Predicting of successful implantation at IVF cycles

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Abstract

Many of the uterine infertility factors are associated with chronic endometritis. Its prevalence reaches 92.6%. Quality of endometrial transformation during the “implantation window” is the basis of successful fertility. In our retrospective comparative study of 101 in vitro fertilization (IVF) cycles, the efficacy of transvaginal Doppler ultrasound (TVDUS) in predicting successful implantation was evaluated. Inclusion criteria were as follows: age younger than 41 years and good quality of embryos. Exclusion criteria were as follows: 41 and older age, poor quality of embryos and uterine cavity lesions. The 1st group included 38 cases with the presence of endometrial blood flow (EBF). The 2nd group included 63 cases with the absence of EBF. TVDUS was performed before embryo transfer (ET). Significant differences of EBF were connected with age and duration of infertility. In women of less than 31 years old, EBF was detected in 47.4% cases versus 26.3% women of older age. EBF was not detected in 74.6% of the cases of duration of infertility for 5 years and more. Pregnancy rate was significantly higher in the 1st group (63.1% versus 26.3% women of older age. EBF was not detected in 74.6% of the cases of duration of infertility for 5 years and more. Pregnancy rate was significantly higher in the 1st group (63.1% versus 39.7%) and when endometrial thickness was 8–11 mm (52.1% versus 30.0%). We offer routine evaluation of endometrial thickness and EBF with TVDUS as a very helpful approach for predicting the implantation in IVF cycles.

Introduction

The number of couples diagnosed with infertility has increased significantly for the last 20 years. For the period from 1998 to 2012, in the Russian Federation, this figure increased by 1.9 times in numbers (from 48 to 78 thousand pers.), and the birthrate has not changed significantly [1]. Infertility prevalence is between 10 and 15% in the general population [2,3]. Its treatment by IVF is becoming increasingly popular in Russia. From 2000 to 2014, the amount of IVF cycles has increased more than tenfold (from 6003 to 69 662 cycles) [4], but IVF failures have no tendency to decrease. Routine methods of assessing the state of endometrium have relatively low predictive value for the fertile possibilities of the uterus, which can be attributed to insufficient knowledge of the endometrium receptation at gynecological diseases.

The endometrium (E) has dynamic features: cyclical growth, desquamation and regeneration. Its main function is to provide the possibility of the time-limited support of implantation of the embryo for further development. Most part of the menstrual cycle E is resistant to the embryo, but acquires special receptive properties in a limited space and time interval of the luteal phase, known as the “implantation window” [5]. “Implantation window” is characterized by morphological and histological changes in E, and is associated with changes in the activity of different functional systems of the participants of this dialog: the woman, E and the embryo.

Knowledge of the mechanisms controlling specific changes during the “implantation window” is the “key” to understanding not only the implantation process, but also the reasons of reproductive failures in gynecological diseases (chronic endometritis, endometriosis, uterine fibroids, hyperplasia). The basis of most gestation complications (preterm delivery, fetal growth restriction, preeclampsia) is placental insufficiency, but there is no consensus about fundamental pathogenetic mechanisms in the earliest stages of syncytiotrophoblast invasion. E receptivity is regulated by various factors, including endometrial perfusion. Its demise can be a significant factor in the basis of infertility. Several data proved the connection of reduced E receptivity and E vascularization deterioration in the luteal phase [6]. Inferiority placentation is characterized with incomplete endovascular trophoblast invasion and partial remodeling of the spiral arteries (SA), which underlies the IVF failures and gestational complications.

The three-layer structure and the thickness of more than 7 mm are the main sonographic markers of E receptivity, but false-positive value of these features is high. Adequate blood supply of E is a vital prerequisite for successful implantation. Normally, the perfusion at the SA level is detected in the luteal phase of the cycle and is associated with the “implantation window”. It is known that high pulsatility index in the uterine arteries is a predictor of implantation failure [6,7]. There is no doubt that the presence of EBF is a sign that has a predictive value in regard to success of implantation at ET. Because blastocyst is implanted in E, it is expedient to indirectly evaluate its receptivity by the adequacy of EBF.
During recent years, the search for predictors of successful implantation by noninvasive methods with a high predictive value remains an important issue.

Methods

Our retrospective comparative study included 101 IVF cycles performed in the assisted reproductive technologies clinic “Test-tube babies” from 1 January 2014 to 30 November 2015. ET was carried out in the protocol of ovarian stimulation (at low risk for developing ovarian hyperstimulation syndrome) and in frozen-thawed ET cycles. The women with primary and secondary infertility caused by various reasons (chronic endometritis, tubal factor, endometriosis, polycystic ovarian syndrome – PCOS), including couples with unexplained infertility were the contingent of the research. Inclusion criteria were as follows: age younger than 41 years and good-quality embryos. Exclusion criteria were as follows: poor-quality embryos, the presence of endometrial pathology (adhesions, submucous uterine fibroids, hyperplasia), fibroids of large size, hydrosalpinx, severe extragenital disorders. The patients were divided into two groups according to Doppler findings: 38 cases of registered EBF were in the 1st group, 63 cases of absence of EBF were in the 2nd group.

Transvaginal ultrasound (TVUS) was performed twice (on day 2 and 9 of spontaneous/induced menstrual cycle) to evaluate the thickness and triple-layer endometrial pattern. TVDUS was performed on day 20–24 in the menstrual cycle, preceding the ET. During the blind TVDUS (the specialist did not know the results of clinical examination), uterine perfusion was evaluated at different levels: the left and right uterine arteries, arcuate arteries, radial arteries, basal arteries, SA. We applied scanner Esaote My Lab 70 (Esaote, Italy), cavital transducer 6–10 MHz. Sagittal and cross-section view of the uterus and ovaries was obtained, the thickness of E was assessed measuring from outside to outside at its widest point. The PWD characteristics in all the examinations were as follows: normal quality of color, pulse repetition frequency of 500 Hz, wall motion filter of 50 Hz, maximum velocity of 6 cm/sec in the SA. Resistance index was evaluated automatically. Resistance index of ≤0.52 at SA level was regarded adequate.

For the 3 months prior to entry into the IVF protocol, all women received folic acid supplements (folic acid 400 mcg + cyanocobalamin 2 mcg/day). In frozen-thawed ET cycles, E proliferation induction was carried out with estradiol (17β-ethinylestradiol at a dose of 0.5 to 2 mcg/day, transdermally). Estradiol administration started at day 2 or 3 of the menstrual cycle in the absence of cysts in the ovaries and the E thickness less than 5 mm. Progesterone (micronized progesterone at a dose of 100 to 400 mg/day, per vaginum) was used for luteal phase support. Peripheral blood levels of β-hCG were evaluated in 2 weeks after ET, pregnancy test was considered positive if β-hCG levels >50 IU/L.

Statistical analysis was performed using Microsoft Office Excel 2010, in 95% confidence interval. Standard deviation was analyzed using t-test, p value <0.05 was regarded as significant.

Results

The groups were matched for age, body mass index (BMI), duration and reasons of infertility. There were no significant differences in the age and BMI. Significant differences of EBF depending on the age, the duration and the reason of infertility were revealed (Table 1).

EBF was registered in 47.4% of cases at the age under 31 versus 26.3% of cases at the age of 31–35 years old, which is 1.8 times less (p<0.05). The results were correlated with duration of infertility. In the 2nd group, infertility duration of ≥5 years predominated (74.6% versus 18.4%, p<0.05). In the presence of chronic endometritis, adenomyosis and unexplained infertility, the absence of EBF is significantly more frequently detected. In the 2nd group, a combination of infertility factors was also significantly higher reported (55.6% versus 18.4%, p<0.05).

A statistically significant difference in the pregnancy rate per ET depending on the E thickness is established (Table 2). At E thickness of 8–11 mm, pregnancy rate was significantly higher (52.1% versus 30.0%) than when the E thickness was less than 8 or more than 11 mm.

Total pregnancy rate per ET was significantly higher in the 1st group (63.1% versus 39.7%) respectively. Thus, the highest pregnancy rate per ET was registered in cases of registered EBF and E thickness of 8–11 mm.

Table 1. Demographic characteristics, duration and reasons of infertility.

| Infertility factors     | 1st group | 2nd group | p Values |
|------------------------|-----------|-----------|----------|
| Women age, years       | N %       | N %       |          |
| 20–25                  | 6 15.8    | 8 12.7    | 0.066    |
| 26–30                  | 18 47.4   | 18 28.6   | 0.028    |
| 31–35                  | 10 26.3   | 28 44.4   | 0.031    |
| 36–40                  | 4 10.5    | 9 14.3    | 0.074    |
| Infertility duration, years |          |          |          |
| <5                     | 31 81.6   | 16 25.4   | 0.049    |
| ≥5                     | 7 18.4    | 47 74.6   | 0.003    |
| Infertility factors    |           |           |          |
| Tubal factor           | 3 7.9     | 5 7.9     | 0.690    |
| Adenomyosis            | 5 13.2    | 27 42.9   | 0.043    |
| Chronic endometritis   | 11 28.9   | 54 85.7   | 0.027    |
| PCOS                   | 21 55.3   | 12 19.0   | 0.041    |
| Unexplained infertility| 2 5.2     | 7 11.2    | 0.044    |

Table 2. Pregnancy rate in IVF cycles.

| Endometrial thickness, mm | 1st group | 2nd group | p Values |
|---------------------------|-----------|-----------|----------|
|                           | n %       | n %       |          |
| <6                        | 2 5.3     | 1 2.6     |          |
| 6–7                       | 6 15.8    | 2 5.3     |          |
| 8–9                       | 14 36.8   | 11 28.9   |          |
| 10–11                     | 8 21.1    | 6 15.8    |          |
| 12–14                     | 7 18.4    | 4 10.5    |          |
| >14                       | 1 2.6     | 0 0.0     |          |
|                           | 4 6.3     | 0 0.0     | 0.085    |
|                           | 13 20.6   | 2 3.2     | 0.081    |
|                           | 24 38.1   | 12 19.0   | 0.038    |
|                           | 15 23.8   | 8 12.7    | 0.044    |
|                           | 4 9.5     | 2 3.2     | 0.057    |
|                           | 1 1.6     | 1 1.6     | 0.092    |
Discussion

The study affirms [5,2] that the E thickness and its structure, as well as its adequate vascularization are useful prognostic factors in relation to ET success in IVF cycles. The data on the minimal E thickness for a successful pregnancy vary in the literature. At E thickness less than 7 mm, pregnancy after ET does not occur in the vast majority of cases; however, other studies [6] refer the cases of pregnancy at E thickness of 6 mm. Some data [7] reported the pregnancy occurrence at E thickness 4 mm. The E thickness of more than 14 mm is associated with a higher risk of pregnancy failure.

In our study, the maximum total pregnancy rate per ET was at a E thickness of 8–11 mm and was 52.1%. Pregnancy occurred in only one case at the E thickness less than 6 mm.

There are conflicting data about correlation between EBF and subendometrial blood flow and implantation rate in the spontaneous/IVF cycles [7]. However, assessment of EBF is a useful clinical approach which has predictive value for determining the likelihood of implantation in IVF cycles. Some studies have shown that the measurement of EBF plays [8] the key role in the indirect assessment of E receptivity and can determine implantation prognosis [6,3], and the detection of EBF prior ET is a significantly reliable sign to predict implantation.

In our study, the pregnancy rate per ET was significantly higher (63.1% versus 39.7%) in the cases with the presence of EBF. In the 1st group, pregnancy rate per ET was 1.6 times higher. This confirms the importance of routine TVDUS for predicting ET success in IVF cycles.

Conclusion

It is advisable to carry out a comprehensive assessment of the E thickness and EBF by TVDUS before ET in IVF cycles to predict implantation success. Being applied routinely, this diagnostic approach will reduce the number of implantation failures and significantly improve the efficacy of IVF procedure.

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Declaration of interest

The authors report no declarations of interest.

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