Management of Normogonadotropic males with idiopathic infertility with bilateral varicocelectomy with and without intramuscular recombinant FSH and HCG course(s): A twenty-year- experience in a prospective, controlled, and randomized clinical study

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doi: https://doi.org/10.37745/bjmas.2022.0375 Published December 23 2023

Citation: Hejase M.J., Hejase A.J., Hejase H.A.N, and Hejase H.J. (2023) Management of Normogonadotropic males with idiopathic infertility with bilateral varicocelectomy with and without intramuscular recombinant FSH and HCG course(s): A twenty-year- experience in a prospective, controlled, and randomized clinical study, British Journal of Multidisciplinary and Advanced Studies: Health and Medical Sciences 4 (6),32-51

ABSTRACT: This study presents a clinical prospective double-blinded study that contains three groups of infertile males with normogonadotropic oligoasthenospermia. All groups A, B, and C were operated on for their bilateral varicoceles. The first included 152 patients who were only operated for bilateral varicocele (nominated group A). The second group of 237 patients constituted those who were operated on, with fertile female partners, and whose preoperative spermogram showed a count lower than 15 million/ml and a 3-hour-motility lower than 20%. This group constituted two categories based on their treatment. Therefore, groups B and C received postoperative courses of intramuscular injections of recombinant follicle-stimulating hormone (rFSH) and human chorionic gonadotropin (HCG), i.e., group B received one course (3 months), and group C received two courses (6 months). The main objective is to determine the improvement in the postoperative seminal parameters in the different groups. The sample constituted 391 infertile males who were recruited conveniently based on their willingness to share their progress information and were also informed that they could stop their participation freely with no questions asked. In our treated patients, in both groups B and C, who received 1 or 2 courses of rFSH and HCG, spontaneous pregnancy occurred in 69 patients and 52 patients, respectively. Likewise, assisted pregnancy occurred in 28 and 19 patients, respectively. So treated males of groups B and C resulted in 91/140 (65%) and 61/96 (63.54%) live offspring, respectively.

KEYWORDS: Fertility, normogonadotropic males, oligoasthenospermia, rFSH, HCG, Lebanon
INTRODUCTION

Medical treatment of male infertility is an extraordinary field for urologists, reproductive biology researchers, scientists, and patients, as it allows for, when effective, a reversal in the decline of man’s fertility potential by simply prescribing medications. Assisted reproductive techniques (ART) are expensive though their success rate is still under debate referring to many variables considered in reporting the success; nevertheless, a success range of 30% to 60% has been reported in the best centers (Ferraretti, Goossens, Kupka, et al., 2013; Kieu, & Polyakov, 2021, p. 12; Lazzari, Potančoková, Sobotka, et al., 2023, p. 10; Lee, & Zhang, 2022).

According to Hull, Glazener, Kelly, et al. (1985), “A male is responsible for infertility in 24% of the cases” (p. 1693), while Thonneau, Marchand, Tallec, et al. (1991) report that "39% of cases both the man and woman presented with disorders. The woman alone was responsible for infertility in one-third of cases and the man alone in one-fifth." More recently, Leslie, Soon-Sutton, and Khan (2023) posit that "The male is solely responsible for about 20% and is a contributing factor in another 30% to 40% of all infertility cases (men and women)."

Researchers contend that hormonal treatment in infertile males increases the success rates of ART (Isidori, Sansone, & Gianfrilli, 2017) and thus reduces the cost of repeated hormonal injection cycles (Van Voorhis, Stovall, Sparks, et al., 1997; Al-Kandari, & Alenezi, 2020). Next, the difference between FSH and rhFSH hormones is worth mentioning. Follicle-stimulating hormone (FSH) “Stimulates testicular growth and enhances the production of an androgen-binding protein by the Sertoli cells which are a component of the testicular tubule necessary for sustaining the maturing sperm cells” (Jabbour, 2023, para 2). Moreover, Liu, Hao, & Wang (2015) describe the difference between FSH and rhFSH as follows: “Recombinant FSH (rFSH) has a higher proportion of less-acidic isoforms than urine-derived follicle-stimulating hormone (uFSH), which has a higher proportion of acidic isoforms. The half-life of less-acidic FSH isoforms is shorter than that of acidic FSH isoforms due to their quicker clearance” (p. 385).

In male idiopathic infertility, follicle-stimulating hormone (FSH) may be empirically used to stimulate residual spermatogenesis and to improve sperm production when FSH serum levels are within the normal range. However, the clinical efficacy of FSH remains a matter of debate. According to Simoni and Santi (2020), “Seventeen controlled clinical trials (too few) and four metanlyses (too many) evaluated so far, the efficacy of FSH administration to the male partner of infertile couples” (p. 536). The FSH type, scheme, and dosage used in clinical trials were highly heterogeneous, as reported by Cannarella, La Vignera, Condorelli, et al. (2020), and no conclusive results have ever been produced about the most effective FSH regimen. However, Simoni and Santi (2020) posit, "A dose-dependent sperm concentration and total sperm count improvement were described in a meta-analysis, which was, however, based on only three studies and with a limited number of patients” (p. 536). With these limitations, the higher the
FSH dose used, the greater the increase in sperm production (Cannarella, La Vignera, Condorelli, et al., 2020). Thus, “Limited evidence suggests that high FSH doses may be useful to stimulate Sertoli cells, providing stronger support to germ cell proliferation and maturation” (Simoni and Santi, 2020, p. 536). As a result, “The number needed to treat (NNT) for naturally occurring and ART-induced pregnancies fell to 12 and six (6), respectively with the administration of FSH at high doses (300 IU daily)” (Ding, Zhang, Li, et al., 2015). Moreover, Foresta, Bettella, Garolla, et al. (2005) reported that “During the follow-up and ART periods (i.e., during the six (6) months after the withdrawal of recombinant human follicle-stimulating hormone (rhFSH) therapy), had 29% (18/62) of cumulative pregnancy in treated infertile males” (p. 659). Furthermore, a large meta-analysis (n=278) including four (4) randomized trials in comparison to placebo or no treatment, three (3) months of gonadotropin therapy significantly increased pregnancy rate in males with idiopathic infertility in 13.4% (19/142) in the gonadotrophin group and 4.4% (6/136) in the control group (Attia, Al-Inany, Farquhar, & Proctor, 2007, p. 1).

Simoni, Santi, Negri, et al. (2016, p. 1960) demonstrated that sperm quality improvement after FSH administration in male idiopathic infertility is evident only after three months of therapy and continues after a further three months of treatment withdrawal. Later, Simoni and Santi (2020) posit, “In addition to the FSH dose, there isn’t enough solid scientific evidence to support the length of the treatment. Spermatogenesis takes between 72 and 90 days to complete, therefore, sperm production would need to be increased through sustained stimulation. It is still unclear whether the three months required to complete at least one spermatogenic cycle treatment that is typically given are sufficient to provide a therapeutic benefit” (p. 537).

Many aspects of male infertility and its causes are still not well understood (De Jonge and Barratt, 2019). Multiple efforts are made with medical as well as supplementary therapies and are still unsuccessful in mitigating the high rates of infertility (Assidi, 2022). Almost all infertile couples are strongly encouraged by their gynecologists to seek assisted reproductive therapy. The first author of this study thinks that the medical therapy with r-FSH and HCG should successfully help a male with normogonadotropic oligoasthenospermia improve his fertile parameters (i.e., the sperm count in millions/ml; the motility percentage of spermatozoa after three (3) hours; and the normal-morphology percentage), thus leading to a less costly and better outcome in paternity. Worth mentioning, as reported by Dabaja and Schlegel (2014), “Human chorionic gonadotropin (hCG) is a subcutaneous/intramuscular treatment, that is administered using doses in the range of 1,500-3,000 IU, 2 times/week, and is FDA-approved for the treatment of infertility due to gonadotropin deficiency. Similarly, the highly purified or recombinant human follicle-stimulating hormone (rhFSH) is a subcutaneous/intramuscular treatment using doses in the range of 100-150 IU, 2-3 times/week, is FDA-approved for the treatment of infertility due to gonadotropin deficiency” (p. 10).
In hypogonadotropic or normogonadotropic patients, the main objective of FSH therapy is not to stimulate spermatogenesis (or testicular growth), but rather to induce pregnancy in the female partner of the infertile pair, leading to the live birth of a healthy child (Behre, 2019).

The expected consequence of pharmacological doses of FSH is, if any, stimulation of spermatogenesis and testis volume over the baseline (Behre, 2019; Simoni and Santi, 2020). Simoni and Santi (2020) posit, "No serious adverse events were ever reported as a consequence of FSH replacement treatment in males, and FSH-producing tumors have no other effects than increasing testis size" (p. 539). Chrusciel, Ponikwicka-Tyszko, Wolczynski, et al. (2019, p. 1) and Lizneva, Rahimova, Kim, et al. (2019, p. 1) reported that extra gonadal effects of FSH are a very much debated issue, and, for the time being, should not be a concern.

According to Behre, Nieschlag, Partsch, et al. (2010) and Behre (2019), “One of the most common dosing schemes of gonadotropins in male hypogonadotropic hypogonadism is the administration of 150–225 IU. FSH two or three times a week in combination with 1000–2500 IU. of HCG two times per week” (p. 182). Groups of physicians initiate the treatment with HCG alone for about three (3) months, as some patients (maybe those with some residual FSH activity) achieve stimulation of spermogenesis by HCG alone (Bouloux, Nieschlag, Burger, et al., 2003; Fraietta, Zylberstejn, and Esteves, 2013; Dwyer, Raivio, and Pitteloud, 2015; Nieschlag, Bouloux, Stegmann, et al., 2017). Also, according to Yang, Zhang, Dong, et al. (2012), “The sperm concentrations seen after HCG therapy alone appear to be lower than those with the combined treatment with FSH plus HCG." Therefore, as Behre (2019) suggests, “FSH should also be added in these HCG-treated patients at some time point to achieve the best treatment outcome (p. 183). Moreover, Behre (2019, p. 4) opined that as the existing FSH plus HCG dose regimens still have the issue of a lengthy treatment period before the desired results, even after the desired pregnancy has occurred, testing appears worthwhile. Various dosages and formulations of FSH and HCG that are carefully planned, randomized, controlled clinical trials increase the effectiveness of male gonadotropin therapy hypogonadism with hypogonadotropins.

Building upon the accumulated experiences as reported in the abovementioned section and the lack of more details about the formulations and dosages used, this paper offers a first-view of twenty years of accumulated experience in the management of normogonadotropic males with idiopathic infertility with bilateral varicocelectomy with and without intramuscular recombinant follicle stimulating and gonadotrophic chorionic hormones course(s). This paper also offers a prospective, controlled, and randomized clinical study. The outcomes compare the results of patients operated on and untreated with r-FSH and HCG (group A in this case) with patients who were operated on and treated with re-FSH and HCG (groups B [3-month period treatment] and C [6-month period treatment], in this case), and then determine the rate of pregnancy and consequently the outcome or paternity rate.
Research question
Can the treatments utilized improve postoperative seminal parameters and thus result in a better fertility and paternity outcome?

This paper consists of five sections. The introduction and background are presented in section one, followed by section two which describes the materials and methods used. Section three shows the results, section four is about the discussion, and section five depicts the conclusion and recommendations.

MATERIALS AND METHODS

Three hundred and ninety-one (391) infertile males were recruited from the office of patients at Saint Therese Medical Center, Hadat, Lebanon from the year 2000 to 2021. All patients had bilateral varicocele as diagnosed clinically (i.e., Scrotal bulging veins on both testicles, causing pain and testicular discomfort) and by a spermatic echo-doppler which showed bilateral varicocele (no matter which grade I, II, or III, upon the standing position). All participants were advised to maintain their current level of physical activity and nutrition during the study and not start any new pharmacotherapy. This population was divided into three groups after two patients withdrew. The first included 152 patients only operated for their bilateral varicocele (nominated group A). The second group of 237 patients constituted those operated on, with fertile female partners, and whose preoperative spermogram showed a count lower than 15 million/ml and a 3-hour-motility percentage lower than 20%. This group constituted two categories based on their treatment with either one (1) course (Group B for three (3) months) or two (2) courses (Group C for six (6) months) of hormonal injections (i.e., recombinant FSH and HCG) administered intramuscularly.

All patients underwent a preoperative spermogram (count, motility percentage after three (3) hours, and morphology), normal blood hormones (FSH, luteinizing hormone (LH), Testosterone, Prolactin, and Inhibin B), and a spermatic echo doppler. A Bilateral inguinal modified Ivanissevich's varicocelectomy was performed on all the patients by the same surgeon. After removing the stitches (10 days), one group (Group A) was given antioxidants and vitamins, and the second, with two categories (Groups B and C), was submitted to Intramuscular injections of r-FSH and HCG in 1 course (141 patients in Group B) or two (2) courses (96 patients in Group C), with each course duration of three (3) months. The r-FSH (150 units) intramuscular (IM) injections were administered three (3) times weekly, and the HCG (5000 units) IM was administered once weekly.

A post-operative spermogram and blood hormones (FSH, LH, Testosterone, Prolactin, and Inhibin B that should be normal) were performed three (3) months after the operation in the first group A and three (3) months after the last IM injection in groups B and C to evaluate the final fertility and paternity outcome in each one of the groups. Subjects who did not father with
their corresponding wives through a spontaneous pregnancy underwent assisted reproductive techniques (ART) whenever possible.

**Data analysis**

Hejase and Hejase (2011) contend that giving data meaning leads to beneficial information. Furthermore, according to Hejase and Hejase (2013), "descriptive statistics deals with describing a collection of data by condensing the amounts of data into simple representative numerical quantities or plots that can provide a better understanding of the collected data" (p. 272). Therefore, primary data were coded and analyzed using the IBM Statistical Product and Service Solution package, SPSS version 26.0. For simplicity, descriptive statistics included percentages and frequencies presented in tables and bar graphs. Moreover, further analysis was performed by either applying the Wilcoxon Signed Rank Test with the statistical significance checked at 5% (95% statistical confidence level) or the Chi-square test of statistical significance testing for differences between the two groups.

**Ethical Considerations**

An ethical committee (Saint Therese Medical Center, Department of Urology, P.O. Box 169, Hadat, Beirut, Lebanon) gave its clearance for every work performed. Patients were made aware of how their information —held at the hospital or their immediate attending physician containing confidential medical records— is used. They were informed that no personal identities or details were disclosed when using their data. Certain results would be used depending on the topic of the academic or professional research to be carried out. Beginning with the initial visit and continuing throughout therapy, all patients were welcomed and given every conceivable measure of comfort and care.

**RESULTS**

*Measuring improvement*

**Group A (Subjects operated on and not treated with hormonal injections)**

A related-sample Wilcoxon signed rank test was applied to group A patients. The resultant null hypothesis that the median of differences between the preoperative sperm count and the postoperative sperm count equals 0 (Sig. P = 0.000 < 5%) was rejected.

That is a non-parametric test since the distributions of the preoperative spermogram count (30 Million/ml) and the postoperative spermogram count (60 million per ml) are not Normal (Gaussian). A significant improvement at a 5% level of significance was observed in the Wilcoxon test (100% improvement in the Median count, i.e., from 30 to 60 million/ml). As for comparing the Medians of the preoperative (30%) and the postoperative motility (50%) another non-parametric Wilcoxon signed rank-test was run, and the resulting p-value= 0.000 (< 5%) implies rejecting the null hypothesis that the Median difference of the preoperative sperm 3-hour-motility and the postoperative sperm motility = Zero (0). Hence, the improvement in the
Median of 66.7% is significant at a 5% significance level, i.e., from 30% to 50% with an increase of 20%.

As for the medians of preoperative (60%) and postoperative normal morphology (68%), the non-parametric Wilcoxon signed Rank test resulted in a p-value of 0.000 (< 5%), implying that the improvement in the Median normal sperm Morphology between the preoperative and the postoperative is significant at 5% level of significance (the improvement amounted to 13.3%, i.e., an increase of 8%). Thus, the null hypothesis that the median of differences is zero, is rejected at a 5% significance level. Table 1 and Figure 1 illustrate the values of the medians for group A.

Table 1. Differences in median sperm parameters for Group A

<table>
<thead>
<tr>
<th></th>
<th>Spermogram Count (Million per ml)</th>
<th>Median Motility (%)</th>
<th>Median Morphology (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>30</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Postoperative</td>
<td>60</td>
<td>50</td>
<td>68</td>
</tr>
</tbody>
</table>

Figure 1. Differences in median sperm parameters for Group A

Group B (Subjects operated on and treated with hormonal injections: Intramuscular injections of r-FSH and HCG in 1 course)

In Group B patients, the improvement in median sperm count difference amounted to 162.5%. The Wilcoxon signed Rank test resulted in a p-value of 0.000 (< 5%), indicating a significant improvement at a 5% level of significance (it was 12 million/ml and became 31.5 million/ml). Likewise, for sperm 3-hour-motility, the median improvement amounted to 100 % (20% became 40%), and the Wilcoxon signed Rank test resulted in a p-value of 0.00, indicating a
statistically significant improvement at 5%. As for the medians of sperm normal morphology, there was no statistically significant improvement in the median sperm morphology (no change in the median was observed), and the non-parametric Wilcoxon signed rank test resulted in a p-value of 0.052 (>5%), thus, accepting the null hypothesis of no change in the median. Table 2 and Figure 2 illustrate the values of the medians for group B.

Table 2. Differences in median sperm parameters for group B

<table>
<thead>
<tr>
<th></th>
<th>Spermogram Count (Million/ml)</th>
<th>Median Motility (%)</th>
<th>Median Morphology (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>12</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Postoperative</td>
<td>31.5</td>
<td>40</td>
<td>60</td>
</tr>
</tbody>
</table>

Figure 2. Differences in median sperm parameters for group B

Group C (Subjects operated on and treated with hormonal injections: Intramuscular injections of r-FSH and HCG in 2 courses)

In Group C patients, a comparison of the preoperative parameters (count, 3-hour-motility, and normal morphology) with the postoperative parameters after having been submitted to two (2) courses (6 months) of hormonotherapy was performed. There was a significant improvement in the sperm count of 300% [increase of 15 million/ml], and using the non-parametric Wilcoxon signed Rank test, the p-value of 0.000 indicates a statistically significant improvement at a 5% significance level. Likewise, for the median sperm 3-hour-motility, there was a statistically significant improvement of 87.5% [increase of 17.5%] (p-value = 0.00); additionally, comparing the median sperm normal morphology, the Wilcoxon signed Rank test resulted in a
p-value = 0.000 implying a statistically significant improvement of 30.4% [increase of 14%] at 5% level of significance. Table 3 and Figure 3 illustrate the values of the medians for group C.

**Table 3. Differences in median sperm parameters for group C**

<table>
<thead>
<tr>
<th></th>
<th>Spermogram Count (Million/ml)</th>
<th>Median Motility (%)</th>
<th>Median Morphology (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>5</td>
<td>20</td>
<td>46</td>
</tr>
<tr>
<td>Postoperative</td>
<td>20</td>
<td>37.5</td>
<td>60</td>
</tr>
</tbody>
</table>

**Figure 3. Differences in median sperm parameters for group C**

**Fathering results**

**Group A (Post-operative with no hormonal therapy)**

This Group did not receive any hormonal therapy. Out of the total of 148, 49 patients (33.1%) did not father any children, while 99 out of the total 148 patients (66.9%) fathered children. Table 4 depicts the distribution of the 99 patients who fathered children.

**Table 4. Patients from Group A who fathered children**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number of Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not father</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1  2  3  4</td>
</tr>
<tr>
<td></td>
<td>49 (33.1%)</td>
</tr>
<tr>
<td>Fathered</td>
<td>24  40  28  7</td>
</tr>
<tr>
<td></td>
<td>99 (66.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>49  24  40  28  7</td>
</tr>
<tr>
<td></td>
<td>148 (100%)</td>
</tr>
</tbody>
</table>

**Group B (Post-operative and received one (1) course of hormonal therapy)**
Out of 140 patients who took the hormonal therapy, 49 patients (35%) had no children, while 91 out of a total of 140 patients (65%) fathered children. Table 5 depicts the distribution of the 91 patients who fathered children.

Table 5. Patients from Group B who fathered children

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number of Children</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not father</td>
<td>49 (35%)</td>
<td>49</td>
</tr>
<tr>
<td>Fathered</td>
<td>-</td>
<td>23 (16.43%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51 (36.43%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 (10.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 (2.14%)</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>23</td>
</tr>
</tbody>
</table>

Note: One patient did not receive any therapy; out of the original 141 patients in Group B.

**Group C (Post-operative and received two (2) courses of hormonal therapy)**

Out of 96 patients who took the hormonal therapy, 35 patients (36.5%) had no children, while 61 out of a total of 140 patients (63.5%) fathered children. Table 6 depicts the distribution of the 61 patients who fathered children.

Table 6. Patients from Group C who fathered children

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number of Children</th>
<th>&gt;5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not father</td>
<td>35 (36.5%)</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Fathered</td>
<td>-</td>
<td>16 (16.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 (31.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 (10.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 (3.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (2.1%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>16</td>
<td>30</td>
</tr>
</tbody>
</table>

Next, Figure 4 summarizes all the aforementioned percentages.
Pregnancy versus different hormone courses

Figure 5 depicts pregnancy, whether spontaneous or assisted, in the different groups. We notice that under the different hormonal courses, the spontaneous pregnancy of two (2) children dominates (36.43% and 31.3% after one (1) and two (2) courses of hormonal therapy, respectively). In postoperative patients who did not receive hormonal therapy (Group A), spontaneous pregnancy occurred in 99 patients, while assisted pregnancy occurred in 4 patients. Moreover, of patients who received one (1) course of hormones (Group B), 69 patients had spontaneous pregnancy and 28 had assisted pregnancy. Of the patients who received two (2) courses of hormonal therapy (Group C), 52 had spontaneous pregnancy, and 19 had assisted pregnancy. It is worth mentioning that 66.89%, 65%, and 64.58% of groups A, B, and C, respectively, had live children. Such results encourage us to administer the aforementioned ‘Hormonotherapy’ scheme after Bilateral varicocelectomy in those patients with moderate to severe normogonadotropic oligoesthenospermia (i.e., sperm count lower than 15 million/ml and 3-hour sperm motility lower than 20%). Another reason to back up the use of hormonal courses is the higher numbers obtained from spontaneous pregnancies over assisted pregnancies as confirmed by Table 7 and the corresponding histogram in Figure 5.

Table 7. Comparison of Spontaneous and Assisted pregnancies for the three groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Assisted Pregnancy</th>
<th>Spontaneous Pregnancy</th>
<th>Total Live Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>4</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Group B</td>
<td>28</td>
<td>69</td>
<td>91</td>
</tr>
<tr>
<td>Group C</td>
<td>19</td>
<td>52</td>
<td>61</td>
</tr>
</tbody>
</table>
DISCUSSION

HMG plus HCG therapy of infertile patients with hypogonadotropic hypogonadism appears to be quite successful regarding stimulation of spermatogenesis and finally clinical pregnancy induction in the female partner. This outcome is conformant to other researchers' results (Fraietta, Zylberstejn, and Esteves, 2013; Behre, 2019). However, Behre (2019, p. 4) opined that as the existing FSH plus HCG dose regimens still have the issue of a lengthy treatment period before the desired results, even after the desired pregnancy has occurred, testing appears worthwhile using various dosages and formulations of FSH and HCG through carefully planned, randomized, controlled clinical trials, increase the effectiveness of male gonadotropin therapy (with hypogonadotropic hypogonadism).

This study adds to the accumulated current reservoir of knowledge and new insights based on physicians' recommendations to share experiences in using rFSH plus HCG therapy of infertile patients with normogonadotropic hypogonadism.

Worth mentioning that according to the Practice Committee of the American Society for Reproductive Medicine (2006) and the physicians’ practices by the groups Cocuzza, Cocuzza, Bragais, & Agarwal (2008), in Brazil, and Amirzargar, Yavangi, Basiri, et al. (2012), in Iran, varicocelectomy was practiced on the male partner in couples trying to conceive when all of the conditions depicted in Exhibit 1 are achieved.
Exhibit 1. Selecting patients for Varicocelectomy

(1) A palpable varicocele,
(2) Documented couple infertility,
(3) A female partner with normal fertility or potentially correctable infertility, and
(4) A male partner with one or more abnormal semen parameters or test results showing abnormal sperm.

Source: As above.

Similar measures were followed in this period of experience in addition to the cases where "Only larger varicoceles, which are typically easily palpable, have been associated with infertility" (Practice Committee of the American Society for Reproductive Medicine, 2009, p. S93). Therefore, an ancillary diagnostic measure, such as a Doppler examination, was performed.

The results of Group A (Subjects operated on and not treated with hormonal injections) show that statistically significant improvements, at a 5% level of significance, were achieved:
Preoperative spermogram count (30 million/ml) and the postoperative spermogram count (60 million/ml) (Wilcoxon signed rank test, p = 0.000); the preoperative median count (30%) and the postoperative motility (50%) (Wilcoxon signed rank test, p=0.000), thus, the improvement in motility with a Median of 66.7% is significant at a 5% level of significance, i.e., from 30% to 50% with an increase of 20%; and the preoperative median count (60%) and the postoperative sperm normal Morphology (68%) (Wilcoxon signed rank test, p=0.000), implying that the improvement amounted to 13.3%, i.e., an increase of 8%.

Researchers are still skeptical about the reported results; some of them report improvement in spermogram counts (Cocuzza et al., 2008; Amirzargar, Yavangi, Basiri, et al., 2012), while others continue to stress the narrow selection of infertile patients to obtain good results (Kantartzzi, Goulis, Goulis, & Papadimas (2007), and other confirm improvements that confirm the results of this paper (Krause, Mueller, Schaefer, & Weidner, 2002).

Finally, this paper reports improvements in the fathering results whereby Group A, which constituted 148 patients, resulted in 33.1% not fathering after the surgery, and 66.9% fathered [one child (16.22%), two children (27.03%), three children (18.92%) up to four children (4.73%) with time]. Krause et al.’s (2002) and Alshehri, Akbar, Altwairgi, and AlThaqufi's (2015) works reached similar findings. On the other hand, Nieschlag, Hertle, Fischedick, & Behre (1995) confirm this paper’s findings by stressing that a meta-analysis that solely considered randomized, controlled trials, and observational research revealed that varicocelectomy significantly enhanced sperm concentration, overall motility, and morphology by WHO guidelines (Anawalt, 2013, p. 3537).

In this study, the treatment scheme adopted 150 IU of rFSH, intramuscular (IM), three (3) times weekly, added to one HCG 5000 IU, IM, once weekly, which proved to be effective throughout the twenty years of experience. Behre (2019) posits that “FSH therapy was tested to see if it could be used successfully in male patients with normogonadotropic idiopathic infertility since
it was found to be quite effective in stimulating spermatogenesis in patients with hypogonadotropic hypogonadism and a high pregnancy rate in their female partners” (p. 4). Early uncontrolled investigations by Schill, Jungst, Unterburger, and Braun (1982) showed that “Tests conducted after three (3) months of ‘HMG plus HCG therapy’ revealed an increase in the total number of sperm in the ejaculate as well as in pregnancy rates in the female partners. However, the biggest improvement in conception rates was shown in individuals who were identified by an increase in sperm output of at least 25 million per ejaculate” (p. 467).

Shi, Hong, Jiang, et al. (2020) posit that “Human menopausal gonadotropin (HMG) that leads to follicle maturation, can be accelerated through the secretion of gonadotropin, which contains both luteinizing and stimulating hormones (LH) and follicle-stimulating hormones (FSH)” (p. 1). Given the aforementioned, Behre (2019) reports that “The efficacy of HCG treatment for three (3+) months plus, in Normogonadotropic patients with oligozoospermia can be only evaluated with randomized, placebo-controlled, double-blind clinical studies that involve a high number of participants to allow conclusions about pregnancy rates” (p. 5).

Santi, Granata, and Simoni (2015) contend, "According to the outcomes of controlled clinical trials that have been published in the literature, both naturally occurring pregnancy rates and pregnancy rates following ART have improved after FSH treatment to the male partner of infertile couples. The strength of these findings, however, is constrained by the heterogeneity of research, the significant risk of bias, and the absence of specific guidelines for administering FSH” (p. R46).

As for the results for Group B (Patients who were operated on and treated with hormonal injections: Intramuscular injections of r-FSH and HCG in one (1) course [three (3) months]), there was a statistically significant (Wilcoxon signed Rank test, p-value of 0.000) improvement in median sperm count difference amounted to 162.5%, i.e., indicating a significant improvement at a 5% level of significance increasing from 12 million/ml to 31.5 million/ml. Likewise, for sperm motility, the median statically significant (Wilcoxon signed Rank test, a p-value of 0.00) improvement amounted to 100% (20% became 40%), which is significant at a 5% significance. As for the medians of sperm normal morphology, there was no statistically significant improvement (the non-parametric Wilcoxon signed rank test, a p-value of 0.052 > 5% level of significance), in the median sperm normal morphology (no change in the median was observed). These results provide better outcomes as compared with those results by Amirzargar, Yavangi, Basiri, et al. (2012) who reported that “Patients treated with 5000 IU/week HCG IM only, showed a significant improvement in sperm normal morphology (p=0.007 < 5%), but no statistically significant change was observed in sperm concentration or motility (p>0.05) as compared with the pre-treatment sperm characteristics” (p. 447). However, when Amirzargar, Yavangi, Basiri, et al. (2012) tested a sample of patients with "75 IU rhFSH sub-cutaneous (s.c.) three times a week for three months caused significant increases in all the conventional semen parameters” (p. 447).
The obtained results of this work provide support to the observations by Yang, Zhang, Dong, et al. (2012), “The sperm concentrations seen after HCG therapy alone appear to be lower than those with the combined treatment with FSH plus HCG,” and Behre (2019) who suggested, “FSH should also be added in these HCG-treated patients at some time-point to achieve the best treatment outcome” (p. 183). Moreover, this paper reports improvements in the fathering results whereby Group B constituted 140 patients (excluding one patient who did not receive any therapy out of the original 141 patients in Group B). Final results were 35% not fathering after the surgery and treatment, and a total of 65% fathered [one child (16.43%), two children (36.43%), three children (10%) up to four children (2.14%) with time]. Notably, our patients in Group B had spontaneous pregnancy in 69 patients, and assisted pregnancy occurred in 28. Moreover, Group B resulted in 91/140 (65%) live offspring.

In the third group, Group C (Subjects operated on and treated with hormonal injections: Intramuscular injections of r-FSH and HCG in two (2) courses [six (6) months]), there was a statistically significant (Wilcoxon signed Rank test, p-value of 0.000) improvement in median sperm count difference amounted to 300%, i.e., indicating a significant improvement at a 5% level of significance increasing from 5 million/ml to 20 million/ml. Likewise, for sperm motility, the median statically significant (Wilcoxon signed Rank test, a p-value of 0.00) improvement amounted to 87.5% (20% became 37.5%), which is statistically significant at a 5% significance level. As for the medians of sperm morphology, there was also a statistically significant improvement (the non-parametric Wilcoxon signed rank test, a p-value of 0.000 < 5% level of significance), in the median sperm morphology (the observed change in the median was from 46% to 60%). These results provide better outcomes as compared with those results obtained by administering either FSH or HCG alone (Yang, Zhang, Dong, et al., 2012; Amirzargar, Yavangi, Basiri, et al., 2012; Behre, 2019), and as suggested by Behre (2019), “FSH should also be added in these HCG-treated patients at some time point to achieve the best treatment outcome (p. 183). Moreover, this research results represent a continuum of Filicori, Cognigni, Taraborrelli, et al.’s (1999) case who posit that their “Patient was treated first with highly purified FSH alone and then received highly purified FSH in combination with low-dose HCG therapy (50 IU/d); this led to markedly reduce the duration of treatment and the dose of highly purified FSH and resulted in a quadruplet pregnancy in a patient in whom several previous ovulation induction procedures had been unsuccessful” (p. 1118). Anawalt’s (2013, p. 3539) and Behre's (2019, p. 4) studies reported positive findings upon using the r-FSH plus HCG combination. Behre (2019) posits “it seems that the efficacy of the various FSH preparations in male patients with hypogonadotropic hypogonadism is quite comparable, regarding stimulation of spermatogenesis and inducing the desired pregnancy in the female partner” (p. 3). As for the parenting results, treated patients in Group C, who received two (2) courses of r-FSH plus HCG, had a spontaneous pregnancy in 52 patients and assisted pregnancy in 19 patients, respectively. So, the treated males of Group C resulted in 61/96 (63.54%) live offspring.
CONCLUSION

Our results are very encouraging in comparison with those published in the literature. The best outcomes were observed in patients treated with the highest FSH dose of 300 I.U. every second day and for the longest treatment duration (the maximum treatment duration in the above study was five (5) months). Ding, Zhang, Li, et al.’s (2015) study involved 354 patients with idiopathic oligozoospermia. It was a recent prospective, double-blind, placebo-controlled clinical trial conducted in China. It is possible to hypothesize that extended treatment of normogonadotropic oligoasthenospermic individuals would likewise increase the likelihood of conception in the female spouse using the knowledge from gonadotropin therapy in hypogonadotropic patients. “Hypogonadotropic hypogonadism is a good example of how causal hormone therapy for male infertility can be applied with high clinical efficacy regarding the induction of pregnancy in the female partner” (Büchter, Behre, Kliesch, et al., 1998 cited in Behre, 2019, p. 5).

Having our results reported, we second the recommendation issued by Behre (2019), that “It remains to reconfirm in a more prospective series, the advantage of r-FSH and HCG therapy for male infertility in normogonadotropic patients with impairment of spermatogenesis” (p. 6), especially with our good results on sperm count and motility in our significantly large group of infertile treated males. We highly recommend the use of injectable (i.m.) r-FSH and HCG for 3- and 6-month courses after the bilateral varicocelectomy in normogonadotropic oligoasthenospermic infertile males (sperm count <15 million/ml and 3-hour-motility <20%), thus favorably increasing the seminal parameters (count and 3-hour-motility, and normal morphology) and consequently increasing pregnancy rates and fatherhood efficiently. In conclusion, there is no doubt that continuous efforts by physicians and researchers are needed for more carefully planned, prospective randomized studies to determine the most effective FSH treatment plans for infertile male patients. It is important to encourage all essential stakeholders in the healthcare system to give the necessary funding and needed resources to maximize the effectiveness of therapy for male infertility.

Declaration of Competing Interest as Authors
The authors declare that they have no conflict of interest.

REFERENCES


