregnancy Rate

Intrauterine insemination has been proposed for a long time as first line treatment for male factor, cervical factor and unexplained infertility[10]. In relation to this, studies have already been conducted to evaluate the predictive value of various semen parameters as well as to determine the threshold values for these parameters below which, IUI will no longer be effective.

Processed Total Motile Count

Processed total motile count has been proven to be a good prognostic indicator for the success of IUI. It has the unique capability of reflecting both sperm concentration and motility as well as the effects of semen processing.[12] The lowest threshold value recorded for a successful IUI was 0.3 x 10^6 and this was in the study of Byrd, et al. in 1987. One decade later, Berg, et al. in a similar study, concluded that there is still a realistic chance for conception with insemination, if more than or equal to 0.80 x 10^6 motile sperms are available.[11] The lowest value for which pregnancy was documented in the present study was a total sperm count of 0.55 x 10^6 and processed total motile count of 0.055 x 10^6.

The exact cut-off value for defining severe male factor has varied from study to study. Threshold value of about 1.0 x 10^6 motile sperm in the inseminate have been reported in several studies[14]. This threshold value was used in this study because most authors agree on this minimum value and recommend IVF when this value is lower.[13]

In the center studied, from January 2005 to June 2009, there were a total of 4, 153 sperm washing and IUI procedures done. Of these, 428 were with inseminates containing 1.0 x 10^6 and less total motile sperm count, making up approximately 10 percent of the total procedures. Results of this study revealed an over-all pregnancy rate of 2.4%, pregnancy rate per couple of 3.3% and live birth rate of 1.6%. These results were in contrast to that of previous studies wherein no pregnancy was documented at counts < 1.0 x 10^6[7] or even at counts < 5.0 x 10^6[5]. On the other hand, these results are comparable with the results of other authors. Campana, et al. (1996) in a study that evaluated the results of intrauterine insemination based on woman's age, sperm quality and total sperm count per insemination, reported a pregnancy rate of 1.8% for PTMC of < 0.5 x 10^6 and a pregnancy rate of 2.6% for PTMC between 0.5 x 10^6 and 1.0 x 10^6[2]. In the said study, all pregnancies were among female subjects who are < 39 years old. Berg, et al. (1997) reported an over-all pregnancy rate of 1.0% for PTMC of 0.8 x 10^6. Above this threshold, however, pregnancy rate markedly improved to 8.2 % (PTMC count 0.8 – 1.2 x 10^6) and reached a plateau of 6.9% - 10.2% (PTMC 1.2 x 10^6 - ≥ 8.0 x 10^6) with only a minor tendency for increase with higher sperm numbers.[11] In more recent studies, higher pregnancy rates of 3.13% per cycle[13] and 6.4 % per cycle[9] were reported. In this study, the mean processed total motile count was lower among the group with documented pregnancies (0.32 x 10^6, SD = 0.26) compared to the group without pregnancy (0.43 x 10^6, SD = 0.28). Analyzing the results of the other semen parameters in relation to this, (Table 2) the mean percent over-all motility as well as the mean percent forward progression was higher among the group with pregnancies (OM = 36.5 %, FP = 38.6 % vs. OM = 33.97 %, FP = 37.25 %). However, after semen processing, similar improvements were seen in both groups (Table 2). Postprocessing sperm motility and sperm progression did not differ much in patients who conceived and in those who did not. In other words, in this study, although sperm motility and forward progression were improved with semen processing, occurrence of pregnancy is not associated with motility in postprocessed specimen. This contradicts the findings in previous studies in which the degree of sperm motility attained after appropriate semen processing has been identified as an important factor that contributes to the success of IUI[3]. The difference lies in the fact, that among the subjects who had successful

pregnancies in the studies mentioned, postprocessing values obtained, for percent overall motility were above the reference range for normality. No pregnancies were obtained among couples in which the males displayed severe asthenozoospermia or a combination of oligoasthenozoospermia. In this study, although levels appeared improved after semen processing, values obtained were still below the reference range set and are still categorized as being asthenozoospermic.

In this study, 2 conceptions resulted from PTMC of 0.055 x 10^6 and 0.073 x 10^6. These levels are way below the threshold values set for successful IUI procedures. It has been suggested, that in intrauterine insemination involving donor sperm, 1-2 percent of presumed pregnancies are the result of the husband's sperm[20]. In the institution studied, all inseminated sperms were from respective male partners. No restrictions were given to the couple with regard to sexual intercourse after IUI such that any pregnancy that may have resulted could have some form of contribution from it.

Percent Normal Morphology

Different studies present different evidences regarding the role of sperm morphology in predicting success with IUI. Earlier studies by Karabinus, et al., in 1997 and Dickey, et al., in 1999 found no relation between sperm morphology and IUI outcome.[5,16] However, in more recent studies, percent normal morphology, appears to be the best indicator of male infertility. The use of this semen parameter, however, is limited by the large number of classification systems that are being used by different andrology laboratories, the subjective nature by which it is examined and the lack of a uniform threshold value by which IUI would still be considered acceptable.[17] Also, many andrology laboratory do not routinely examine sperm morphology at the time of semen processing. In this study , data on these were gathered from previous semen analysis results. The limitation here lies on the fact that semen quality varies from ejaculate to ejaculate. Thus, it may be misleading to draw inferences pertaining to morphology when the data available do not pertain to the actual specimens used for insemination. To minimize on this particular restriction, we used the average value from all the semen analysis results done previously for every male subject. To get a more representative data on morphology for each patient, most clinicians usually request for at least two semen analysis and get the average of all available results. During the interpretation of subsequent semen processing data, since percent normal morphology is no longer determined, the clinician typically refers back to the initial semen analysis for this information.

Universally, the most common classification system used to classify sperm morphology for the purpose of intrauterine insemination is the World Health Organization (WHO) (1987, 1992) criteria. In this study, the andrology laboratory used this classification system. From the data collected, the recorded mean percent normal morphology in the group with documented pregnancy and the group without pregnancy were all below the WHO (1987) reference value. However, the mean value among the group with pregnancy (20.30%, SD = 11.39) was higher than those without pregnancy (14.47%, SD = 14.39). From these results, it appears that insemination of a low number of spermatozoa may be compensated for by improved sperm quality in terms of sperm morphology.

Age of Female Partner and Severe Oligospermia

When combining the effect of age and the processed total motile sperm count at insemination, it appears that in males with severe oligospermia, the age of the female partner becomes a significant predictive factor in the success of IUI. As expected, increasing female age results in reduced chances at pregnancy[14] because of reduced oocyte quality and age-related impairment in uterine receptivity. Pregnancy was only observed if the female partner is younger than 35 years old in the study by Badawy, et al. (2009) and in < 39 years old in the study by Campana, et al. (1996)[7,18] Many authors therefore suggest that if a woman is older than 38 years, she should begin directly with IVF and ICSI. In this study, although a pregnancy was documented in a 41 year old female, the mean age of the female partner with pregnancy (33.29 years, SD = 4.79) was within the < 35 years age limit. The mean age among the female subjects who had conceptions was lower than the mean age of the female partner without pregnancy (33.29 years, SD = 4.79 vs. 34.32 years, SD = 5.13). This is compatible with the results of the two previous studies.

No conclusions, however, could be drawn on the effect of age on pregnancy in this study since the mean age of the group with pregnancies is comparable to the mean age of the group who did not have pregnancies.

Ovulation Induction and Severe Oligospermia

All female subjects included in the present study underwent some form of ovarian stimulation using either clomiphene citrate (CC) only or in combination with recombinant follicle stimulating hormone (rFSH). This is based on the premise that controlled ovarian stimulation improves the success rates of IUI linearly, when more

than one follicle could be induced to develop into maturity.[17] However, in cases of IUI with severe male factor infertility, this may not be applicable. It has been mentioned that for conception to occur either with sexual intercourse or even with intrauterine insemination, a substantial number of normal sperms must be able to reach the fallopian tube where fertilization will occur. With severe oligospermia, this may not be possible, such that even with multifollicular cycles, pregnancy may not take place. In the present study, despite various ovarian stimulation protocols, the over-all pregnancy rate as well as the live birth rate was very low. This is in agreement with the findings of Cohlen, et al. (1998), that in couples with moderate to severe male factor infertility (processed total motile count of < 10.0 x 10^6), the use of ovarian stimulation does not improve IUI outcome.[22]

Semen Processing in Severe Oligospermia

The type of semen processing procedure and its suitability is critical in the final quality of the inseminates. In this study, 94.6% (403/426) of the raw samples were with moderate to severe oligospermia (SC_t < 10.0 x 10^6). Also some form of asthenospermia was observed in 84. 3% (359/426). In the present study, gradient processing and fiberwool filtration technique were used among the majority of specimens both in the group with pregnancies and the group without pregnancy. Straight wash was only resorted to among specimens in which the initial semen quality was very poor in order to obtain the maximum processed motile sperm count. As mentioned, this procedure is not very ideal, because the final inseminates would still contain dead and abnormal sperms admixed with the normal ones. Swim-up procedure, traditionally is the most simple washing technique which gives a yield of highly motile spermatozoa[19]. However, this is good if you're working with normal semen samples containing large concentrations of highly motile sperms. In the present study, the swim-up technique was used only for appropriate samples and in those with concomitant pyospermia.

There is very little evidence in literature that would support the superiority of any sperm preparation technique in intrauterine insemination. The same is true with the results of this study. Choosing an appropriate sperm preparation method largely depends on the quality of the raw semen samples and to a lesser extent on the clinical experiences of each particular laboratory in handling different forms of semen impairments.

Spontaneous Pregnancy Rates

The issue now is whether or not the pregnancy rate obtained in this series of patients is acceptable and would justify doing intrauterine insemination among couples using inseminates containing 1.0 x 10^6 or less of motile sperms. In vivo conception requires successful penetration of the male partner's sperm through the cervical mucus and successful arrival at the ampullary segment of the fallopian tube where fertilization occurs.[23] However, the minimum sperm count required for in vivo fertilization is still not known. In a study by Sripada, et al. (2009) on the relationship between semen parameters and spontaneous pregnancy, sperm concentration was not found to be a significant predictor of pregnancy.[24] However, male factor infertility was found to be more prevalent among the couples who did not get pregnant. In a two-year follow-up study conducted by Matorras, et al. (1996) among couples waiting for artificial insemination by a donor because of severe male factor infertility, the reported spontaneous pregnancy rate was 6.5 % (3/46) in the group with total motile sperm count of 0.1 x 10^6 – 1.0 x 10^6.[25] In a similar study by Almagor M, et al. (2001) of male spouses with sperm counts and motility of < 1.0 x 10^6 and < 30% respectively, the spontaneous pregnancy rate was 5.9% (5/85 couples).[25] All the subjects in the previous studies did not receive any medications for fertility and had no surgical treatments. A repeat analysis of the semen parameters after the natural conception was established did not show any significant changes from the previous evaluations. In both studies, there was note of a trend towards a more favorable outcome among couples who are younger (mean age for females, 29.7 years and mean age for males, 34.2), and with shorter subfertility duration. Compared with the over-all pregnancy rate obtained in our series of patients (2.4 %), the spontaneous pregnancy rates in the two previous studies appear more acceptable. In this study, we tried to obtain the spontaneous pregnancy rates among the couples who did not get pregnant during their IUI cycle treatments. Out of the 297, 8 had documented spontaneous pregnancies during the 5 year follow-up period (Table 4). This gives a spontaneous pregnancy rate per couple of 2.7 percent which is comparable with the pregnancy rate obtained by doing intrauterine insemination. Mean age of the female partners was 30.4 years, younger than those who got pregnant with intrauterine insemination. The mean age of the male partners on the other hand, is 36.6 years. This is comparable to the mean age level of the male partners of couples with pregnancy after IUI.

There are no means to determine whether the pregnancies that resulted from IUI in the present study could have some form of contribution from acts of sexual intercourse done before and after the procedure. It can only be inferred that this could be possible because of the comparable number of patients who eventually got pregnant after discontinuation of treatment.

Semen Parameters (Raw and Processed Samples) in Males with Severe Male Factor Infertility

A summary of the semen parameters of both raw and processed samples is presented in Table 2. There is a uniform trend towards improvement in all of the parameters studied after appropriate semen processing. However, even with these improvements, all values, with the exception of forward progression (Over-all: 22.68 % vs 37.29 %), were still below the WHO (1987) standards for normal. These results are major contributors to the very low pregnancy rates obtained in this sub-group of infertile couples. As expected, severe oligospermia is usually associated with some form of asthenospermia and teratozoospermia. Recent studies suggest a deleterious multiplicative effect on the pregnancy outcome in the presence of more than one defective parameter compared to isolated oligospermia alone[25]. This makes it more not feasible to obtain a significant number of spermatozoa that could effectively result in a pregnancy.

Conclusion

Among the different semen parameters analyzed, it is the percent normal morphology which was notably higher in the group with documented pregnancy compared to those without. However, data on the actual inseminates, if made available, could have been used more reliably to correlate with the pregnancies obtained in this study.

Based on the IUI data presented, it appears that the pregnancy rate after insemination in couples with severe male factor infertility is not negligible and is still possible even with processed total motile count of $< 0.10 \times 10^6$. However, this chance is very low (2.4%) and is comparable to the spontaneous pregnancy rate obtained (2.7%). It may not be prudent at all, to let these patients undergo standard IUI procedures, with the additional physical and emotional burden and related cumulative medical costs, despite having minimal chances of success. Even the improvement in the different semen parameters that were observed after semen processing, failed to result in a more acceptable pregnancy rate. These data should guide clinicians in their decision making as regards doing intrauterine insemination in this sub-group of infertile couples and steer them towards the more appropriate IVF-ICSI procedure.

Recommendations

The present study has several limitations and these would constitute the authors' recommendations for future investigations. It has been an established fact that the success of intrauterine insemination does not depend only on the processed total motile count but on a lot of other factors. These include the presence of any concomitant female factor infertility, the number of years of infertility/ subfertility, previous reproductive outcome of the female and the number of attempted cycles at insemination. These factors were not taken into account in this study because of the paucity of patient data available in the database of the andrology laboratory and the limited access to the patients' records in the clinics. It is recommended that andrology laboratories and assisted reproductive technique centers should include these into their database. These are important considerations in the evaluation of their present systems and will aid future researches.

Similar controlled prospective studies may benefit from the determination of the percent normal morphology on the actual inseminates. This would make any inferences with regard its effect on the success of pregnancy with IUI more valid.

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