Kumulativna stopnja zanositve in živorojenih otrok pri intrauterini inseminaciji in in vitro fertilizaciji pri parih z nepojasnjeno neplodnostjo

Cumulative pregnancy and live birth rates following intrauterine insemination and in vitro fertilization in couples with unexplained infertility

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Izvleček

Namen: *Zdravljenje nepojasnjene neplodnosti zajema številne možnosti, med katerimi sta najpogosteje uporabljeni intrauterine inseminacija (IUI) ter in vitro fertilizacija (IVF). Namen raziskave je bil analizirati in primerjati uspešnost IUI in IVF v zdravljenju nepojasnjene neplodnosti.*

Metode: *Retrospektivna raziskava je vključevala 914 ciklusov IUI, opravljenih pri 355 parih, in 302 postopka IVF pri 161 parih z nepojasnjeno neplodnostjo, zdravljenih v UKC Maribor med leti 2012 in 2014. Analizirali smo razlike med stopnjo zanositve ter stopnjo živorojenih otrok, stopnjo večplodnih nosečnosti ter napovedne dejavnike za uspešnost IUI.*

Rezultati: *Razlika v kumulativni stopnji zanositve in stopnji živorojenih*

Abstract

Purpose: *There are multiple options for the treatment of unexplained infertility. Two of the most commonly used treatments are intrauterine insemination (IUI) and in vitro fertilization (IVF). The aim of our research was to analyze and compare the success rates of IUI and IVF procedures in the treatment of unexplained infertility.*

Methods: *This was a retrospective study including 914 cycles of IUI performed for 355 couples, and 302 IVF cycles performed for 161 couples. All cases involved unexplained infertility and were treated in our department between 2012 and 2014. We analyzed differences in pregnancy, live birth rate, multiple pregnancy rate, and predictive factors for IUI.*

Results: *There was a significant diffe-*

otrok med IUI in IVF po 4 ciklih je bila statistično pomembna (22,0 % vs. 71,8 %; p < 0,001 za stopnjo zanositve in 16, % vs 64,8 % za stopnjo živorojenosti). Razlika med stopnjo večplodnih nosečnosti ni bila pomembna (16,4 % vs 17,6 %; p = 0,936). Z uporabo logistične regresije smo za pomembne napovedne dejavnike za uspešnost IUI opredelili trajanje neplodnosti, celokupno število semenčic ter tip stimulacije jajčnikov (p = 0,014, p = 0,036 in p = 0,046).

Zaključek: *Skladno s pričakovanji se je IVF izkazal za superiorno metodo glede na stopnjo zanositve in živorojenih otrok. Kljub temu IUI ostaja pomembna metoda v zdravljenju neplodnosti, saj nudi dobre rezultate ob manjši invazivnosti. Za zagotavljanje najboljše uspešnosti IUI je potrebno pri izbiri parov upoštevati napovedne dejavnike.*

rence between IUI and IVF in terms of cumulative pregnancy and live birth rates after 4 cycles (22.0% vs. 71.8%; p < 0.001 for clinical pregnancy rates and 16.1% vs. 64.8% for live birth rate). Differences between the two techniques in terms of twin live birth rates were not significant (16.5% for IUI vs. 17.6% for IVF; p=0.936). Using logistic regression, we found that the duration of infertility, total sperm count, and the type of stimulation, were significant predictive factors for IUI (p = 0.014, p = 0.036 and p = 0.046, respectively).

Conclusion: *As expected, according to pregnancy rate, IVF is a better option for the treatment of idiopathic infertility than IUI. However, IUI should not be underestimated since it offers reasonable success rates with significantly less invasiveness. To improve the outcome of treatment for unexplained infertility, we suggest that treatment methods should be chosen with respect to predictive factors.*

INTRODUCTION

Infertility is defined as the inability to achieve pregnancy after one year of regular, unprotected intercourse. Current data indicate that at least 1 out of 10 couples in Western countries experience infertility, a condition caused by male factors, ovulatory dysfunction, uterine abnormalities, tubal obstruction, peritoneal factors, or cervical factors (1–4).

The diagnosis of unexplained infertility can be made only after excluding common causes of infertility using standard fertility investigations, which include semen analysis, the assessment of ovulation, and tests for tubal patency. However, it is estimated that a standard fertility evaluation will fail to identify an abnormality in approximately 15% to 30% of infertile couples, which presents an important subset of couples seeking treatment for infertility (5).

The treatment options for cases with unexplained infertility have been described in a rather empirical manner by many previous authors, and involve a range of techniques, including expectant management, superovulation, IUI (intrauterine insemination) and IVF (in vitro fertilization); this wide ranging list of options reflects the uncertainty associated with this diagnosis (6). One must also consider that unexplained infertility is perhaps best characterized as subfertility, as some couples will conceive without intervention or waiting for interventions (7).

IUI is often used as the first line treatment after expectant management and is usually combined with controlled ovarian stimulation (COH), using clomiphene citrate or gonadotropins. With COH, it is possible to obtain a good number of healthy fertilizable oocytes and therefore correct subtle ovulatory dysfunctions (8,9). The addition of IUI ensures that sufficient numbers of sperm overcome any cervical barrier. However, there are several disadvantages associated with treatment involving gonadotropins and IUI, including cost, the risk of ovarian hyperstimulation syndrome, and higher rates of multiple pregnancy (10). In vitro fertilization, has also been used in treatment of unexplained infertility. While IVF is widely considered as a superior method, with far better pregnancy rates, it also presents a more invasive method, with higher costs (11).

The approach to the treatment of unexplained

infertility is the source of much debate. The most relevant question relates to which method of treatment we should first choose and when to proceed to the next level of management. There is an opinion that in couples with a good prognosis, a more expectative approach, or a less invasive procedure, may be undertaken for spontaneous conception. However, for couples with a worse prognosis, more invasive procedures, such as IVF, should be performed as the first method of choice. Some studies have shown that no statistically significant differences exist between IVF with single-embryo transfer, and in IUI with gonadotropins, in couples with unexplained infertility (6,11).

On the other hand, some authors propose the immediate inclusion of all patients for more invasive procedures, such as IVF, based on superior results and compared to less invasive approaches, and claim that IVF produces superior results. Although some studies were unable to demonstrate that IVF is a more successful method, other papers have shown that IVF may accelerate the time to clinical pregnancy (6,12).

The aim of this retrospective study was to analyze and compare the success rates of IUI and IVF procedures in the treatment of unexplained infertility by considering cumulative pregnancy rates and live birth rates. By analyzing a range of clinical parameters, we successfully identified some prognostic factors that influence the success rates of IUI in the treatment of idiopathic infertility.

MATERIAL AND METHODS

This was a retrospective observational study featuring 914 cycles of IUI performed in 355 couples, and 302 IVF/ICSI cycles performed in 161 couples. All cases were diagnosed with idiopathic infertility and were treated at our clinic between 2012 and 2014. Overall, 59% of the couples (n = 95) treated with IVF/ICSI had been previously treated with COH and IUI procedures at our center.

First, we reviewed the medical documentation of all couples diagnosed with unexplained infertility. All couples underwent a basic fertility workup, consisting of medical history, hormonal status, transvaginal ultrasound examination, sperm analysis, Chlamydia trachomatis serology and endoscopic confirmation of tubal patency. Our study cohort involved only couples for whom these basic fertility tests failed to identify the cause of infertility; thus, unexplained infertility was considered as the main diagnosis.

The standard course of treatment for couples with unexplained infertility consisted of 1 – 4 cycles of IUI with either gonadotropin stimulation, clomiphene citrate, or in few cases, even letrozole or natural cycles. A proportion of the women (41%) were treated by IVF or ICSI without first performing IUI. The choice of treatment was made individually by the attending physician.

All women treated with IUI who underwent stimulation by either clomiphene citrate (n = 344), letrozole (n = 22), or gonadotropins (n = 521), were screened by vaginal ultrasonography prior to stimulation and were followed-up during stimulation. For COH, we either used 50 mg to 150 mg of clomiphene citrate on a daily basis (Clomid, Pantheon France SAS, France) beginning on the 5th to the 9th day of the menstrual cycle. When stimulating with gonadotropins, we began with recombinant rFSH (Gonal, Merck Serono, Switzerland) with an initial dose of 75 IE daily. This was administered in the form of a subcutaneous injection, beginning on the 2nd to the 5th day of the menstrual cycle. Subsequently, when the follicles had reached 17 mm in size (for gonadotropin stimulation) and up to 18 mm (for clomiphene citrate), we administered 250 mcg of choriogonadotropin alpha (Ovitrelle, Merck Serono, Switzerland). We controlled the number of follicles in a strict manner and allowed a maximum of 3 follicles measuring more than 14 mm. Where more follicles were counted, the IUI procedure was not performed and women were discouraged to have unprotected sexual intercourse over the following days. In some women (n = 41), IUI was performed in their natural cycle.

Samples of sperm were collected form male partners 4 hours prior to the IUI procedure following 2-3 days of sexual abstinence. Sperm were concentrated using a swim-up method and evaluated on the basis of the number of progressively motile sperm. IUI was performed either 24 or 36 hours after hCG injection in

the lithotomy position using an IUI Kitazato catheter (Kitazato Medical Co., LTD., Japan). Women were encouraged to rest in the same position for another 15 minutes after the procedure had been completed.

Patients undergoing the IVF/ICSI procedure underwent 1 - 4 cycles of COH with either a long protocol [down-regulation with the gonadotropin (GnRH) agonist triptoreline (Diphereline; Ipsen, France)] or a short protocol [with the GnRH antagonist cetrorelix (Cetrotide; Merck Serono, Switzerland)]. COH was initiated with 150 - 225 IU of recombinant FSH (Gonal, Merck Serono, Switzerland). Treatment was continued until at least three follicles measuring 17 -18 mm had developed. Ovulation was induced by 250 mcg of choriogonadotropin alpha (Ovitrelle; Meck Serono, Switzerland) and oocytes were recovered by transvaginal ultrasound-guided retrieval 36 hours thereafter. One or two embryos were transferred on days 3 or 5. Remaining good-quality embryos were cryopreserved by vitrification on either the 5th or 6th day.

All of the women in the IUI group were instructed to conduct urine pregnancy tests 14 days after the IUI procedure and those with positive results were invited for clinical examination and the determination of hCG levels. For all IVF patients, we performed quantitative hCG tests directly, without urine testing. All patients with positive results were scheduled for ultrasonic examination to determine the number of gestation sacs. Clinical pregnancy was defined as a positive hCG test, the ultrasonic measurement of crown-rump length, and the visualization of heart activity.

For all females, we used a standardized form to collect a range of data, including the age of both partners, the duration of infertility, semen parameters, the cause of infertility, the type of ovarian stimulation, and the ultrasonic status prior to hCG administration. Statistical analysis was performed using IBM SPSS version 25.0.0 (Armonk, NY: IBM Corp.). Mann-Whitney and Kolmogorov-Smirnov tests were used for data that did not show a normal distribution while chi-square, and Phi and Cramer's V, tests were used to compare nominal variables. Kaplan-Meier analysis was used to calculate cumulative pregnancy rates while binary logistic regression was used to calculate odds ratios and the predictive values of variables. An approval from the ethics committee was not required owing to the retrospective nature of this study and the fact that the study data completely excluded the identification of patients. All patients had given consent at the time of treatment for the future use of their clinical data in research.

RESULTS

We analyzed and compared 914 IUI cycles and 302 IVF/ICSI cycles. Mean female age was 31.7±3.7 years (range: 19-45 years) for the IUI group and 34.8±3.8 years (range: 19-43 years) for the IVF/ICSI group of patients. There was a significant difference between the two groups with respect to mean age ($p < 0.001$). Pregnancy and live birth rates for each successive IUI and IVF/ICSI cycles are presented in Table 1.

Table 1: *Clinical pregnancy and live-birth rates per cycle in IUI and IVF group (p is presenting significance of pregnancy rate difference between respective cycles)*

		Pregnancy rate	Live birth rate	Sig.
IUI	1st cycle (N = 355)	9.7%	8.5%	p = 0.060
	2nd cycle (N = 299)	9.4%	8.7%	
	3rd cycle (N = 182)	7.3%	6.0%	
	4th cycle (N = 79)	8.9%	5.1%	
	Total (N = 915)	8.8%	7.8%	
IVF	1st cycle (N = 161)	46.6%	38.5%	p = 0.224
	2nd cycle (N = 78)	28.2%	23.1%	
	3rd cycle (N = 40)	42.5%	35.0%	
	4th cycle (N = 23)	39.1%	34.8%	
	Total (N = 302)	39.3%	31.7%	

Cumulative pregnancy and live birth rates

Figures 1 and 2 show cumulative pregnancy rates and live birth rates after 4 successive procedures for either IUI or IVF/ICSI. The cumulative pregnancy rate after 4 cycles of IUI was 17.9% (95% confidence interval [CI]: 15.7 - 20.1) while the cumulative live-birth rate was 16.1% (95% CI: 13.5 - 18.7).

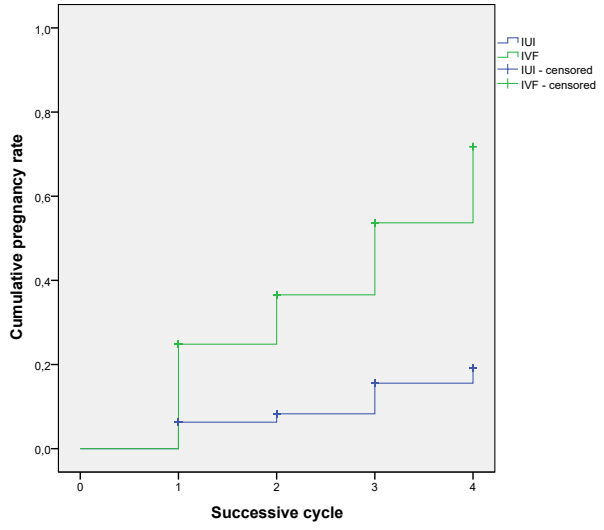

Figure 1. *Cumulative clinical pregnancy rate according to treatment type.*

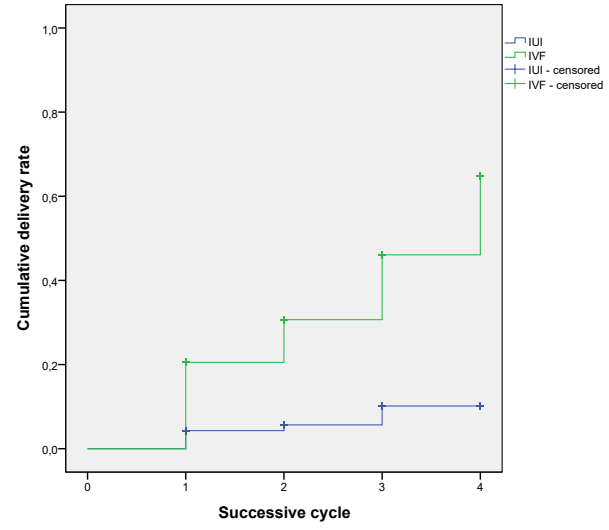

Figure 2. *Cumulative live birth rate according to trement type.*

After 4 cycles of IVF/ICSI, the cumulative pregnancy rate was 71.8% (95% CI: 66.4 - 77.2) and the live birth rate was 64.8% (95% CI: 58.7 to 70.9). The differences between IUI and IVF/ICSI in terms of cumulative pregnancy and live birth rate were statistically significant ($p < 0.001$ in both cases).

IVF/ICSI procedure

In the IVF/ICSI group, 36.3% of women underwent IVF, 28.4% underwent combined IVF and ICSI, and 33.6% underwent ICSI only. Of these, 16.4% of ICSI procedures were performed because of low sperm quality while 76.4% were performed due to indications that were not related to sperm quality, such as advanced female age or low sperm quality in a previous IUI procedure.

In 45.3% of IVF/ICSI cycles, a single embryo was transferred, in 43.0% of cycles two embryos were transferred, in 0.9% of cycles, 3 embryos were transferred, and in 9.4% of cycles, no embryo transfer was performed. The clinical pregnancy rate of single embryo transfer was 48.4% per cycle and 38.8% when two embryos were transferred. In 50.3% (n = 172) of the IVF/ICSI procedures, resultant embryos were frozen (mean number of frozen embryos: 3.6±2.9 (range: 1 - 18).

Multiple pregnancies

The rate of multiple pregnancies for the IUI procedures was 12.7% for double, 2.5% for triple, and 1.3% for quadruple pregnancies; thus 16.5% of the resultant pregnancies were multiple. All multiple pregnancies that involved more than two fetuses were reduced. When investigating deliveries, we observed that the ratio of singleton and twin deliveries shifted slightly with 18.2% live-born twins.

In the IVF arm of this study, only twin pregnancies were observed. Overall, 17.6% of cases experienced clinical twin pregnancy, and 10.1% of all deliveries were twins. Differences between the IUI and IVF/ICSI groups with respect to clinical multiple pregnancy, and twin live birth rate, were not statistically significant ($p = 0.936$ and $p = 0.122$, respectively).

Predictive factors for IUI

Finally, we used binary logistic regression to analyze a range of parameters and identify important predictive factors. A range of parameters were evaluated, including the age of the couple, the duration of infertility, the type of stimulation and dosage, endometrial measurements, follicle number and measurements, the number of successive IUI procedures, time after hCG injection, and various sperm parameters. Analysis showed that the duration of infertility, the total sperm count ,and the type of stimulation, were statistically significant ($p = 0.014$, $p = 0.036$ and $p = 0.046$ respectively); age was not significant. The odds ratio (OR) for the duration of infertility lower than 2 years was 1.81. The OR for a total sperm count higher than 11.5 was 1.27, while the OR for stimulation with gonadotropins was 1.52.

DISCUSSION

In this study, we analyzed and compared the outcomes of IUI cycles and IVF/ICSI procedures that had been performed for couples with unexplained infertility. To obtain cumulative pregnancy and live birth rates, we completed a longitudinal analysis with repeated observations in a cohort of couples treated in our center over a period of 3 years. Our results showed that the clinical pregnancy rate per IUI cycle varied between 7.3% and 9.7%; these data are similar to those described previously in the literature (7.1%–11.5%) (13–15). Cumulative clinical pregnancy rates, and live birth rates, after four IUI cycles reached 17.3% and 16.1%, respectively. Although these results were in line with European standards, some existing studies have report significantly higher pregnancy rates. One example is Allegra's study in which cumulative pregnancy rate was reported to be 28.3% after four IUI cycles performed in couples with unexplained infertility (16). In Allegra's study, almost all of the patients underwent stimulation with gonadotropins. This was unlike our approach in which 40% of the IUI cycles involved stimulation with clomiphene citrate. It is therefore difficult to compare our results to previous studies due to discrepancies in methodology. The major differences lay in study design, particularly the inclusion criteria; some papers included different age groups, different laboratory methods, and different protocols for ovulation induction. Differences in success rates are also related to differences in the rate of multiple pregnancies.

We specifically investigated live birth rate as a definite positive outcome of IUI and IVF/ICSI. Our data showed that 7.8% of IUI procedures were successful and led to a live birth while 31.7% of IVF/ICSI procedures met the same outcome. There were significant differences between the two procedures in this respect ($p < 0.001$). This result is not consistent with some previous publications. For example, Goverde compared live birth rates between IVF and IUI in natural cycles and stimulated cycles and found no significant difference (17). Goverde's results show a 24% live birth rate for natural cycles, and a 36% success rate for stimulated cycles; our present data show only a 16.1% live-birth rate for IUI. We suspect that this difference is due to the fact that Goverde treated women with 6 cycles of IUI, while our data referred to no more than 4 successive cycles. When exploring the reasons for differences between our results and the paper published by Goverde, we also noticed that the rate of multiple pregnancies reached 29% in Goverde's study, but only 16.5% in our study. This could be explained by differences in the inclusion criteria. We excluded all women with more than 3 follicles greater than 14 mm in diameter; Goverde's study was not as strict in this respect. It is generally assumed that higher stimulation doses, and greater follicle numbers, lead to higher pregnancy rates and multiple pregnancy rates (18).

A cumulative pregnancy rate of 71.8%, and a live birth rate of 64.8%, after 4 successive cycles can be considered as very successful for the application of IVF/ICSI for cases with unexplained infertility. In a previous paper, Heijnen et al. reported a cumulative pregnancy rate of 44.7% with standard IVF treatment within one year, which would be comparable to our 3-4 cycles (19). Similar results were also reported in Denmark; Dansk Fertilitetsklinik reported a pregnancy rate of 42.9% for women <35 years, and 31.7% for women between 35 and 39 years of age (20). Our center tends to promote elective single embryo transfer (eSET) in selected cases;

eSET was performed in almost half of our patients. It is interesting that the success rate of eSET was higher than when transferring two or more embryos (48.4% vs 38.3% per cycle). This can be easily explained by patient selection; the patients undergoing eSET were <36 years old, undergoing their 1st or 2nd cycle, and had good quality embryos. This clearly demonstrates that eSET is a very good choice for selected patients. In addition, half of the IVF/ICSI cycles led to embryo freezing, with an average of 3.6 embryos being frozen. This will eventually lead to a significant increase in success rate, although clearly, this effect was not apparent in the present study.

When comparing our results to a previous study published by Van Rumste et al., we noticed significantly higher pregnancy rates from IVF when the duration of infertility was less than 2 years; these patients were 1.81 times as likely to conceive compared to those with a longer duration. Another important factor was the type of stimulation. The use of gonadotropins is clearly superior to clomiphene citrate or IUI in a natural cycle. Our logistic regression model showed that the odds ratio of achieving pregnancy using gonadotropin stimulation was 1.52. This finding is consistent with many previous studies (6,21,22).

When comparing our results to study performed by Van Rumste et al., we notice significantly higher pregnancy rates from ICSI procedure with eSET (48.4% vs. 24%). Unlike results arising from IVF, Van Rumste reported that the success rates for IUI was higher and reached 21% (11). Considering the difference in pregnancy rates between IUI and IVF, we can consider the results of the FASTT trial (The fast track and standard treatment trial), in which patients were treated with either three cycles of IUI with clomiphene citrate stimulation, or three cycles of IUI with gonadotropin stimulation and then six cycles of IVF. Another arm went directly from three unsuccessful IUI cycles with clomiphene citrate to IVF. Reported pregnancy rates were similar to those obtained in our study (7.6% pregnancy rate per IUI cycle for CC/IUI, 9.8% FSH/IUI and 30.7% for IVF). The FASTT trial also showed that the arm with 6 IUI cycles had a median time to pregnancy of 11 months while the other arm, with only three IUI cycles followed by IVF, showed a median time to pregnancy of only 8 months (12). These results clearly show the benefit of accelerating the treatment towards a faster inclusion in IVF cycles, as would perhaps be reasonable based on the differences in pregnancy and live birth rates observed in the present study.

When comparing the rates of twin deliveries, we observed 17.6% for IVF and 18.2% for IUI; these differences were not significant, even though patients treated with IUI sometimes resulted in triple and quadruple pregnancies (these were later reduced); with IVF, only twin pregnancies were noted. Twin pregnancies were never reduced. With a good strategy, IUI can be a very cost-effective first-line treatment, with a similar risk of multiple pregnancies than IVF, these findings are also consistent with previous data reported by Cohlen and Van Rumste (11, 23).

We compared the overall success rates of IVF and IUI and detected significant differences. In the setting of our study, we can say that IVF/ICSI is a superior method for the treatment of unexplained infertility. However, as noted by Bahadur, our data does not allow us to conclude whether IVF would be preferable as a first-line treatment (24). Clearly, the advantages and disadvantages of both methods have to be considered. IVF/ICSI procedures are more effective, but these methods are invasive and expensive; for certain couples, with a good prognosis, these methods may not be necessary. IUI procedures are less effective, but they are cheaper and less invasive. However, they are probably more sensible for couples with a good prognosis for conception as a first-line method. When considering IUI, it is important to consider prognostic factors; our present data indicated that the duration of infertility is a very important factor to consider. Further studies are now needed to evaluate IVF and IUI procedures with regards to economic aspects, multiple pregnancy rates, IVF availability, and the effect of the treatment on the patient (24). Future studies also need to assess the true value of IUI versus IVF and to present quality guidelines on timing the different treatment options.

Finally, we tried to identify the most important prognostic factors. Of all the parameters tested, we found that the duration of infertility, total sperm count, and the type of stimulation, all had a statistically significant impact on the procedure outcome. We then used our data to identify a potential decline in fertility with age. Many studies imply such a relationship; however, our regression model did not indicate a significant relationship between fertility and age (13,25). This fact could simply reflect the age distribution within the IUI group of women, which consisted mostly of younger women. With increasing patient age, our centre tends to include women in IVF treatment on a much quicker timescale than adhering to a strict number of IUI procedures. Apart from age, the duration of infertility is another well-known prognostic factor for the success of IUI (21,26). We confirmed a difference in distribution of successful IUI procedures among couples with different durations of infertility.

The main limitation of this study is its retrospective nature; consequently, it featured a non-homogeneous group of participating couples. Our patient group consisted only of couples treated at our center, aged 19 - 45 years. No data separation was performed between groups and age was not uniformly distributed. There was a significant dropout in the IUI group but not from the IVF procedures. Another significant limitation was the heterogeneity of the controlled ovarian hyper-stimulations carried out in the IUI group, since this procedure showed wide variation, involving gonadotropins, clomiphene citrate, letrozole, and also spontaneous cycles. These differences make it difficult to analyze and compare our data, but on the other hand, represent the actual situation in an infertility clinic.

CONCLUSIONS

Our data show that IUI and IVF are both efficient methods with which to treat idiopathic infertility, yet differences exist in the success rates of these procedures. As expected, IVF remains the superior method for the treatment of idiopathic infertility with high single and cumulative success rates. We showed that the multiple pregnancy rate of IVF does not significantly differ from that obtained by IUI procedures. The question emerges as whether it is reasonable to begin treatment with IUI when such a notable difference in success rates exists. If IUI is to be used as a first line treatment, then it should follow strict inclusion criteria. Our data identified several prognostic factors for IUI; the duration of infertility was the most important prognostic factor, followed by total sperm count, the type of stimulation, and the timing of IUI after hCG injection. Since IUI is significantly more effective in patients with a shorter duration of infertility, this finding highlights its role as a first line treatment, particularly because of its availability, non-invasiveness and reduced association with side effects.

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