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Research Article

Preliminary results from research on the factors affecting the success of intrauterine insemination procedures

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SUMMARY: The best-developed and most commonly used method these days with sterile couples is intrauterine insemination. The review and analysis of materials in this field and our data lead to the conclusions that the methods are most successful with young patients, with low BMI, on a stimulated cycle, with slight male factor and when a soft catheter is used. The purpose of this research is to find in what way the various factors affect the success of asisted reproductiv tehnic (ART) procedure intrauterin insemination (IUI). Retrospective research was conducted of couples with primary and secondary infertility that underwent a treatment course and intrauterine insemination at Medical Center for Reproductive Health Dr Shterev Ruse in the period 2012-2015. Their total number was 162 cycles for a 4-year period from March 2012 to December 2015. Out of them 141 cycles were autologous and 21 were with sperm from donors. Our average pregnancy percentage was 10.49 % for the whole group of all couples. The group up to 30 years old was with the highest percentage – 33.33%, followed by the group 31-35 years of age - 21.74 %. For the group 36 up to 40 years of age the success was 7,70 %. With the couples over 41 years old there were no pregnant women. Our conclusion is that couples who are young up to 30 years of age and with a slight male factor that don't have comorbidities have the highest chance of getting pregnant. With the couples that underwent re-insemination on the next day the success was higher. Factors such as body mass index (BMI) , type of catheter and volume of material for application are not significant to increase the success percentage.

Keywords: asisted reproductiv tehnics, intrauterin insemination, success factors

Introduction

With the development of science, the discovery of new techniques for sperm processing and increase of the procedure success various types of insemination are applied, differing mainly in the approach in what way to administer the semen: intravaginal, intracervical, intrauterine and intrafallopian insemination. The essence of the procedure is in the application of preliminary processed husband or donor's sperm directly in the woman's uterus. The method is non-invasive and significantly cheaper than the various modifications of the in vitro fertilization(IVF). A condition for intrauterin insemination (IUI) is to have at least one open fallopian tube. On the day when the ovulation is expected, the husband provides material (semen), which is processed in a laboratory. The factors are of different nature as the most common are as follows: The woman's age is probably the most researched and discussed factor, which we and (1) monitor. This is due mainly to the egg cell quality, which after 30 years of age drastically decreases. Even if there is ovulation, the probability to have a suitable egg cell after 30-35 years of age decreases greatly. The male factor, according to most of the authors, is the next of importance, which we find. According to (2) in the research of 720 couples, the success is 9 % that increases to 11 % and 14 % after the application of two methods of selection of couples with better chance. The use of different types of catheters influenced the results even though in a small degree. In our research the use of a soft catheter resulted in 10.67% compared to a rigid catheter respectively 6.45%. According to (3) using catheter Wallace with included 180 women for 372 cycles the percentage of pregnancy is 16,4% and with catheter Tomcat with included 184 women for 375 cycles 18,1% are positive. This difference is not statistically significant ($p = 0.61$), and our higher percentage we explain with the small group compared to the quoted authors. The women and men body mass index (BMI) is also researched but its effect is relatively weak having impact on the percentage of pregnant women as our results are about 25 % with men and women. In a research of (4) from 260 (IUI) the percentage of pregnancy is 19.6% as it's not influenced by the BMI as we saw it. In a comparison between natural and stimulated cycles was observed significant increase of the pregnancy percentage. The stimulated cycle compared to the spontaneous one according to (5) also increases the % of multiple pregnancy. Authors such as (6) also inform that the induction of ovulation with

Clomiphene or folikul stimulation hormone (FSH) double increases the number of pregnant women from 4 to 8 %. In the process was evaluated the applied sample volume and it was found that it didn't affect the success. Author such as (7) informs that not the volume but the number of performed successive procedures is with the highest percentage after the third attempt.

The purpose of this research is to explore the effect of some of the main factors, defining the successful outcome of a procedure of intrauterine insemination thus to make correct selection.

Materials and methods

Retrospective analysis was conducted concerning the cycles of intrauterine insemination of women who underwent a treatment course at Medical Center for Reproductive Health Dr Shterev in the period 2012-2015. Their total number was 162 cycles for a 4-year period from March 2012 to December 2015. Out of tem 141 cycles were autologous and 21 were with material from donors. All patients filled in a standard form of informed agreement and they were tested for sexually transmitted diseases in detail pursuant to Regulation no. 28 of the Ministry of Health. The couples were separated in groups depending on their age, BMI, partner's semen analysis, ovulation stimulation, etc.

1.1. Information and survey methods - taking of past and family case history of the couple, explaining the procedure.

1.2. Clinical methods - taking of obstetric case history of the woman – analysis of her objective condition and gynecological status, andrological examination of the man and confirmation of pregnancy. Result – between 10^{th} and 12^{th} day after the intrauterine insemination, was found by the values of beta horion gonadotropic hormone (beta-hCG).

1.3. Sperm processing methods - after analysis of semen, it should be processed to isolate the well moving sperm. The processing methods that are used are two: swim up and gradient centrifugation (DGC). The processing method is chosen by the result of sperm analysis.

Preliminary results

The analysis of the relevant materials for the last 15 years reveals that with conventional intrauterine insemination with partner's sperm the results greatly vary (between 3 and 26% according to different authors). The factors, affecting the results of the intrauterine insemination procedures are plenty, as they generally are divided in two groups: physiological and technological. The physiological group consists of woman's age, general health status and analysis of the man's sperm. The technological factors are semen processing, cycle stimulation, volume of insemination sample, type of catheter, etc.

Table 1. Distribution of patients according their age and success %.

Age Female	Number	Pregnant	% Pregnant
<30	33	11	33.33
31-35	23	5	21.74
36-40	13	1	7.70
>41	4	0	0,00
Total	**73**	**17**	

Compared to the women's age groups (**Table 1**), it is seen that the insemination of women younger than 30 years of age is the most effective. With a group step of 5 years older, the percentage of pregnant women declines, while over 41 years of age, regardless of the small number of patients, is seen that the intrauterine insemination practically is useless.

Table 2. Distribution of male patients in age groups

Age M	Number	Pregnant F	% Pregnant
<40	65	17	26.15
>41	8	0	0.00
Total	**73**		

picture, but here we don't think that this difference is indicative because most probably Table 2 depending on the husband or partner's age up to 40 or over 41 shows a similar with the men over 41 their partner is approximately at this age and it is possible it to affect the percentage of pregnant women under 40 and over 41. To prove such a correlation especially for the men it is necessary to research a bigger group of patients.

Tabl. 3 BMI women

BMI F	Number	Pregnant	% Pregnant
<18	16	3	18.75
19-25	49	12	24.49
>26	8	2	25.0

It is clear from the table(3) that the BMI for women who undergo intrauterine insemination doesn't affect the percentage of pregnancy, however there is a certain trend for reduction of pregnancy with women who have lower weight. It is known from the relevant materials that the women with lower weight - BMI under 18 or over 26 the chance of getting

pregnant changes. Most probably almost the identical results for women with normal weight and overweight is due to the fact that the overweight is with small significance. Tabl.4 Tape of male factor

Semen Analysis	Number	Pregnant F	% Pregnant
olygoastenoteratozoospermia (OAT)	14	4	28.57
Astenoteratozoospermia (AT)	47	11	23.40
Normozoospermia (N)	12	2	16.66
Total	**73**		

Comparing pregnant women in table **4**, in relation to the degree of disruption of spermatogenesis, with oligoasthenospermia or asthenozoospermia were observed differences in the percentage of pregnant women, which can hardly be interpreted because of the number of tested men and number of cycles with insemination are too small to make a certain conclusion. Most probably the percentage of pregnant women here in the table is affected also by the relevant conditions or reasons for infertility of women for these paradoxically obtained results.

Table 5:Natural or stimulated cycle

Type of cycle	Number	Pregnant	% Pregnant
natural	28	5	17.87
stimulated	45	12	26.66
Total	**73**		

Table 5 shows the stimulated cycle advantage, regardless of the small number of researched on the account of the data of cycles. This is a logical result, because with the intrauterine insemination, the stimulation is limited. The dominant follicles are two or three at the most and it is normal with the bigger number of generally dominant follicles with ovulation to have more matured female reproductive cells than with the natural cycle and respectively with the results received.

Table 6. Type of catheter and sample volume

Catheter	Number	Pregnant F	% Pregnant
Long, flex	139	15	10,79
Short, flex	32	2	6,25
Volume			

Our results(tabl.6) show an average percentage of pregnancy from insemination - 10%. In practice different types of catheters are used as they vary in length, size, location of the distal end (distal or lateral disperse system), degree of sturdiness and resistance. As a whole there are some technical specifications, which are similar for all insemination catheters. Firstly, they should be easy to use, be hard enough to go along the curves of the cervix, but be also soft not to traumatize the endocervix and/or endometrium, the opening at the top of the catheter to be small to minimize the reflux of the insemination sample.

Discussion

There are some basic steps we should take when we diagnose infertile couples. Firstly, we determine whether it is about a male or female factor. The next step is to decide whether the problem can be solved with easier methods such as treatment of the couple, induction of ovulation or intrauterine insemination. The cases that will be affected by these methods should be separated or we should direct the couples for in vitro procedure.

The duration of infertility affects the type of method, which we'll apply. IUI shall be applied for treatment of couples that have unsuccessfully been making attempts to get pregnant for a year. An important moment is to forecast all aspects of the procedure and to exclude the cases for example with tubal and very severe male factor that are senseless. The duration of infertility appears to be one of the main factors defining the insemination result. A number of retrospective analyses among which and these of (8) reveal the direct connection between the duration of infertility and the percentage clinically pregnant women – about 10% with over 72 months, and 20% with less than 72 months the longest period is up to 5 years and it is always accompanied with fits of anxiety and depression. This dependence has been confirmed through the years by a number of authors, and so it stands out as one of the important factors for success. With the years it is getting more and more evident that the male factor equals the female one. To specify the male factors it is necessary to remove the reasons caused by women, with couples who undergo therapy before IUI. Microscopic examination of slides is mainly used for diagnostics. A standard or extensive sperm analysis is made. The lack of standard methods of sperm analysis is another thing that is difficult. At the moment the criteria proposed by the World Health Organization seem to be most standardized but the ranges of some of them can tolerate changes. The existence of more than one factor from men is rather a prerequisite to initiate an asisted reproductiv tehnic (ART)-procedure, than IUI. But for male subfertility, the IUI is a proven method of treatment, although the success in such cases is low. Semen analysis values – when an insemination is made, it is of high importance the husband's semen analysis to meet certain conditions. Normally, the values of the semen analysis to turn to insemination are as follows: concentration of sperm is about 15M/ml or 39 Mil in the whole sample; the values of progressively motile sperm shall be more than 32%.

After material processing, the values of the semen analysis shall be as follows: >1 M/ml with hyperactive sperm > 70-80%. The bigger the concentration, the better chance of success. Another aspect such as the sperm motility is of significant importance for fertilization. The mammals' sperm perform longitudinal sliding motion through rhythmic tail movements. Apart from the forward movement, there is rotational (helical) motion along the axis, which is favored by the asymmetrical structure of the head. The sperm motility is determined visually, as depending on the motion speed gametes group themselves in four classes World health organization (WHO), (9) What's the picture like with the woman is probably the most frequently asked question by the gynecologists in their practice. The female factor consists of some key elements. The first one is the patient's age. It's been proven that the woman's age directly corresponds to the quality and quantity of egg cells in the follicles. As a descriptive range is generally accepted that the woman up to 35 years of age has the best quality of egg cells. Up to this age and the percentage of normal pregnancy is very high. After 36 years of age the quantity and quality of egg cells and embryos drastically declines. Another problem – the thin endometrium. The normal endometrial thickness shall be 10-12 mm of M type on 10-14 day of the menstrual cycle. With values of the endometrium under 8 mm the receptivity and possibility of implantation of embryo decline. Some authors like (10) share this problem and try to solve it by low doses of Aspirin. This way, it increases its success from 9 to 24 %. Endometrium decreases after multitude of abrasions that lead to Asherman syndrome. The use of stem cells according to (11) leads to increase of the endometrial thickness with women who have the Asherman syndrome. The ultrasound testing gives the fullest picture of whether the cervical canal is stenotic or not. A series of scanning are made on the 5, 7 and 10^{th} day to evaluate the accumulation of secretion in the canal and whether its quantity corresponds to the type of endometrial epithelium. In the best case and according to us and (12), (13) and (14) on $1\text{-}12^{th}$ day with mucosa type 'M' 8-12 mm there should be about 2-3 mm in diameter secretion in the canal and it should have a triple layer look. In the cases of stenosis there is no SR syndrome and the secretion is scarce. Then dilatation of the cervical canal under anesthesia is made. It is diluted to Hegar number 8, which guarantees that up to 6 months after manipulation the canal will stay open. We believe that the best time for this is on the $8\text{-}10^{th}$ day of the menstrual cycle. Then the tissue is the softest and most susceptible. The factors that have purely technical effect are mainly four. The first one is the number of cycles with performed insemination. For the last 20 years plenty of suggestions of the maximum number of insemination cycles have been made, for example (15) suggests double IUI before to initiate in vitro insemination. Every country, as well as every reproductive clinic independently set the duration of treatment with IUI depending on the type of infertility, woman's age and other factors. Their average number is from 3 to 10. What type of catheter to be used in the procedure? Different types of catheters are used in the practice as they vary in length, size, location of the distal or lateral disperse system), type of rigidity and stability. Generally, there are some technical specifications that are similar to all insemination (16) catheters. Firstly, they should be easy to use, rigid enough to pass along the 'curves' of the uterine but also soft enough to avoid causing traumas on the endocervix and/or endometrium, catheter opening to be small to minimize the reflux of the insemination sample. Most authors and our experience prove that the type of catheter directly affects the success in IVF cycles and IUI – 15.3% success of IUI with the use of flexible catheter (soft) to 7% with the use of rigid catheter (hard).

Sample volume as a factor. With classical IUI and according to (17) the volume of the applied sample is 0.5 or lower, with high concentration of sperm cells (>20 M/ml). After 1991 a new method of IUI was introduced, which uses bigger insemination sample volume (4 ml) - uterine perfusion is made. The advantage of this method hasn't been proven undisputedly. With the evaluation of the sample volume deposited for IUI with a method of application hysterosalpingography was found that the first 0.4 ml of contrast reach the uterus, isthmus and the tube ampule. The infusion of big volume of material is not needed to reach the fallopian tubes. Through the years it has been found that the optimal quantity of insemination material is between 0.4 and 1 ml. Reinsemination – with available of more than one follicle or the application of hCG not all follicles got disrupted and the insemination is repeated on the next day. This is probably the most used technique as it is considered that its purpose is for the unclear of sperm velocity and the length of uterine tubes.

The processing of semen is carried out in specialized IVF laboratories, equipped with the apparatus and the suitable environment needed for this purpose. The processed sperm is applied in the uterus with a special, individual and disposable plastic catheter. The purpose of processing is to separate the fastest sperm cells as at the same time the gametes are washed away from the seminal plasma that consists of prostaglandins, lymphokines, cytokines, as well as antigens and infectious agents. The application of unprocessed ejaculate in the uterus can cause severe infections and even anaphylactic shock.

The indications to apply controlled intrauterine insemination are as follows: for men – moderate oligozoospermia; asthenozoospermia. In the cases with azoospermia or severe oligozoospermia is applied insemination with donor's sperm. For women the most frequent is the cervical factor, unclear infertility and impossible coitus due to ejaculation problems, impotence or vaginism.

Conclusions

The couples with the highest chance of success are those in which the woman is under 30 years of age with cervical or anovulatory infertility; the BMI of both partners is between 20 and 25; available normally motile sperm more than 10 M/ml.

Stimulated cycles should be preferred rather than unstimulated ones.

The best results are observed with the use of soft catheter. The insemination sample volume doesn't affect .

The success with IUI is 10-11 % and correlates with most of the other sources.

The results of donor inseminations are better in the cases with male infertility with azoospermia.

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