

THICKENING OF THE JUNCTIONAL ZONE (EXCEEDING 10MM) IS AN INDEPENDENT RISK FACTOR FOR DECREASED IMPLANTATION RATES

Surcel M.¹, Micu R.¹, Axente D.², Nemeti Georgiana¹, Zlătescu Cristina¹, Gârlovanu
Marinela¹, Surd Stela¹, Caracostea Gabriela¹

1 Obstetrics- Gynecology 1 Clinic, Cluj –Napoca, Romania

2 Surgery V Clinic „ Clujana”, Cluj- Napoca, Romania

Abstract

Introduction: The junctional zone is a distinct entity with a significant role in the implantation process. The aim of this study is to evaluate the impact of junctional zone thickening on the process of implantation in patients undergoing in vitro fertilization (IVF) procedures.

Material and method: Patients undergoing IVF protocols were divided into three subgroups according to the thickness of the junctional zone (JZ): group A (JZ < 6mm), group B (JZ 7-9mm), group C (JZ > 10mm). The main parameters noted were implantation rates, pregnancy rates and abortion rates.

Results: The study group included 88 patients, 38 patients in group A, 32 patients in group B and 18 patients in group C. Pregnancy rates were 47,2% (group A), 40,6 % (group B) and 16,6% (group C) (p- 0,02, comparison between groups A and C) and implantation rates were 30,3% (group A), 27,2 % (group B) and 12,5% (group C) (p- 0,01, comparison between groups A and C).

Conclusion: Patients with JZ thickness over 10mm have a poor prognosis of implantation. Patients with JZ thickness ranging 7-9mm treated in the long protocols with gonadotropin releasing hormones (GnRH) agonists presented similar pregnancy rates with the general population.

Rezumat: Îngroșarea zonei joncționale (peste 10 mm) este un factor de risc independent pentru ratele scăzute de implantare

Introducere: Zona de joncțiune este o entitate distinctă cu un puternic rol în procesul implantării. Scopul studiului este de a evalua impactul îngroșării zonei de joncțiune asupra procesului de implantare la paciente aflate în proceduri de fertilizare in vitro (IVF).

Material și metoda: Pacientele aflate în protocol IVF au fost divizate în trei grupe în funcție de grosimea zonei de joncțiune (ZJ): Grup A (ZJ < 6mm), Grup B (ZJ 7-9mm), Grup C (ZJ > 10mm). Parametrii principali urmăriți au fost: rata de implantare, rata de sarcini și rata de avort.

Rezultate: Lotul studiat a cuprins 88 de paciente: 38 grup A, 32 grup B și 18 grup C.

Rata de sarcini a fost 47,2% (grup A), 40,6 % (grup B) și 16,6% (grup C) (p- 0,02 comparație grup A și grup C), iar rata de implantare a fost 30,3% (grup A), 27,2 % (grup B) și 12,5% (grup C) (p- 0,01 comparație grup A și grup C).

Concluzie: Pacientele cu dimensiuni ale ZJ peste 10 mm au un prognostic slab de implantare. În schimb pacientele cu zona de joncțiune cu dimensiuni 7-9 mm aflate sub protocol cu AgGnRh au prezentat rate de sarcina similare populației generale.

Cuvinte cheie: FIV, zonă joncțională, implantare

Introduction

Assisted reproduction techniques (ART) have advanced in the past 20 years. Alongside the more intimate understanding of the reproductive phenomenon there was a parallel technologic leap. The greatest obstacles identified by the authorities in the field are embryo quality and faults in the implantation process. Most studies were focussed on assessing endometrial receptivity. Recent data discuss the importance of uterine contractility or the junctional zone (1).

The junctional zone was first characterised by Werth in 1898 but morphological and functional data regarding its role were available only in later decades. It represents the internal portion of the myometrium, with a common embryologic origin to the endometrium in the paramesonephric ducts, fact which individualizes it from the external portion of the myometrium of non-paramesonephric origin (1).

From a functional point of view, the JZ is the starting point for non-obstetrical uterine contractions being thus implicated in phenomena such as menstruation and implantation.

From a pathogenetic point of view the dysfunctionality of the JZ may have clinical serious consequences: dysmenorrhea, menorrhagia or infertility.

Imaging studies conducted in the last years allowed the more detailed examination of the uterus and the JZ (2,3). Alterations in the behaviour of the junctional zone were firstly described in the context of adenomyosis. However, there is a current of opinion launched by Tocci which states that damage to the JZ is not attributable solely to adenomyosis but it affirms the existence of a distinct endometrial-subendometrial myometrium unit disruption disease (4).

Clinical research targeting implantation were focussed on certain pathologies (adenomyosis, endometriosis, leiomyoma) not taking into consideration a possible involvement of the JZ.

In the present study we aimed to evaluate the impact of JZ thickness on implantation in IVF procedures.

Material and method

This an observational-retrospective study conducted in the Obstetrics-Gynecology I Clinic Cluj-Napoca on infertile patients undergoing IVF treatment during January 2016 – July 2017.

Patients followed the standard investigation protocols which included the evaluation of the uterine cavity by sonohysterography. Patients enrolled in the study were aged 25-35 years, had a normal ovarian reserve (antral follicle count 12-22), body mass indices 20-29, and had no associated pathologies such as endometriosis or uterine pathology - adenomyosis, uterine fibroids, uterine malformations. We also excluded from the study those patients in whom sonohysterography showed images suggestive of adenomyosis (obviously, except for those with JZ thickening).

When performing the sonohysterography, according to the thickness of the JZ we divided the patients into three subcategories: group A (JZ < 6mm), group B (JZ 7-9mm), group C (JZ > 10mm).

In order to attain a better homogeneity of the study groups we only enrolled patients stimulated with a long protocol (GnRH agonists). The stimulation protocol was the same in all patients, the gonadotropin dose (Menopur 75, Gonal F, Puregon) being the set according to clinic and paraclinic parameters. Follicular development was monitored by ultrasound. HCG trigger was accomplished when we reached > 3 mature follicles (>18mm) with ovarian puncture 36 hours later. The embryos obtained were evaluated according to the standard classification (ASEBIR consensus). The number of embryos transferred were decided by each couple. Only patients where A class embryos were enrolled into the study groups. Luteal phase support was done by means of vaginal progesterone administration (300mg/day), acetylsalicylic acid (75mg/day) and folic acid (400mcg/day). We performed the pregnancy test 14 days following embryo-transfer, values higher than 25 IU/ml being considered as successful pregnancy. The number of embryos implanted was evaluated 5 weeks after the time of the ovarian puncture. A new examination was then performed at 10 weeks following the ovarian puncture

in order to establish the first trimester miscarriage rate.

The following tests were performed for the statistical analysis: the student test, the F (ANOVA) test, for ordinal variables – the Mann Whitney test, and for dichotomic variables the logistic regression curve. The statistical relevance threshold used was $p < 0.05$.

Results

Following the selection process we included in the study groups 88 patients which were randomised in the three groups described above as follows group A (ZJ < 6mm) = 38 patients, group B (ZJ 7-9mm) = 32 patients, group C (ZJ > 10mm) = 18 patients. Demographic characteristics were relatively uniform in the three study subgroups, there were no statistically significant differences (table 1).

The intrauterine pregnancy rate was similar between groups A and B (a small difference, no statistical significance). However between groups A and C there was a statistically significant difference (47,2% vs 16,6%). The same tendency was noted

regarding implantation rates between groups A and C (30,3% vs 12,5%). The miscarriage rate was also very high in group C compared to the other study groups (33,3% vs 11,1%) but without statistical significance (table 2). We tried to identify the threshold thickness of the JZ which may lead to altered implantation potential, but the study population was too small to achieve statistical significance.

Discussions

The data obtained from our study confirm the negative impact of the JZ thickening upon implantation rates. Moreover, we can make a distinction between the slight thickening (7-9mm) with minimal changes (without reaching statistical significance) and the important thickening (>10mm) with very low implantation rates (with statistical significance). We could not make correlations between the thickening of the JZ and endometrial thickness or hormone levels.

Considering our study design which meant eliminating those cases with certified adenomyosis or endometriosis, we have solid arguments to affirm

Table 1: Demographic characteristics of the study populations.

	Group A: 38 patients ZJ 3-6mm	Group B: 32 patients ZJ 7-10mm	Group C: 18 patients ZJ > 10mm	p1	p2
Age	32,2 +/- 2,1	30,8 +/- 3,2	29,7 +/- 2,9	NS	NS
Duration of infertility	4,2 +/- 2,6	3,9 +/- 3,2	5,1 +/- 1,8	NS	NS
Body mass index	23,7 +/- 3,2	24,7 +/- 2,8	22,9 +/- 3,9	NS	NS
Endometrial thickness (HCG timing)	10,2 +/- 2,1	10,8 +/- 3,1	11,2 +/- 2,9	NS	NS
Number of day3 embryos transferred	2,2 +/- 0,8	2,0 +/- 0,6	1,8 +/- 0,2	NS	NS
Estradiol level on the HCG day	2900 +/- 1859	3300 +/- 1987	3300 +/- 1690	NS	NS
Progesterone level on the HCG day	0,7 +/- 0,3	0,6 +/- 0,2	0,7 +/- 0,2	NS	NS

p1 = group A- group B ratio, p2 = group A-group C ratio.

Table 2. Procedure results

	Group A: 38 patients ZJ 3-6mm	Group B: 32 patients ZJ 7-10mm	Group C: 18 patients ZJ > 10mm	P1	p2
Implantation rate	24/79 (30,3%)	18/65 (27,2%)	5/40 (12,5%)	0,08	0,01
Pregnancy rate	18 / 38 (47,2%)	13/32 (40,6%)	3/18 (16,6%)	0,251	0,02
First trimester miscarriage rate	2/18 (11,11%)	2/13 (15,3%)	1/3 (33,3%)	0,356	0,153
Ectopic pregnancy rate	1/18 (11,11%)	-	-	-	-

p1 = group A- group B ratio, p2 = group A-group C ratio.

that the JZ may represent an important factor in the process of implantation failure. The only slightly altered results obtained in the group with JZ thickness between 7-9mm may be due to the effect of the GnRH supression. In exchange, in the group of patients with JZ exceeding 10mm the effect of the GnRH agonist could not mask the alteration of the JZ.

Recent studies published in literature confirm the results of our study. The research of Moubon who addressed the impact of junctional zone thickness upon implantation rates objectified a much more pronounced involvement of the JZ with altered pregnancy rates. The discrepancy is partially explained by the lack of systematic use of GnRH aganists, respectively by the fact that patients with overt pathology (adenomyosis, endometriosis) were not excluded from the study (5,8).

There is clear data which attest the detrimental effect of adenomyosis on implantation (6,7,9,10,11). The underlying mechanisms in adenomyosis are diverse and consis in local steroid production imbalance (12,13), alterations of the immune system (14), modified interleukin expression and (15,16), obviously, chenage sin uterine kinetiks by alterations in the JZ or the adjacent myometrium (1,2,4). Administration of GnRH agonists preceding IVF procedures improved these dysfunctions in such a way that similar implantation rates with the general population were obtained (8).

Our study results allow us to place infertile patients with JZ over 10 mm in a category with poor

implantation prognosis compared to the general population. At the same time, for the category of patients with JZ between 7-9mm, the long protocole seems to be a reasonable solution leading to values similar to those in the general population. Moreover, we may state that changes in the junctionl zone may appear as a distinct pathologic entity, even in the absence of other imagistic pathologic elements.

The main limitations of this study are the small number of cases and the retrospective character of our analysis. Another confusion factor which was only partially controlled was represented byembryo quality. It is obvious that day 3 embryos, even if graded class A, may present anomalies incompatible with implantation which may not be detected by the current techniques and may thus directly alter the implantation process.

Conclusions

In conclusion, we may say that JZ thickness exceeding 10mm has a negative impact upon implantation. Patients with junctional zone thicknes of 7-9mm will present pregnancy rates similar to the general population when stimulated in the long protocole with GnRH agonists. Future studies will have to prospectively analyze this aspect as well as other possible therapeutic interventios for patients with JZ thickness >10mm, such as prolongation of the GnRH agonist supression from 6 weeks to 3 months.

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