Original Article

Accurate Diagnosis as a Prognostic Factor in Intrauterine Insemination Treatment of Infertile Saudi Patients

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Abstract

Background: The study meant to define the prognostic factors that help in prescribing intrauterine insemination (IUI) for infertility treatment which remains an area of continuous improvements.

Methods: The diagnostic indications of a cohort of IUI-treated patients and their corresponding pregnancy rates (PRs) were randomly and prospectively studied among Saudi cohort of 303 patients for a period of 20 months. The indications of IUI cases were statistically analyzed for those eligible patients over a period of twenty months (January 2010 till August 2011), and the PR that corresponded to each group was investigated as well. P-value less than 0.05 was considered significant.

Results: The highest PR, 18.87%, of the polycystic ovarian syndrome (PCOS)-only diagnosed patients, was significantly higher than the average PR of all other indications combined, 7.22%, (p=0.011, compared to all other groups combined). The second highest PR, 14.0%, of the tubal factor (TF)-only indication, was double the PR average of all other indications combined, though it did not reach significance. However, PCOS and TF accompanied by other indications caused the PR to drop to 5.88% and 5.56 %, respectively. However, a group of some hormonal-imbalance based indications had the least PR (0.0% to 2.70%). Those indications were elevated serum FSH, hyperprolactinemia, hypogonadotrophy, hypothyroidism and endometriosis. The rest of the indications had an average PR (8.33% to 11.11%).

Conclusion: There is a reasonable chance of conception after IUI treatment for female factor infertility except in cases with sever hormonal imbalance. The PCOS cases having the best success chances.

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Received: Feb. 3, 2014
Accepted: Jun. 25, 2014

Keywords: Diagnosis, Endometriosis, Intrauterine insemination, IUI, Male factor, PCOS, Pregnancy rate, Tubal factor.
To cite this article: Isa AM, Abu-Rafea B, Alasiri SA, Al-Mutawa J, Binsaleh S, Al-Saif S, et al. Accurate Diagnosis as a Prognostic Factor in Intrauterine Insemination Treatment of Infertile Saudi Patients. J Reprod Infertil. 2014;15(4):184-189.

Introduction

The outcome of IUI treatment after mild ovarian stimulation (OS) was early known for treating patients with slight male factor, cervical factor, immunological factor or in cases with unexplained infertility (1). IUI has also been presented as a less expensive and less invasive treatment when it is compared with the full *in vitro* fertilization-embryo transfer (IVF-ET) procedure (2). Pregnancy rate results after IUI treatment differ because of the variations between the studied groups of patients and the studied parameters (3-7). The etiology of infertility is important factor to achieve remarkable IUI success (8). Generally, results from numerous studies indicate a considerable degree of uniformity; however, some variations are evident probably because of population

differences and because of the circumstances under which different studies were conducted (1).

The objective of the present study was to evaluate prospectively the clinical outcomes of IUI treatment of infertile couples. Specifically, the purpose was to determine whether or not the clinical outcomes were related to the indications of infertility, and whether or not all infertility indications could be treated with IUI.

The outcome of this study will definitely help us to propose and manage our future IUI treatments, and reasonably predict how successful the treatment would be. We have attempt to study the varieties of diagnostic factors of IUI-treated infertility patients and the corresponding pregnancy rates of each, as a prognostic study to help prescribe the most suitable treatment for our infertility patients.

Methods

In this random prospective study, the indications of IUI in a cohort study in our Assisted Conception Unit of King Khalid University Hospital in Riyadh- Saudi Arabia on eligible infertile women were analyzed- after signing the appropriate informed consent forms for the study- over a period of twenty months from January 2010 till August 2011, and the pregnancy rates that corresponded to each group were investigated.

After examining the infertile couples and gathering all infertility-related history of patients, both partners had undergone extensive evaluation. The examinations included at least two semen analyses (one of which included analysis before and after sperm wash) was done to get a full idea on the total motile sperms count (TMSC) expected for the IUI procedure. If necessary, further evaluation for the male partners included measuring serum levels of Follicular Stimulating Hormone (FSH) and Testosterone. For female patients, baseline hormonal levels of FSH, Luteinizing Hormone (LH), Thyroid Stimulating Hormone (TSH) and prolactin were evaluated. After prescribing the IUI procedure to those who were eligible for the couples accepted to participant in study, the informed consent were signed. Clomiphene citrate or gonadotropins stimulation protocol was assigned. The procedure was explained and the patients were monitored by ultrasound for the proper timing of the IUI procedure. When the leading follicle(s) of no more than two developing follicles was/were 17 *mm* in diameter, the female patient was reminded of injecting herself with 5,000 IU of Human Chorionic Gonadotropin Hormone (HCH) 36 hr before the insemination.

On the day of insemination, the semen specimen was centrifuged through two-layered density gradient (PureSperm 40/80 from Nidacon International-Sweden, Catalogue No. PSK-020) for 20 *min* at 18000 *rpm*. The sperm pollets were then washed twice with HEPES-buffered media (Quinn's Advantage Medium, with HEPES, from SAGE Company, Cat. No. 1023), supplemented with serum (Quinn's Advantage Serum Protein Substitute SPS from SAGE Company, Cat. no. 3010), where final sperm product of each specimen was constituted within 0.5 *ml* of the same media where it became ready for IUI. All data of pre- and post preparation semen parameters were recorded for patients.

The collected twenty month data was then analyzed to gain an insight on different infertile patients' characteristics, treatment factors, and how these factors affected the final IUI treatment results.

Ethical considerations: The institutional review board of the College of Medicine at King Saudi University approved the above project. Complete informed written consents were obtained from all human adult participants in the study ahead of all work done.

Statistical Analysis: SPSS, version 19 was used for statistical data analysis. Chi-Square test was used to compare pregnant and non-pregnant groups with respect to all variables. The difference was considered significant when $p<0.05$.

Results

All female partners' ages of this studied group ranged between 18 and 43, with Body Mass Indexes range of 20 to 35, with all cases succeeded to complete the treatment till final pregnancy test two weeks after the IUI was done. Wide varieties of diagnostic etiologies were represented within the pool of IUI-treated patients of our study. However, some of them were significantly better represented than others (Table 1). The male factor (MF) constituted 23.65% of the cases, of which more than two-thirds (16.42% of the total) were MF-only with a success rate of 10.71%. The rest had MF beside other infertility indications (7.23% of the total) resulted in PR of 8%. The pure female related indications constituted 43.13% of the total number of the cases, while the mixed male-female related indications were 21.02% of the total number of cases. The Polycystic Ovarian Syndrome (PCOS) constituted 20.53% of the cases, about three-quarters of which (15.54%) were

Table 1. Different categories of infertility diagnosis and the corresponding success rate for each

Infertility diagnosis	Number of patients (%)	Pregnant	p-value
AMA only	18 (5.90%)	2 (11.11%)	
AMA + others	12 (3.52%)	1 (8.33%)	
High FSH (all patients)	37 (10.85%)	1 (2.70%)	
Hyperprolactinemia	11 (3.23%)	0	
Hypogonadotrophy	3 (0.87%)	0	
Hypothyrodism	6 (1.76%)	0	0.571
Endometriosis	3 (0.87%)	0	(Overall)
Mild male factor only	56 (16.42%)	6 (10.71%)	
Mild male factor + others	25 (7.23%)	2 (8%)	
PCOS only	53 (15.54%)	10 (18.87%)	0.011
PCOS + others	17 (4.99%)	1 (5.88%)	
Tubal factor only (One side)	14 (4.11%)	2 (14%)	0.286
Tubal factor + others	18 (5.28%)	1 (5.56%)	
Undiagnosed	71 (20.82%)	6 (8.45%)	

PCOS-only, and those resulted in PR of 18.87%, the highest in all diagnosed groups (p=0.011) (Table 1). However, the rest of PCOS cases (4.99% of the total) were combined with other infertility factors and resulted in a much less PR, 5.88%. High base-line FSH-level patients were 10.85%, and resulted in 2.7% PR, one of the lowest PRs in all studied groups. Patients with tubal factors (TFs) constituted 9.39% of all cases, about half of them had only a TF, with a PR of 14% (the second highest PR group in our study, p=0.286). However, the second half had other infertility causes beside TF and resulted in a PR of 5.56%. Advanced maternal age (AMA) patients amounted to 9.42%, more than half of which, 5.90%, were AMA-only, with a PR of 11.11%, and the rest with AMA plus other indications, 3.52% of the total resulted in a PR of 8.33%. The uterine factor (endometriosis) involved 0.87% of the total pool of the patients and resulted in no pregnancy. Other infertility implications and causes such as hyperprolactinemia, hypothyroidism, and hypogonadotropic reasons (3.23%, 1.76%, and 0.87% of the total, respectively) were also represented and all resulted in no pregnancy as well. Surprisingly, there were a big group of patients who sought infertility treatment but could not be diagnosed with any clear indications, and those were labeled as "unexplained" or "undiagnosed". This group comprised 20.82% of the total number of the patients and their treatment resulted in PR of only 8.45%. It is worth mentioning that the final PR average throughout the study group was 10.56%.

Discussion

In this study, an attempt was made to investigate the varieties of diagnostic indications of some IUI-treated in our IVF clinic within a twenty-month period. The overall clinical PR per cycle was 10.56%, which was a little higher than the 8.75% PR of IUI (9). The total infertile couple number of the patients in the study was 303; though the total number looked bigger because of the diagnosis overlaps between some groups. The total number of pregnancies of all groups without any overlaps was 32 patients.

Patients diagnosed with PCOS alone stood out with a PR of 18.87%, which was significantly higher than the average PR of the rest of all groups combined, p=0.011. This is probably because of the interrupted period of PCOS patients which once adjusted and time of ovulation was determined, conception possibilities were enhanced. However, this PR dropped dramatically to 5.88% when there were other infertility indications beside PCOS. That gives a higher success potential to PCOS patients, provided that this class of patients' ovulation induction is done conservatively and watched closely to avoid any unwanted hyper-stimulation. Based on the above results, PCOS combined with other infertility indications makes the case more challenging and is very likely to affect the success expectations. The PR of 18.87% in PCOS-only cases were more than double what was reported by other authors, like Abu Hashim H who reported 7.89 % clinical PRs per cycle, which was comparable to timed

intercourse according to their data (10). However, comparable to our results were the results of Rajashekar L, et al. where the authors reported a clinical pregnancy rate of 17.09% per cycle for PCOS patients (11), and Ahinko-Hakamaa K who reported 19.2% pregnancy rate per cycle for the same category (12). Furthermore, Lan VT reported a much higher success rate per cycle for PCOS patients (13). They reported a clinical PR of 35.5% after IUI of selected group of PCOS patients. The only difference was that all of the patients they selected for their study had low or normal body mass index. Data close to this success rate of PCOS patients was reported by Kamath MS, et al. (9). They stated that anovulatory patients along with those of unexplained infertility causes had the highest results and those with male factor and endometriosis had the least, though their differences was not significant. In our presented results, the highest PR per cycle in diagnosed patients was that of the PCOS only (18.87%), followed by the tubal factor only (14% per cycle), then the male factor only patients (10.71% per cycle).

The second highest PR was that of the patients diagnosed with only defects in one of their fallopian tubes, the TF-only. Those patients comprised 4.11% of the total number of patients, and their IUI treatment resulted in a PR of 14%. This promising PR did not reach a statistical significance (p-value was 0.286). This result though it proved that having only one patent fallopian tube would adversely affect the conception process, raised a question about the significant effect of having only one patent fallopian tube and if this could be considered as an infertility reason; especially after the success rate dropped to 5.56% when other infertility indications (like advanced maternal age, male factor, but not those based on hormonal imbalance like endometriosis or high FSH) were involved, which was in 5.28% of the cases. Other factors may be involved especially sperm count, sperm progression, and the corresponding of ovary producing the egg with the patent fallopian tube in those cases. These results are not in agreement with the findings of Montanaro Gauci M who stated that data in analysis of 495 cycles reviewed retrospectively by stepwise regression analysis revealed a negative impact of the diagnosis of endometriosis or tubal factor on IUI outcome (14).

In this study, patients of 38 or older were considered AMA. This is due to decline chances of conception greatly from the age of 35 along with significant higher chances of chromosomal aberrations that highly affect conception and normal live births. This group of patients responded well to IUI treatment, with a PR of 11.11%. A 44-year old was our oldest patient with a successful IUI cycle. When AMA patients had other causes of infertility, which was the case with 3.52% of the total number of patients, the PR was 8.33%. A patient of forty years old with an FSH of 14 had a successful IUI. This result is encouraging, and probably suggests a redefinition of the AMA range as an indication of infertility. More data should be collected to see whether or not, this suggestion can be supported.

Patients suffered from a moderate, borderline, to somewhat sever male factor (MF) comprised 16.42% of all IUI treated patients of our study, and had a reasonable success rate of 10.71% those who suffered from other infertility causes beside the MF (7.23%) had a comparable PR of 8.0%. Thus, it can be concluded that whenever the MF is the cause of infertility, then it is probably the main reason, as other indications of infertility did not affect the outcome. However the above success rate is encouraging, however, not in agreement with Kamath MS whose results indicated that COH/IUI was not an effective option in couples with infertility due to a male factor (9). Probably they meant sever male factor. For example, in this study, there was a case of total motile sperm count (TMSC) of only one million sperm before wash, and 0.5 million sperm post processing that resulted in pregnancy. Another case that also was successful had one million motile sperms post wash. That indicates IUI treatment for some severe oligoozospermic cases can be still successful. This report is in agreement with Centola GM who suggested that acceptable pregnancy rates can be achieved with IUI, even in severe oligozoospermic specimens (15).

Patients who suffered from a high base-line blood value of FSH, 10 *IU/L* or more, formed a considerable percentage of the total number of patients (10.85%), but the PR among them was only 2.7%. That means in high-FSH patients, follicles are not stimulated easily, and hence a low number of developing follicles is usually expected, but also high FSH may affect other parameters like egg quality, fertilization possibilities, embryos quality and then embryo implantation. It was reported by Burwinkel TH that high baseline FSH infertile patients were unlikely to respond to medications for ovulation induction

and hence they were unlikely to get pregnant (16). Especially with the IUI stimulation protocols that cannot be aggressive, as the aim is to stimulate only one or two follicles, managing the high-baseline-FSH patients becomes challenging.

Patients with hyperprolactinemia, hypothyroidism, hypogonadotropic causes and endometriosis (a hormone-dependant, estrogen-related disorder) were represented by a considerable number of studies. These cases altogether added up to 23 patients, *i.e.* 6.73% of the total number of patients, and none of those cases had success with IUI treatment. They needed to proceed directly with the full IVF procedure to increase their success chances. Our future studies will look into the results of the IVF procedures of this kind of cases. Kamath MS, et al. reported that endometriosis patients had about 4% pregnancy rate per IUI cycle (9). In addition, it was reported by Rajashekar L, et al. that pregnancy rate was the lowest with the endometriosis patients (11). In our study, endometriosis was the infertility cause in only 0.87% of cases. It was concluded by Ozkan S, et al. that endometriosis comprised 25-40% of infertile women in general including those who sought IUI treatment (17). More data collection is needed on all these infertility categories; etiology, and treatment, so that more concrete conclusions could be drawn.

The last group, or the cases that suffered from some hidden reasons that delayed or prevented their natural conception, comprised 20.82% of the total number of patients. The PR for this group was 8.45%. This relatively lower pregnancy rate confirms the assumption that the "unexplained or unknown" term for this group of infertile patients was well representing them and that they are not void of infertility causes that are yet to be revealed. Moreover, those infertility causes are somewhat more complicated than one would predict; otherwise the PR of this group should have been noticeably higher than the groups of diagnosable infertility causes. It was suggested by Hughes EG, et al. that other factors may also be operative in the unexplained infertility cases, since the combination of IUI with ovarian stimulation has been found to give better results than ovarian stimulation with timed intercourse (18). However, Duran HE, et al. concluded that unexplained and anovulatory causes of infertility are aetiologies with relatively better prognostic value in terms of pregnancy (19). Also, Nuojua-Huttunen S, et al. stated that the information available indicated that IUI should be considered as a first-line approach prior to more expensive IVF in patients with unexplained infertility (4).

Conclusion

In conclusion, unless the cause of infertility is severe hormonal-imbalance based, there is a reasonable chance of conception after IUI treatment (s), with polycystic ovarian syndrome having the best success chances.

Acknowledgement

The authors would like to express their appreciation to the College of Medicine Research Center, the Deanship of Scientific Research, King Saud University for supporting this work and its authors. The authors also would like to greatly thank the Andrology Laboratory team for their hard work and especially for putting together the data used for the study above.

Conflict of Interest

It is worth mentioning that none of the authors or any of their family members had any kind of conflict of interest whatsoever with any of the companies that were producing the medications used in this study.

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