

Pregnancy Rates and Sperm Parameters of Infertile Filipino Men With and Without Varicoceles*

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Objectives: To report and compare the pregnancy rates and sperm parameters of infertile Filipino men with and without varicoceles in an infertility clinic.

Materials and Methods: Charts of couples consulting in an infertility clinic from 2008 to 2015 were reviewed. After applying the inclusion/exclusion criteria, a total of 135 infertile men were included in the final analysis (mean age = 33.6 ± 5.7 , range = [25, 58]). Sperm parameters (motility and sperm count) were categorized as "abnormal" if they were below the lower reference limit based on WHO 1999 criteria. Presence of varicocele was noted along with type of management. Pregnancy rate was the main outcome measure.

Results: Prevalence of varicocele for the entire sample was 24.4%, with pregnancy rate of 15.2% after conservative treatment. Subjects without varicocele had 2.5 times higher chances of pregnancy than subjects with varicocele who underwent conservative treatment. For subjects with normal sperm parameters, pregnancy rates of men with varicocele versus without varicocele were not significantly different. However, among subjects with abnormal sperm parameters, pregnancy rate was significantly lower for those with varicocele. Baseline sperm motility, sperm count and total motile sperm count (TMSC) of men with varicocele were significantly lower than those without varicocele. After varicocele repair, sperm count and TMSC significantly increased but no significant difference was observed in terms of motility. Pregnancy rate after varicocelectomy was 26.3%, but with no significant difference noted between men with normal sperm parameters versus abnormal sperm parameters at baseline. Pregnancy rate after conservative management of infertile men without varicocele was not significantly different from the pregnancy rate after varicocelectomy.

Conclusion: Infertile Filipino men who have normal and abnormal sperm parameters may have varicocele. Gynecologists and infertility specialists should suspect varicocele for unexplained male infertility with normal sperm parameters. Infertile Filipino men with varicocele and without varicocele benefited from conservative treatment. Varicocelectomy significantly improved the sperm parameters in terms of sperm count and total motile sperm count. Varicocelectomy showed similar beneficial effect as with treatment for other cause-specific treatment of male infertility.

Key words: varicocele, male infertility, varicocelectomy

Introduction

Varicocele is an abnormal dilatation of the veins of the pampiniform plexus in the spermatic

cord, it occurs predominantly on the left side but isolated right-sided and bilateral are also seen.¹ Incompetent or inadequate valves within the veins along the spermatic cord cause a varicocele. The abnormal valves obstruct normal blood flow causing a backup of blood, resulting in enlargement of the veins.² Despite the several different theories that aim to explain the impact of varicocele on

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testicular function, none can fully clarify the variable effects of varicocele on human spermatogenesis and male fertility.³ Proposed mechanisms include hypoxia and stasis, testicular venous hypertension, autoimmunity, elevated testicular temperature, reflux of adrenal catecholamines, and increased oxidative stress.⁴

A variety of vitamins, nutritional supplements and anti-inflammatory agents have been used in the empirical therapy of male infertility. However, with few exceptions, none of these therapies has been shown to be effective in repeated controlled studies.⁵

Varicocelectomy is a surgery for the relief of a varicocele by ligation and excision and by ligation of the dilated veins. It is used to correct varicoceles and is speculated to reverse the adverse effects to testicular function. However, controversy still remains regarding the benefit of varicocele repair to improve male fertility. Evidences exist both in favor and against it.³ Decision analysis-based comparisons of assisted reproductive technology (ART) and varicocelectomy suggest that varicocele repair is more cost-effective than the use of ART in men with impaired semen parameters.^{6,7}

We present a retrospective study on sperm parameters of infertile Filipino men with and without varicocele and pregnancy rates after treatment. Pregnancy outcome is the true measure of the effectiveness of a treatment for male infertility. Findings of this research would have implications on the counseling and management of infertile male by gynecologists and fertility specialists.

Objectives

General

To report and compare the pregnancy rates and sperm parameters of a group of infertile Filipino men with and without varicoceles in an infertility clinic

Specific

1. To describe the sperm parameters of this group of infertile Filipino men in terms of motility, sperm count and total motile sperm count.

2. To determine the overall prevalence of varicocele in this group of infertile Filipino men
3. To compare the prevalence of varicocele among subjects with normal versus abnormal sperm parameters
4. To compare the pregnancy rates after conservative treatment of the male partner:
 - 4.1 with normal sperm parameters: with varicocele versus without varicocele
 - 4.2 with abnormal sperm parameters: with varicocele versus without varicocele
 - 4.3 with varicocele versus without varicocele regardless of sperm parameters
5. To compare the baseline sperm parameters and total motile sperm count (TMSC) among the subjects, with varicocele versus without varicocele
6. To compare the sperm parameters and total motile sperm count (TMSC) before and after varicocelectomy
7. To determine the pregnancy rate following varicocelectomy of male partner with normal and abnormal sperm parameters
8. To compare the pregnancy rate between subjects who underwent varicocelectomy versus subjects without varicocele

Materials and Methods

Study Design

This study used a cross-sectional analytic study design.

Participants

A total of 135 infertile Filipino men consulting in an infertility clinic were included in this study (mean age = 33.6 + 5.7, range = [25, 58]). Excluded were men with azoospermia and men with female

partner with age ≥ 40 year old, with suspected or documented bilateral tubal obstruction, with severe pelvic endometriosis. A total of 135 infertile men remained in the study, grouped into those having normal sperm motility and sperm count and those having abnormal sperm motility and/or sperm count based on WHO 1999 criteria. Subsequently, these men were further subdivided into those having varicocele or not. Furthermore, they were divided into those who underwent varicocelectomy or not. Pregnancy rate and sperm parameters of each subgroup was obtained and compared with each other after conservative and surgical treatment (Figure 1).

Study Procedure

All the data for this study were collected through patient chart review.

The following data were extracted by the researcher from the patient charts using a structured data extraction template in Microsoft Excel:

- Female factors
 - o age
 - o anovulatory/ovulatory with or without drugs
 - o presence/absence of one or bilateral tubal obstruction and
 - o presence of severe pelvic endometriosis
 - o gravidity and parity upon consultation
 - o pregnancy outcome after conservative treatment of male partner
 - o pregnancy outcome after surgical treatment of male partner when applicable
- Male factors
 - o age
 - o nationality
 - o presence and absence of varicocele of male partner by scrotal ultrasound and Doppler velocimetry
 - o whether the male partner underwent varicocelectomy or not

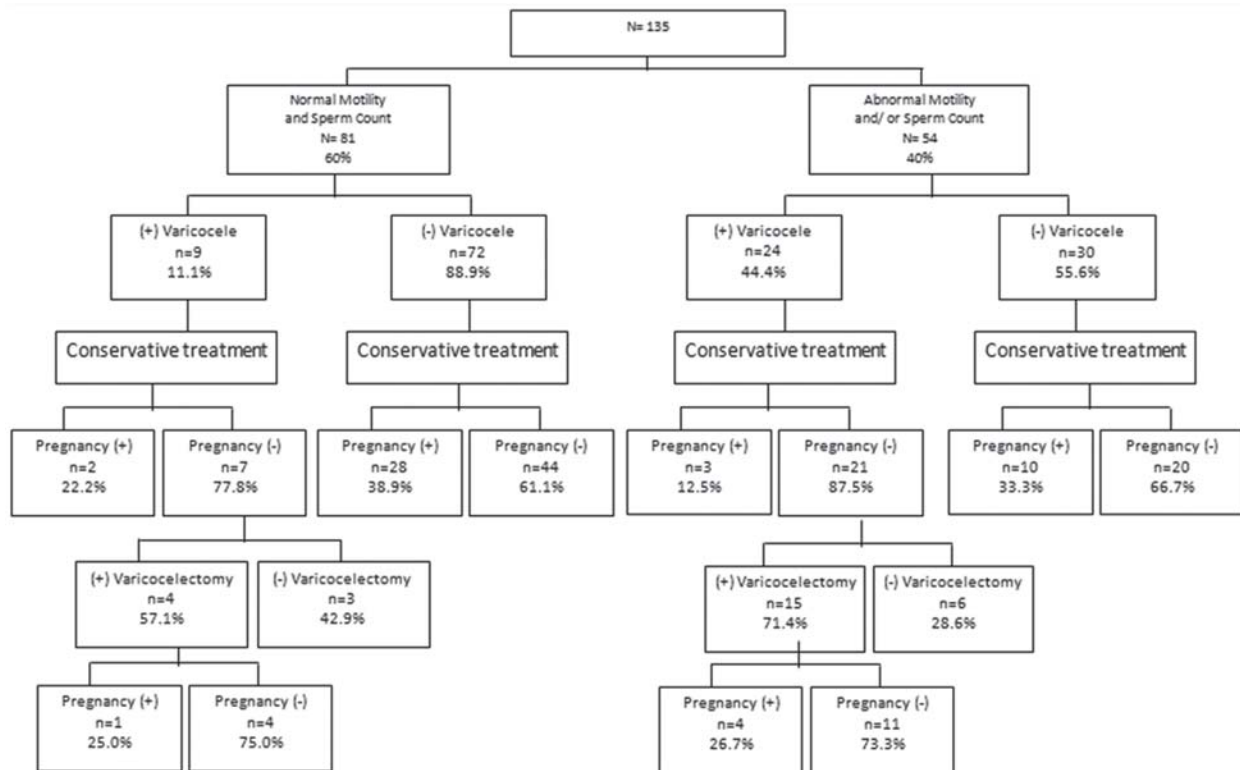


Figure 1. Algorithm on division of subjects

- o sperm parameters, particularly, sperm count and motility (total % motile spermatozoa) before and after surgery when applicable. These data were based on semen analysis conducted in three (3) laboratories.
 - Normal: \geq Lower Reference Limits based on WHO 1999 Criteria
 - Abnormal: $<$ Lower Reference Limits based on WHO 1999 Criteria

Data Analysis

- Descriptive statistics:
 - Frequency and percent distributions for categorical data
 - Mean \pm standard deviation for normally distributed numerical data
 - Median for non-normally distributed numerical data
- Chi-square and z tests for differences in proportions
- Independent t-test or Mann Whitney test for differences in means / medians
- P-values less than 0.05 were considered significant
- All statistical procedures performed using Stata IC version 13

Results

Out of 135 men in this study, 54 (40%) had at least one sperm parameter less than the lower reference limit (LRL) of WHO 1999 criteria (total motile sperm count (TMSC) median = 6%) (Figure 2). While 81 (60%) had sperm parameters more than or equal to the LRL (TMSC median = 33%) (Figure 2). Out of 135 men, 33 had varicocele giving a prevalence of 24.4% (Figure 3) with a median TMSC of 14.86 (Figure 8). After conservative treatment, pregnancy rate of this group regardless of sperm parameters is 15.2%, while the pregnancy rate of men without varicocele is 37.3%. The chance of pregnancy in infertile men without

varicocele is 2.5 times higher than men with varicocele after conservative treatment (Figure 6). Out of 54 men with abnormal sperm parameters, 24 had varicocele giving a prevalence of 44.4% (TMSC median=6%) while out of 81 men with normal sperm parameters, 9 had varicocele giving a prevalence of 11.1% (TMSC median=34%) (Figure 3)

Out of 9 men with normal sperm parameters but with varicocele, 2 had a positive pregnancy test (TMSC median=31%) after conservative treatment giving a pregnancy rate of 22.2% (Figure 4).

Out of 72 men with normal sperm parameters and without varicocele, 28 had a positive pregnancy test (TMSC median=40%) after conservative treatment giving a pregnancy rate of 38.9% (Figure 4).

Pregnancy rate of men with normal sperm parameters but with varicocele is not significantly different from the pregnancy rate of men with normal sperm parameters and without varicocele (p -value = 0.329) (Figure 4).

Out of 24 men with abnormal sperm parameters and with varicocele, 3 had a positive pregnancy test (TMSC median=5%) after conservative treatment giving a pregnancy rate of 12.5% (Figure 5).

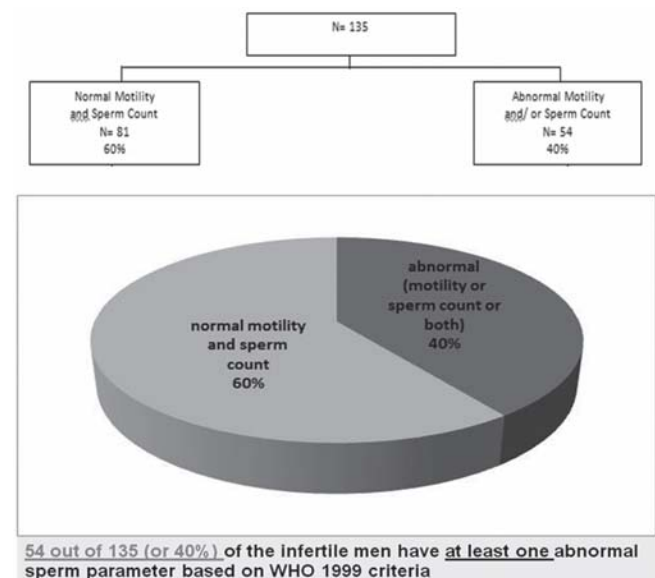


Figure 2. Sperm parameters of a group of infertile Filipino men in terms of motility and sperm count consulting in an infertility clinic from 2008-2015

Prevalence of varicocele among this group of infertile Filipino men with normal and abnormal sperm parameters

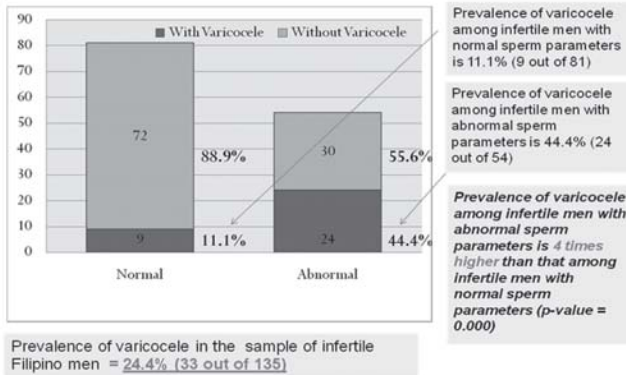


Figure 3. Prevalence of varicocele among this group of infertile Filipino men with normal motility and sperm count and those with abnormal motility and sperm count.

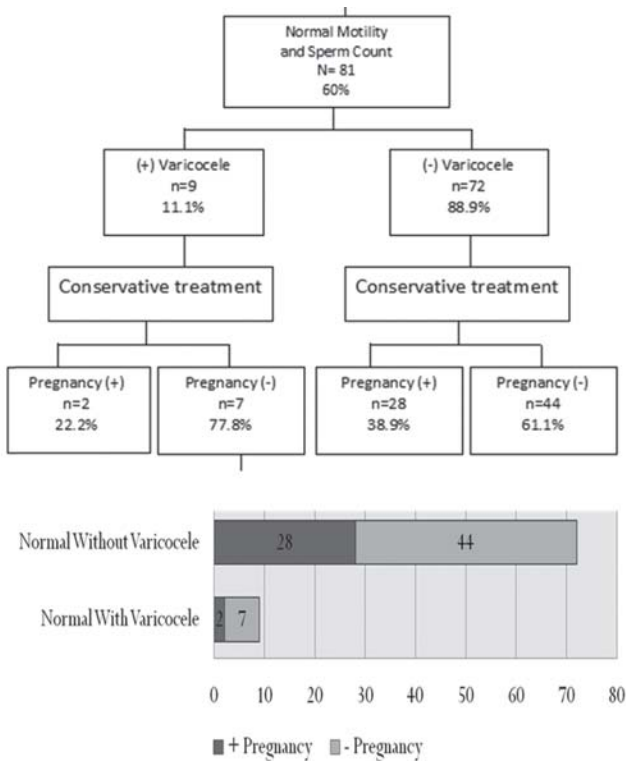


Figure 4. Comparison of pregnancy rate of infertile couples after conservative treatment of male partner with normal sperm parameters with and without varicocele.

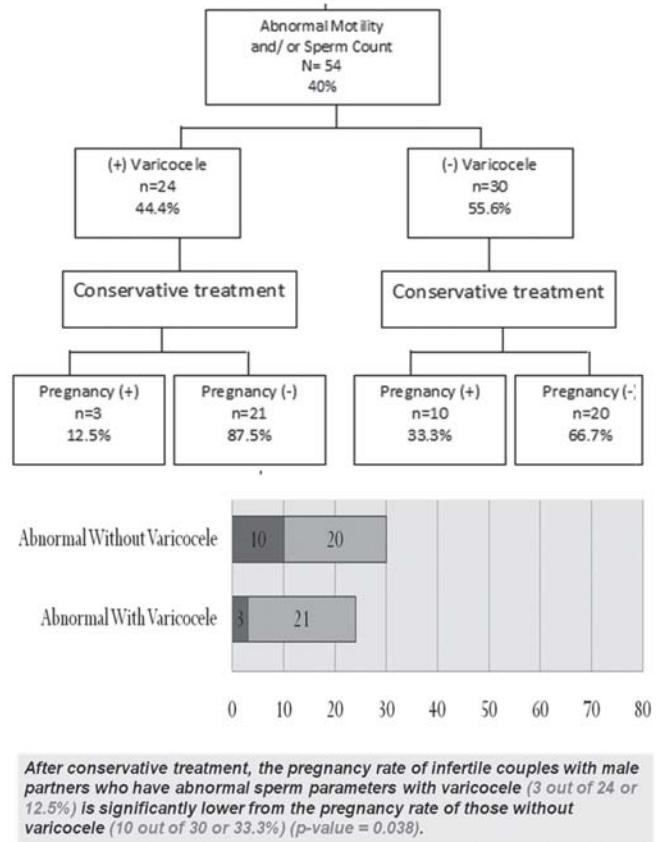


Figure 5. Comparison of pregnancy rate of infertile couples after conservative treatment of male partner with abnormal sperm parameters with and without varicoceles.

Out of 30 men with abnormal sperm parameters but without varicocele, 10 had a positive pregnancy test (TMSC median=10%) after conservative treatment giving a pregnancy rate of 33.3% (Figure 5).

Pregnancy rate of men with abnormal sperm parameters and with varicocele is lower than the pregnancy rate of men with abnormal sperm parameters and without varicocele (P-value= 0.038) (Figure 5).

Baseline sperm parameters of men with varicocele in this group in terms of motility (median 60%) and sperm count (median of 17.8×10^6 /mL) were lower than men without varicocele in terms of motility (median 75%) and sperm count (median of 35.15×10^6 /mL) (P-value = 0.001 and P-value = 0.000, respectively) (Figure 7).

After varicocele repair, sperm count (mean = 38M) and TMSC (mean = 22.6×10^6 /mL) of

infertile men in this group are higher compared with their sperm count (mean = 21.1 x 10⁶/mL) and TMSC (mean=12.4 x 10⁶/mL) before surgery (P-value = 0.008 and P-value = 0.004, respectively). However, no significant difference was observed in terms of motility (Figure 8).

Out of 15 men with varicocele and with abnormal sperm parameters who underwent varicocelectomy, 4 had positive pregnancy test (TMSC median=9%) giving a pregnancy rate of 27% (Figure 9).

Out of 4 men with varicocele but with normal sperm parameters who underwent varicocelectomy, 1 had positive pregnancy test (TMSC median=20%) giving a pregnancy rate of 25% after varicocele repair (Figure 9).

Pregnancy rate of men with varicocele and with abnormal sperm parameters after surgery is not significantly different from the pregnancy rate of men with varicocele but with normal sperm parameters (P-value = 0.946) (Figure 9).

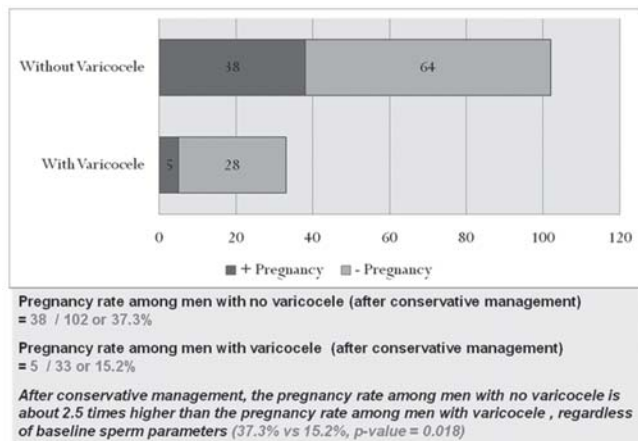
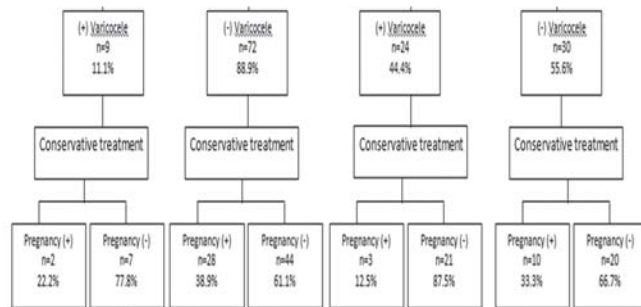


Figure 6. Comparison of pregnancy rate of infertile couples after conservative treatment of male partner with and without varicocele.

Out of 19 men with varicocele who underwent varicocele repair, 5 had positive pregnancy test giving a pregnancy rate of 26.3% regardless of sperm parameters (Figure 10).

Out of 102 men without varicocele regardless of sperm parameters, 38 had positive pregnancy test giving a pregnancy rate of 37.3% after conservative treatment (Figure 10).

Pregnancy rate of men with varicocele who underwent surgery regardless of sperm parameters is not significantly different from the pregnancy rate of men without varicocele given cause-specific treatment (p-value = 0.360) (Figure 10).

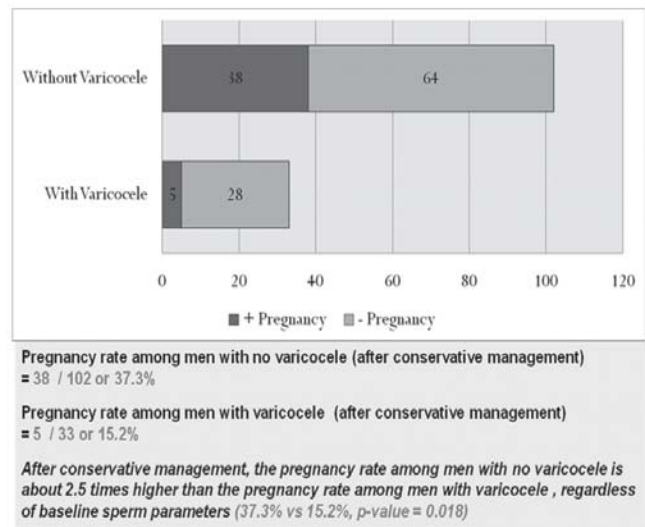
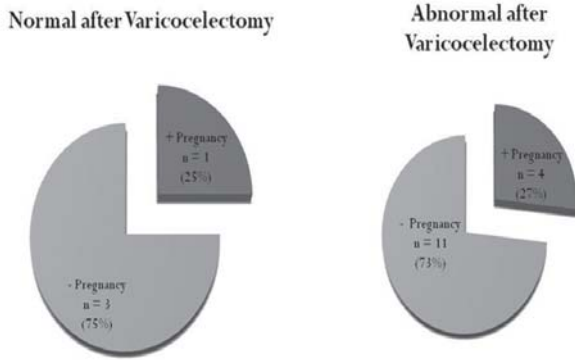


Figure 7. Comparison of baseline sperm parameters and total motile sperm count (TMSC) of this group of infertile Filipino men with and without varicocele.

	N	Mean	Std. Deviation	p-value
Motility (before)	12	50.4%	18.5	
Motility (after)	12	57.9%	19.5	
Sperm count (before)	16	21.1M	21.5	0.008
Sperm count (after)	16	38.0M	29.6	
TMSC (before)	12	12.4	11.4	0.004
TMSC (after)	12	22.6	19.0	

Sperm parameters and total motile sperm count (TMSC) of the infertile Filipino men with varicocele after varicocelectomy were significantly higher but no significant difference in motility.

Figure 8. Comparison of the sperm parameters and total motile sperm count (TMSC) of the infertile Filipino men with varicocele before and after varicocelectomy.

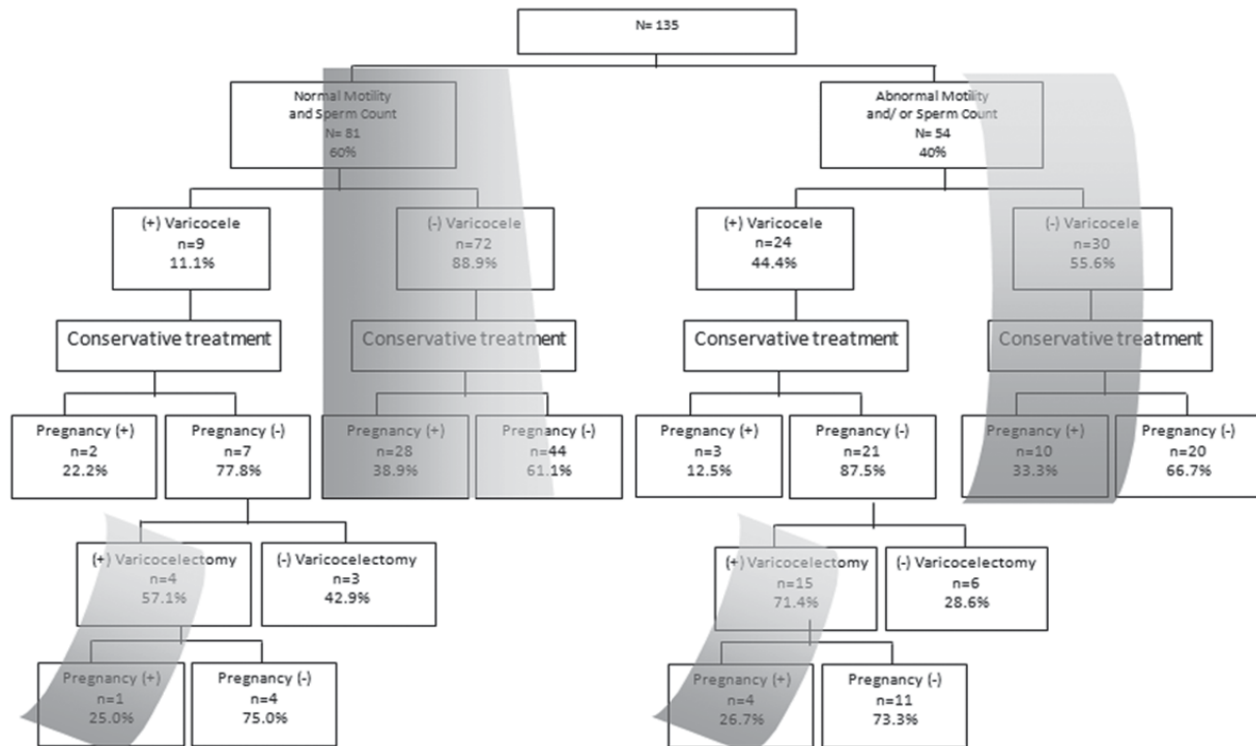


There is no significant difference in the pregnancy rates of infertile couples following varicocelectomy of male partner with normal and abnormal sperm parameters (25% and 27%, respectively; p-value = 0.946).

Figure 9. Pregnancy rates of infertile couples following varicocelectomy of the male partner with normal and abnormal sperm parameters.

Discussion

Infertility is considered one of the main public health issues, as it affects about 15% of the couples of reproductive age. The male factor is involved in 40% - 50% of infertility cases.⁸ One of the major causes of male infertility is varicocele which is 26.4% from a group of 2,383 infertile male who attended a tertiary center for male reproduction.³ Out of 135 infertile men who are included in our study, 24.4% have varicocele and the rest have other causes of male infertility which include infectious, and gonadotoxin exposure. Varicocele is found in 25% of men with abnormal semen analysis¹⁰ but in our study, 24 had varicocele out of 54 infertile men with at least one abnormal sperm parameter, giving a higher prevalence of 44.4% which increased the association on effects



There is no significant difference in the pregnancy rates of infertile couples following varicocelectomy of male partner (5 out of 19 or 26.3%) with the pregnancy rate of those without varicocele after cause specific treatment (38 out of 102 or 37.3%) (P-value = 0.360).

Figure 10. Pregnancy rate of infertile couples following varicocelectomy of male partner with the pregnancy rate of those without varicocele after cause specific treatment.

of varicocele to sperm parameters of infertile men. After a thorough history taking, and series of semen analysis, infertile men underwent conservative treatment. The infertile men who were screened for varicocele with the aid of color Doppler ultrasound (CDU) are those who complained of scrotal pain or discomfort and/or swelling upon lifting heavy objects and/or prolonged standing, with abnormal sperm parameters, with normal sperm parameters not responsive to conservative treatment and unexplained male infertility. CDU is one of the noninvasive modalities and regarded as the best diagnostic tool whenever the physical examination is inconclusive or difficult to perform.³ Infertile men diagnosed with varicocele by this modality will be graded as having subclinical varicocele according to Dubin grading system for varicocele. Pain has been reported to be present in men with varicocele at around 2-10%⁹ but many men who have a varicocele have no symptoms.¹⁰ Among those infertile men who have normal sperm parameters in this study, an 11.1% chance of having varicocele was observed thus not only male with abnormal sperm parameters should be screened for varicocele but also those who have unexplained infertility or with normal sperm parameters not responsive to conservative treatment.

Non Surgical Treatment and Male Infertility

Currently, the etiology of suboptimal semen quality is poorly understood, and many physiological, environmental, and genetic factors, including oxidative stress, have been implicated.¹¹ Known gonadotoxin exposures such as high temperatures, tobacco use and alcohol abuse were avoided by our subjects. Treatment of medical illnesses was managed by specialist.

Non surgical treatments for male infertility can be specific or non specific/empiric. Specific therapies include treatment for genital tract infection, reactive oxygen species, hypogonadotropic hypogonadism, and hyperprolactinemia. Specific therapeutic therapy directed against the etiological cause of infertility

should be attempted. If no specific etiology can be identified, empiric therapy can be introduced in an attempt to improve semen parameters and fertility potential through natural intercourse. Empiric therapies include antiestrogen, aromatase inhibitors, antioxidants, gonadotropin, and gonadotropin releasing hormones.⁵ In this study, infertile men with normal sperm parameters but with varicocele were empirically treated with antioxidants for reactive oxygen species. This resulted to not statistically different pregnancy rate compared to infertile men with normal sperm parameters and without varicocele treated with antioxidant. Our result showed that in men with normal sperm parameters, presence of a varicocele does not adversely affect the outcome of conservative treatment thus implicating that screening for varicocele can be delayed until sufficient time was given.

Infertile men with abnormal sperm parameters with varicocele were empirically treated with antioxidants for reactive oxygen species, antiestrogen and scrotal cooling for varicocele. This resulted to lower pregnancy rate compared to infertile men with abnormal sperm parameter without varicocele treated with antibiotic for leukocytospermia and antioxidant. There is a higher chance of pregnancy after conservative management of men with abnormal sperm parameters but without varicoceles implying the effectivity of cause-specific treatment of male infertility.

All patients with varicocele regardless of sperm parameters benefited from nonsurgical treatment with pregnancy rate of 15.2% implying that surgery can be delayed until at most 6 months since pregnancy was observed in this study after a month to 6 months had passed. This result is strongly in accordance with the recommendation of other authors in the literature that when empiric pharmacologic therapy is going to be used, treatment should last at least 3 to 6 months to incorporate a full 74-day spermatogenic cycle.⁵

Varicocelectomy and Male Infertility

Surgical repair is the gold standard treatment currently accepted for varicocele.³ Our results

showed that sperm count and total motile sperm count after varicocelectomy of this group of infertile men were significantly improved. Surgery benefited the infertile couples with the pregnancy rate of 26.3% regardless of their sperm parameters before surgery. Also our results showed that varicocele repair was comparable to other cause specific treatment of male infertility. In one local retrospective study on the role of varicocelectomy in male factor infertility, they concluded that varicocelectomy improves semen quality in 27 percent of men.¹² However, pregnancy rate was not the scope of their study. However, in a new meta-analysis on varicocele and male factor infertility treatment, the authors reported that there is no conclusive evidence that varicocele repair improves spontaneous pregnancy rates, but improves sperm parameters (count and total and progressive motility), reduces sperm DNA damage and seminal oxidative stress, and improves sperm ultramorphology.¹³

Conclusion

Infertile Filipino men in this group who have normal and abnormal sperm parameters may have varicocele. Gynecologist and infertility specialist should suspect varicocele for unexplained male infertility with normal sperm parameters since many men with varicocele are asymptomatic. Infertile Filipino men with varicocele in this group may benefit from conservative treatment. Varicocelectomy significantly improved the sperm parameters in terms of sperm count and total motile sperm count of this group of infertile Filipino men. After failed conservative treatment of this group of infertile Filipino men with varicocele, pregnancy rate was 26.3% after varicocelectomy. Varicocelectomy as a specific treatment for varicocele showed similar beneficial effect with treatment for other causes of male infertility.

Recommendations

All infertile men with abnormal semen analysis should be screened for varicocele, and all infertile men with unexplained infertility should also be screened for varicocele.

Infertile men with varicocele should be given conservative management because 15.2% will benefit from it.

Men who did not respond to conservative management should be advised to undergo surgery after at most 6 months because 26.3% will benefit from it.

Limitations

WHO 1999 criteria for semen analysis results interpretation was used in this study since cited literatures used the same criteria and semen analysis of the infertile men population were also based on WHO 1999 criteria.

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