
ORIGINAL PAPER

INTRAUTERINE INSEMINATION IN IDIOPATHIC INFERTILITY

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SUMMARY

Introduction: Infertility currently affects approximately 1 in 7 couples and is defined as the absence of conception after a year of unprotected sex. The diagnosis of idiopathic infertility is only made if the results of the basic infertility evaluation tests (semen analysis, tubal patency test, highlighting ovulation) show no faults to justify the absence of pregnancy. The incidence of infertility of unknown cause is 15-30%.

Purposes: The purpose of our study is to determine the efficacy of IUI for couples suffering from idiopathic infertility, regarding both the rate of obtaining a pregnancy and the rate of living newborns compared to other methods (scheduled intercourse with constant ultrasound monitoring of the ovulation and Assisted human reproduction techniques).

Material and Method: We have conducted a prospective, comparative study in a group of 65 patients aged under 37, between 2014 and 2015. We have randomly divided the 65 persons study group into 3 subgroups taking into account the patient's wish: Group A - for which the chosen treatment option was waiting, constant ultrasound monitoring of the ovulation and scheduled intercourse; Group B - for which the chosen treatment option was IUI and Group C - for which the chosen treatment consisting in assisted human reproduction techniques.

Results: Out of a total number of 65 patients that were included in our study, 9 patients (13.85% out of the total patients) have obtained a pregnancy, and 44.44% of the pregnancies were achieved via IVF treatment (4 pregnancies obtained with IVF-subgroup C- compared to a total of 9 pregnancies within A, B and C subgroups). Out of the 9 pregnancies obtained 3 were multiple which led to a rate of 33.33% chance of multiple pregnancy.

RÉSUMÉ

L'insémination intra-utérine dans l'infertilité idiopathique

Introduction: L'infertilité affecte habituellement environ 1 parmi 7 couples et elle est définie comme l'absence de la conception après une année de sexe non protégé. Le diagnostic de l'infertilité idiopathique est mis seulement si les analyses d'évaluation de l'infertilité de base (l'analyse du sperme, le test de la potence tubaire, l'ovulation) ne montrent aucune erreur qui justifie l'absence de la grossesse. L'incidence de l'infertilité de cause inconnue est de 15-30%.

Buts: Le but de l'étude est de déterminer l'efficacité de l'IU pour les couples qui souffrent d'infertilité idiopathique, tant en ce qui concerne le taux d'obtenir une grossesse que le taux de nouveau-nés vivants par rapport à d'autres méthodes (l'acte sexuel programmé avec surveillance constante échographique de l'ovulation et les techniques de reproduction humaine assistées).

Matériel et méthode: Nous avons conduit une étude prospective, comparée dans un groupe de 65 patientes âgées au-dessous de 37 ans, entre 2014 et 2015. Nous avons divisé au hasard les 65 personnes du groupe d'étude en 3 sous-groupes, selon le désir de la patiente: le groupe A - pour lequel l'option du traitement choisi était le monitoring échographique constante (périodique) de l'ovulation et l'acte sexuel programmé; le groupe B, le traitement choisi était IUI et le groupe C, le traitement choisi résidait en la technique de la reproduction humaine assistée.

Résultats: Parmi le nombre total de 65 patientes incluses à notre étude, 9 patientes (13,85% du total des patientes) ont obtenu une grossesse et 44,44% des grossesses ont été obtenues par FIV (fertilisation in vitro) (4 grossesses obtenues par FIV - sous-groupe C, comparées au total de 9 grossesses des sous-groupes A, B, C). A

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Conclusion: We consider assisted human reproduction as the therapy of choice regarding this pathology, even more because any other treatment option is time consuming, and the patient's age is a main variable when it comes to the success of the procedure.

Key words: idiopathic infertility, intrauterine insemination, IVF

partir de 9 grossesses obtenues, 3 étaient multiples, ce qui conduit à un taux de chances de grossesse multiple de 33,33%.

Conclusion: Nous considérons la reproduction humaine assistée comme une thérapie de choix concernant cette pathologie, d'autant plus que toute autre option de traitement est une consommation du temps et l'âge de la patiente est une variable principale lorsqu'il s'agit du succès du procédé.

Mots clefs: l'infertilité idiopathique, l'insémination intra-utérine, la fécondation in vitro

INTRODUCTION

Over the last few years, progress has been rapid and spectacular in the diagnosis and treatment of couple infertility and it is more than likely related to the development of assisted reproductive technologies, their widespread use and cost their prices relative to income. Therapeutic options depend on the cause of infertility, a correct and precise diagnosis in this regard being, in most cases, the key to success [1].

Infertility currently affects approximately 1 in 7 couples and is defined as the absence of conception after a year of unprotected sex. The diagnosis of idiopathic infertility is only made if the results of the basic infertility evaluation tests (semen analysis, tubal patency test, highlighting ovulation) show no faults to justify the absence of pregnancy. The incidence of infertility of unknown cause is 15-30% [2,3].

Semen analysis is still the main element in the investigation of the masculine factor, and if an abnormality is revealed, the test should be repeated within a month in a laboratory that works according to WHO criteria. Postcoital test has been shown to have a weak correlation with both spermogram parameters and pregnancy rate values, which is why it is currently abandoned by most specialists.

Ovulation defects occur in approximately 40% of the feminine infertilities cases and 15% of the couple infertilities cases and are easily and properly investigated based on the personal medical history, hormonal dosages in dynamics, endometrial biopsy and the ultrasound monitoring of the ovulation. Although mapping the basal body temperature is the cheapest method of investigating feminine infertility, it is no longer a part of the routine testing of ovulation for it has been proved that it is imprecise when compared to the methods mentioned above which have become mandatory in the routine testing of ovulation (hormonal dosages in dynamics, endometrial biopsy and the ultrasound monitoring of the ovulation) [3].

Determining the ovarian reserve is currently mandatory in all cases of infertility, the most important parameters being the number of antral follicles which are counted during an ultrasound in the early follicular phase and the antimüllerian hormone value (AMH). The results of these tests are not absolute indicators of infertility, but if abnormalities are revealed they correlate very well with a poor response to the stimulation of ovulation and pregnancy rates of IVF.

The role of laparoscopy has significantly changed over the past few years; initially it was considered an almost mandatory step in the evaluation of infertility, but now it is only addressed to selected cases. According to the ASRM protocol it is only indicated when endometriosis is suspected, in unexplained infertility and also in pelvic adhesion syndrome.

Therefore, the diagnosis of idiopathic infertility can be made only after a full evaluation that does not indicate any fault at any level. Treatment is, in this cases, by definition empirical because it cannot be addressed to an etiological or pathophysiological factor nor to an organic malfunction. The main alternatives are scheduled sexual intercourse with constant ultrasound monitoring of the ovulation, ovarian stimulation with clomifen citrate and intrauterine insemination (IUI), ovarian stimulation controlled with gonadotropins and IUI or assisted human reproduction techniques.

Epidemiological studies have indicated a low fertility rate in women who smoke, who have a body mass index either too small or too big or who excessively drink alcohol.

The pregnancy rate in couples with infertility of unknown cause is less than the one in fertile couples, but still greater than zero, which could mean that these couples might actually be situated at the base of the distribution curve of fertility in general population thus explaining the „subfertility” term. Meanwhile, it is possible that in some of these cases there might be an actual cause of the infertility which is so subtle that it makes it impossible to be detected using available tests. Recent studies have indicated a cumulative rate of pregnancy of 10 to 15% in these couples per year without any treatment [2,3]. As expected, the woman's age negatively influences the rate of pregnancy in couples who have been having scheduled sexual intercourse. This therapeutic option is definitely the cheapest, but the success rate is low when compared to other methods. Anyhow, it can be considered a first line option if the woman is young and the depletion of ovarian follicles is out of the question.

Laparoscopy is still an option in the case of idiopathic infertility for it could identify a cause that cannot be revealed with other methods like minimal and mild endometriosis. Data gathered from various studies is controversial; A Cochrane review conducted in 2002 shows that laparoscopy performed in minimal and mild endometriosis increases the pregnancy rate, but that additional studies are still required. Currently there is no review that supports laparoscopy as a

mandatory investigation or as a treatment for these patients. [5]

Intrauterine insemination involves placing prepared sperm into the uterine cavity at the exact time of ovulation. This procedure can be performed in terms of a natural cycle with ultrasound monitoring or in terms of a stimulated ovulation achieved via clomifen citrate or gonadotropins treatment. It is now certain that, in the case of an intrauterine insemination, the pregnancy rate is higher when ovulation is artificially stimulated by treatment.

PURPOSES

Considering the fact that there are no certain indications regarding the therapeutic sequence in the treatment of idiopathic infertility, the Infertility Specialists' Community recommends that the first treatment applied to these patients would consume fewer resources- the constant ultrasound monitoring of ovulation and scheduled sexual intercourse- and only if this method fails, should we take into account treatments consuming resources proportionally higher. Although many experts are currently using clomifen citrate in order to achieve a controlled ovarian hyper-stimulation, studies show that ,without a doubt, there is no increase in the rate of living newborns coming from these couples that suffer from idiopathic infertility in patients with ovulation confirmed [4].

Laparoscopy is now indicated by experts both as a part of the diagnosis scheme and as a treatment option.[5] The reasons behind this approach are relatively clear, many women diagnosed with idiopathic infertility are suffering from occult endometriosis or pelvic adhesion syndrome which could be treated with the help of diagnostic laparoscopy. However the American Society for Reproductive Medicine indicates laparoscopy only for young patients who suffer from a long time infertility (more than 3 years) and to whom no other faults were identified. [6]

Even though Intrauterine Insemination- preceded or not by a stimulated ovulation- is a widely used method in treating the infertility of unknown cause, randomized studies show conflicted results on the effectiveness of this method. It has been proved that associating IUI with controlled ovarian hyper-stimulation has a higher rate of success- the rate of obtaining a pregnancy is, according to some authors, 33% in this case- when compared with simple IUI that has an 18% success rate.[7] In the event of the failure of the first IUI cycle we ask ourselves if this procedure should be repeated or not and when we decide when to try another treatment option. A 2011 study shows that the efficiency rate of IUI after 3 cycles is stationary therefore repeating it after the third cycle's failure is not going to bring significant benefits, this being the moment when other therapeutic methods should be taken into account and proposed to the patient. [8]

In Vitro Fertilization (IVF) has been proven as the most effective method and it is, in many cases, the last resort in the treatment of idiopathic infertility. Data provided in 2006

by SART (Society for Assisted Reproductive Technology) suggests an increased efficacy of this technique both in women aged under 35 (the rate of living newborns- 40.5%) and in women aged between 35 and 37 years, age group in which the success rate is 38.9%. Even though IVF is often associated with ICSI (Intra-Cytoplasmic Sperm Injection), studies have not shown an improvement in the success rate of a joint venture of the two. [9][10]

The purpose of our study is to determine the efficacy of IUI for couples suffering from idiopathic infertility, regarding both the rate of obtaining a pregnancy and the rate of living newborns compared to other methods (scheduled intercourse with constant ultrasound monitoring of the ovulation and Assisted human reproduction techniques).

MATERIAL AND METHOD

We have conducted a prospective, comparative study in a group of 65 patients aged under 37, between 2014 and 2015. We have included in the study group patients who suffered from infertility, who could not obtain a pregnancy despite their various attempts periods between 1 to 5 years, who have not been subjected to any infertility treatment before our study and whose partners' spermograms were normal according to WHO criteria. The main criterion used for including these patients into the group was the diagnosis of infertility based on the ASRM (American Society for Reproductive Medicine) protocol. We have evaluated the ovarian function by dosing the progesterone at the middle of the luteal phase with a cut-off value of 3ng/ml and the ovarian reserve using both the AFC (Antral Follicle Count) and the AHM concentration (Serum Antimullerian Hormone). ASRM defines the antral follicle as the follicle sized 2 to 10 mm, mentioning that a low AFC (3 to 6 follicles) is often associated with a poor response to ovarian stimulation during IVF. [11] We have included in this study those patients whose AMH was higher than 1ng/mL - an AMH situated below this value is associated with a poor response to ovarian stimulation and a low quality of the embryo- the results of the IVF being in most cases below our expectations. [12] We have excluded uterine and Fallopian tubes (salpinges) pathology using HSG (Hysterosalpingography) as it was the most convenient and cheap method, even though studies show that its sensitivity is low when compared to sonohysterography, the method of choice for the present cases. [13][14][15] For patients with a clinical, laboratory and personal history indicating a peritoneal cause of infertility (endometriosis, pelvic adhesion syndrome) laparoscopy was used as a diagnostic step in order to exclude or include them into our study group.

We have randomly divided the 65 persons study group into 3 subgroups taking into account the patient's wish:

- Group A - 17 patients for whom the chosen treatment option was scheduled sexual intercourse associated with constant ultrasound monitoring of the ovulation;
- Group B - 34 patients for whom the chosen treatment option was:

- ◆ for 7 patients- IUI without ovarian stimulation;
- ◆ for 10 patients-IUI associated with ovarian stimulation with clomifen citrate;
- ◆ for 17 patients – IUI associated with ovarian stimulation with Gonadotropins;
- ◆ Group C- 14 patients for whom the chosen treatment consisting in assisted human reproduction techniques.

RESULTS

Scheduled sexual intercourse

To the 17 couples in group A, for whom we have chosen scheduled sexual intercourse associated with constant ultrasound monitoring of the ovulation, lowering their BMI (Body Mass Index) was indicated as well as reducing alcohol drinking, coffee drinking, smoking, the stress level, better yet completely dropping them, if possible. These patients were not recommended any other methods of determining the ovulation like measuring the basal body temperature or ovulation tests [16]. After a 6 months period, only one of these patients was able to get pregnant and to give birth to a living newborn-representing a 5.88% success rate. The patient was 29 years old and has been suffering from infertility for 15 months previous to our study. No pregnancy ending in spontaneous abortion was achieved. It is important to remember that the patients included in this subgroup have tried to get pregnant on their own for 1 to 2 years previous to the beginning of this study. Because of the small number of patients included in this subgroup the failure or success of only one of them majorly modifies the data obtained.

Intrauterine insemination

- Group B - 34 patients for whom the chosen treatment option was:
 - ◆ for 7 patients- IUI without ovarian stimulation;
 - ◆ for 10 patients-IUI associated with ovarian stimulation with clomifen citrate;
 - ◆ for 17 patients – IUI associated with ovarian stimulation with Gonadotropins.

Patients who underwent IUI without ovarian stimulation were recommended to monitor their ovulation using urinary detection tests of the LH level starting in the 12th day of the menstrual cycle and performing the IUI procedure 20 to 30 hours after the LH peak level. A maximum of 0.5 ml of sperm suspension- that was previously prepared according to the current standards- were placed in the uterine cavity via a 10 cm long intrauterine insemination catheter. Couples were recommended to avoid sexual intercourse starting from day 12 of the menstrual cycle until the day after the IUI procedure. On the 7 patients who underwent 1 to 3 cycles of IUI- a total number of 16 cycles of IUI were performed- the success rate was of 14,28% per case (1 out of the 7 was able to obtain a viable pregnancy) and of 6,25% per procedure (1 positive result out of 16 performed procedures). None of the 16 procedures ended with a

spontaneous abortion. We remind you again that that small number of patients included in this subgroup has represented a disadvantage for this study for it only takes a minimal change in a single variable to majorly influence the final results.

In the case of applying controlled ovarian stimulation associated with IUI, a cycle of clomifen citrate involved administering 50 mg of CC daily starting in the 3rd day of the menstrual cycle, doing a trans-vaginal ultrasound and dosing the progesterone in the luteal phase previous to performing the actual IUI. Following 1 to 3 cycles of IUI per patient associated with clomifen Citrate- a total number of 22 IUI procedures were performed- 1 out of the 10 patients has obtained a singleton pregnancy which led to a success rate of 10% per case and 4.54 per procedure (1 positive result out of 22 performed procedures).

For the subgroup of 17 patients for whom we have used the IUI associated with ovarian stimulation with Gonadotropins (Monopur, Gonal F, Purgeon) 1 to 3 procedures per case were performed- a total number of 45 procedures were made. 2 patients out of 17 managed to get pregnant which led to a success rate of 11.76% per case and 4.44 per procedure (2 positive results out of 45 performed procedures). Out of the 2 pregnancies achieved via this therapeutic method one was a multiple pregnancy which means a 50% chance of obtaining a multiple pregnancy using this treatment.

Out of the 27 cases of IUI associated with ovarian stimulation- 10 of which via clomifen citrate treatment and 17 via Gonadotropins treatment- for which a total number of 67 IUI procedures were performed, 3 pregnancies were achieved leading to a success rate of 11,11% per case and 4,47 per procedure (3 positive results out of 67 performed procedures). Out of the 3 pregnancies obtained only one was multiple. Within the B subgroup treated with IUI, 4 out of 34 cases obtained a pregnancy which means a 11,76% rate of success- significantly higher compared to the A subgroup success rate that was only 5,88%.

In vitro fertilization

Within the C subgroup for which we have chosen the assisted human reproduction techniques as a treatment, IVF was applied in 1 to 3 procedures per case (a total of 20 procedures)- 10 of these cases come from the B subgroup that underwent IUI but could not obtain a pregnancy and the other 4 cases were treated with IVF as a first line option. The rate of the pregnancies achieved via this method was of 28.5% (4 living newborns) relative to the number of patients involved and of 20% relative to the number of procedures performed (4 pregnancies obtained after a total number of 20 procedures made). Out of the total 4 pregnancies achieved via IVF, 2 were multiple (50% chance of obtaining a multiple pregnancy via IVF).

Basically, out of a total number of 65 patients that were included in our study, 9 patients (13,85% out of the total patients) have obtained a pregnancy, and 44,44% of the pregnancies were achieved via IVF treatment (4 pregnancies obtained with IVF- subgroup C- compared to a total of 9 pregnancies within A, B and C subgroups).

Out of the 9 pregnancies obtained 3 were multiple which led to a rate of 33.33% chance of multiple pregnancy.

DISCUSSIONS

Before settling for unexplained infertility as the correct diagnosis, a couple should undergo various tests including analyzing the seminal material, testing the ovulation, evaluating the ovarian reserve, imagistic investigations that allow us to determine the permeability of the Fallopian tubes and last but not least laparoscopy which helps us investigate both the uterine and peritoneal factors.

Once this diagnosis is made, the main methods of maintaining a pregnancy are: scheduled sexual intercourse and constant ultrasound monitoring of the ovulation, simple ovarian stimulation using clomifen citrate, Intrauterine Insemination associated with ovarian stimulation with CC or Gonadotropins, Intrauterine Insemination without ovarian stimulation and assisted human reproduction techniques. When options for couples who suffer from unexplained infertility are analyzed it is recommended that a simple treatment should be of choice before turning to more complex ones and to balance what is already known about the efficiency of these treatments versus their costs and their benefits versus their risk of adverse reactions.

Intrauterine insemination of the sperm may improve the chance of getting pregnant by overcoming the cervical barrier as a main mechanism. Observational studies suggest a tripling of pregnancy rate in patients diagnosed with unexplained infertility via IUI associated with gonadotropic ovarian stimulation (superovulation). Superovulation correlated with IUI is highly superior regarding the rate of living newborns when compared to IUI without ovarian stimulation, but as a downside it involves the risk of obtaining a multiple pregnancy and an ovarian hyper-stimulation. In order to understand the rate of success of IUI we found that it takes 37 IUI procedures without ovarian stimulation for obtaining a living newborn. [17][18]

Oral clomifen citrate is a popular choice of treating idiopathic infertility for it is a cheap option, does not require a strict clinical monitoring and it is believed that it corrects the subtle ovarian malfunction. The disadvantages of this procedure consist in a higher chance of obtaining a multiple pregnancy and a higher chance of developing ovarian cancer. In order to choose this option you need to understand and balance both the risks and the benefits. The rate of living newborns is not higher in patients with unexplained infertility and confirmed ovulation to whom clomifen citrate was administered compared to unstimulated intrauterine insemination. It has been shown that, according to the studies, it takes 40 cycles of clomifen citrate for obtaining a viable, on term pregnancy. Gonadotropins therapy is superior to the clomifen citrate one and they are both more efficient when associated with IUI. [4]

CONCLUSIONS

The results of our study reinforce and confirm the data provided by other expert studies.

The global rate of IUI with or without ovarian stimulation is lightly higher regarding the living newborns obtained when compared to scheduled sexual intercourse and constant ultrasound monitoring of the ovulation method. Therefore, the empirical use of IUI associated or not with ovarian stimulation in the cases of unexplained infertility does not significantly improve the pregnancy rate compared to scheduled sexual intercourse and constant ultrasound monitoring of the ovulation attitude. Out of the 2 techniques of IUI, the one associated with ovarian stimulation has been proved to be more efficient.

Clinical trials show a decrease in the efficiency rate of the IUI as the woman grows older, so if we had chosen a patient group aged over 37 years old we believe we would have obtained a significantly lower success rate.

Considering the total number of the patients included in this study, our conclusions should be reinforced by randomized studies involving a much higher number of patients.

Consistent with our expectations the most efficient treatment of the idiopathic infertility was via assisted human reproduction techniques with a success rate of 28.5%.

We consider assisted human reproduction as the therapy of choice regarding this pathology, even more because any other treatment option is time consuming, and the patient's age is a main variable when it comes to the success of the procedure.

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