The Association between The Thickness of the Endometrium at the Day of Human Chorionic Gonadotrophin Injection and the Outcome Intracytoplasmic Sperm Injection

Zainab Alkhafajy[1], Zainab Abd alkathem fatnan[2], Hayfaa Dinar Jaber AL Habeeb[3]

[1]Consultant OBG at AlZahraa Teaching Hospital Assistant Professor at Kufa Medical School, [2]Specialist OBG at Alzahraa Teaching Hospital At Kufa Medical School, [3]Specialist OBG At Almanathera Hospital

Abstract

Background: Clinically during ICSI, controlled ovarian stimulation (COS) is a famous way to increase the number of mature oocytes picked up. This method must be asseeed with a substantial danger of ovarian hyper stimulation syndrome (OHSS), which occurred if follicular induction is very strong. Along with multifollicular growth, COS is also resulting in increased serum concentration of estradiol (E2) that in turn may has effect on the receptivity of the endometrium .The high serum E2 concentration through COS may resulting either with an increased chance of pregnancy or an impaired reproductive score secondary to change in endometrial receptivity. **Aim of the study**: to assess the impact of thickness of the endometrium at the day of hCG administration on the winning of intracytoplasmic sperm injection (ICSI) cycles. **Patients and method**: A retrospective study in which 235 women who were undergo one time of ICSI cycle were evaluated in this retrospective study, All patients were treated with gonadotrophin agonist either short or long protocol. The patients were according to endometrial thickness they were categorized into three groups I (<7mm), II (7-14mm), and group III (>14mm). **Results**: the rate of clinical pregnancy was increased in-group II (7-14mm) than other two groups depending on endometrial thickness measurement.

Conclusion: endometrial thickness 7-14mm is associated with higher rate of clinical pregnancy.

Keyword: Endometrial thickness, *ICIS, controlled ovarian stimulation (COS), IVF*

Introduction

In vitro fertilization and embryo transfer (IVF-ET) is only way of assisted reproductive technique that make the couples to meet their chance of having a baby into a reality.(1)

IVF was firstly used to solve the problem of tubal blockage, however, is now widely used for treatment of other types of infertility including: unexplained infertility, endometriosis, male factor and ovarian dysfunctions (2,3)

Corresponding author:
Dr. Zainab Abd alkathem fatnan,
email: zainaba.alshebly@uokufa.ed.iq
Phone number: +9647800789894.

The implantation of an embryo found to be the most important way of the reproductive method. It includes a special biological phenomenon, by which the blastocyst closely attached to the maternal surface of endometrium to make the placenta that will form a connection between the developing baby and the maternal blood flow. (4) A good implantation needs a receptive endometrium, a good embryo at the stage of blastocyst and a rhythmic connection between maternal and fetal tissues. Implantation happened about 9 days after ovulation (6-12) days. (5)

Endometrial receptivity:

Endometrial receptivity defined as a special series of events that make the endometrium accepted to the receiving of an embryo. (6) The thickness of endometrium can be used as an indirect indicator for endometrial receptivity. (7) In sufficient uterine receptivity in IVF

is found to be account for about two third of failure of implantation, while the embryo itself is responsible one third of these failures. (8)

Factors that affect the receptivity of the endometrium:

1- Maternal age:

There is significant decline in human fecundity with increasing maternal age. (9)

2- Hormonal factors:

a- Estrogen and progesterone;

Serum levels of estradiol (E2) have a little value in assessing endometrial maturation, although there is association between endometrial thickness and estradiol levels in both natural and stimulated cycles. (10)

b- Gonadotropin hormones;

The conception rates is found to be increased in previously amenorrheic patient than in patient with normal cycle. This may be due to a beneficial effect of the higher gonadotropin levels on endometrial receptivity, in amenorrheic women (11)

c- GnRH agonist and GnRH antagonist;

The impact of the GnRh-agonist or GnRh-antagonist on corpus luteum or on endometrium and then on endometrial receptivity cannot be ignored because GnRh receptors have been recognized in both compartments. (12)

3-endometrial thickness and pattern:

Transvaginal ultrasound can be used as an alternative method in the assessment of endometrial receptivity. It has been found that the pattern and thickness of endometrium on the day before oocyte pickup may be a marker of the likelihood of having a pregnancy. (13)

4-endometrial volumetry:

A minimum volume of 2ml was needed for a receptive endometrium and no pregnancy occur when endometrial volume measured <1ml. (13)

5-Genetic factors:

There are many genetic factors are responsible for the success or failure of implantation. (14)

The aim of the study

This retrospective study was performed to assess the effect endometrial thickness at the time of hCG injection on ICSI patients who were undergone controlled ovarian stimulation (COS).

Patients and Method

A retrospective study was done in the fertility center of Al-Sader teaching hospital in Al-Najaf city. From February 2018 to February 2019, (235) couples underwent ICSI cycles because of tubal, ovarian, male and unexplained infertility. Exclusion criteria for the study including the presence of known intrauterine anomalies and ovarian stimulation other than GnRH agonist protocol (short & long).

In cycle day 2-3 hormonal assay in form of (FSH, LH, Prolactin,and E2) done along with vaginal ultrasound to detect the antral follicles count and to rule the presence of ovarian cysts or other pelvic pathology and seminal fluid analysis for the partner reviewed then according to above results, stimulation protocol was selected. Patients were screened and were negative for infection with HIV, hepatitis B and C.

Stimulation protocol:

Gonadotrpin releasing hormone (GnRH) agonist used for all women. Two main protocols used in this study;

1- long protocol: for suppression of the pituitary gland, GnRh agonist (decapeptly 3.7mg) was administered on the day of 21 of the menstrual cycle (mid luteal phase) vaginal ultrasonography was performed on day 2 or 3 of the next menstrual cycle to rule out the presence any functional ovarian cyst more than 10mm in size. Gonadotropin stimulation include 1-2 ampoules per day of recombinant FSH (Gonal-F^{R,} 75 UI). The starting dose was individualized according to patient's age, ovarian reserve test tailored according to her response after the first 4-5 days of stimulation.

2- short protocol or flare-up protocol: involves agonist treatment (decapeptyl 0.1mg S.C daily) for 10-14 days started one day before or concurrently with ovarian gonadotropines stimulation and the dose of gonadotropines adjusted as the long protocol(as described above).

For both protocols, follicular development was monitored by vaginal ultrasonography and serum E2 level starting from cycle day 8 or 9 and then every other day. At the day of human chorionic gonadotrophine (hCG) injection, the endometrial thickness was calculated by trans- vaginal ultrasound using mid-sagittal plane through the uterine body

All measurement were done by the same gynecologist.

Endometrial thickness was classified into three groups:-

I -(<7mm), II-(7-14mm), III-(>14mm).

Thirty- four to 36 hours following 10,000 IU of hCG administration, oocyte retrieval was performed under general anesthesia and by guided of transvaginal ultrasound. After aspiration, oocytes screened and injected (ICSI). The fertilization rate calculated as (number of embryos obtained per number of injected oocytes). After transfer embryo of, all women were receive luteal phase support using vaginal pessaries (progesterone 400mg twice a day (Cyclogest ^{R}) Started at day of ovum pick up for 16 days and continued if pregnancy occurred up to 10-12 weeks. Two weeks after embryo transfer, we check the level of βhCG and then after the clinical pregnancy was confirmed two weeks later by sonographic detection of the gestational sac and positive heartbeat. Clinical pregnancy rate calculated as the women with clinical pregnancy per number of women that did embryo transfer.

Embryos were classified according to the number of blastomeres, percentage of fragmentation & blastomere appearance as type 1, 2, 3 or 4.

Regarding the equality of embryos, good quality embryos are those of grade 1 and 2, while bad quality embryos are those of grade 3 and 4.

Statistical Analysis

After data entry the analysis were done by using SPSS (statistical package for social science) version 23. In which we use chi sequare(x^2) for categorical data and independent sample T-test for measurement data. P value <0.005 were considered significant.

Results

Table (1) shows clinical pregnancy rate was higher in group II 70/194(63.9%) than in group III 3/21(14.3%) and group I 1/20 (5%) it was statistically significant (p=0.003)

Table (1): Shows the comparison of the ICSI outcome according to endometrial thickness on the day of hCG injection.

		Endometrial thickness			P value
		<7 (N=20)	7-14 (N=194)	>14 (n=21)	
Clinical pregnancy rate	Negative	19 (95%)	124 (63.9%)	18 (85.7%)	0.003
	positive	1 (5%)	70 (36.1%)	3 (14.3%)	

Table (2) shows demographic characteristic of three groups according to endometrial thickness were no statistically different regarding age, BMI, hormonal assay (FSH,LH,E2 &Prolactin) and period of infertility.

Table (2): Demographic characteristic of women according to endometrial thickness at day of hCG administration.

Characteristic	Endometrial thickness			P value
	<7 Mean±SD	7-14 Mean±SD	>14 Mean±SD	
Age/ years	32±4.2	30±5.9	29.2±6.5	0.852
BMI(kg/m2)	25.5±4.9	27.3±3.1	28±2.4	0.638
FSH(IU/L)	2.5±3.4	4.7±2.5	3.2±2.3	0.2
LH(IU/L)	1.6±0.4	3.1±2.6	1±1.3	0.177
E2(pg/ml)	29±16.9	37.3±18.9	19.4±9	0.092
Prolactin(ng/ml)	21±2.8	25.5±18.5	23.4±8.5	0.911

Table (3): Shows that there is no significant differences found between types of the protocols and the type of infertility with endometrial thickness (P>0.05).

Table (3) the type of protocol and indication of ICSI according to endometrial thickness.

Variable		Endometrial thickness(mm)			P value
		<7	7-14	>14	
Protocol	Long	6	26	5	0.198
	Short	14	168	16	
Indication	Female	7	71	10	0.970
	Male	11	110	10	
	unexplained	2	13	1	

Discussion

Assessment of thickness of endometrium on the day of hCG injection is of great clinical importance. [15] In current study, we evaluate clinical pregnancy rate after classifying the endometrial thickness into three groups. We found that higher pregnancy rate reported in group 7-14mm (36.1%), while those level above 14mm the clinical pregnancy rate was (14.3%) and rapid decrease in clinical pregnancy rate in women with endometrial thickness <7mm (5%) but this difference is statistically significant (p=0.003).

An implantation failure occurs in thin endometrium. This finding is agree with Gonen Y, [13] this may be associated with oxygen tension. When the thickness of

endomertium measured by ultrasound and it is <7mm, the functional layer is thin or absent, and the implanting embryo would be much closer to the spiral arteries and the higher vascular and oxygen concentration. The high oxygen concentration near the basal layer could be detrimental compared with usual low oxygen tension of the surface endometrium. (13)

A limited number of studies have reported a detrimental impact of greatly increased endometrial thickness on pregnancy outcomes.

Weissman et al, found that an endometrial >14mm resulted in significant reduced implantation and pregnancy rate (16). This was supported by the finding of Rashidi et al. (17) Our results were with agreement to these both studies.

Higher pregnancy rate was found in group 7-14mm thickness and this agree with Kuc et al., 2011 stated that endometrial thickness of 12-13mm was associated with highest pregnancy rate (18). Okohue et al., reported the highest pregnancy rate with an endometrial thickness of 7-14mm (19).This also confirmed by Traub et al.,(20) and Chen et al,.(21)

However, the optimum endometrial thickness that predicts successful pregnancy is not definite yet.

Conclusion:

We can conclude that the endometrial thickness of 7-14 mm is associated with a higher pregnancy rate.

Recommendations

We advocate that in each ICSI center the effort should be made to institute protocols that will improve endometrial development as a mean of improving cycle outcome and avoid both thin and thick endometrium. Further larger randomized studies with more cases are needed and for longer duration of follow up to define appropriate protocols in clinical practice of ICSI cycle.

Conflicts of Interest: No

Funding Source: Self

Ethical clearance: from the Ministry of health and Environment/ scientific committee

References

1- Catherine M. Marin, Alan H. Decherney, Alan S. Penzias, & Ian H. Throneycroft. In Virto Fertilization & Related Techniqes, Alan H. De Cherney, Lauren Nathan, Current obstetric & Gynecology Diagnosis & Treatment, 9th Edition 2003;1012.

2- Steptoe PC, Edwards RG, Purdy JM. Clinical aspects of pregnancies established with cleaving embryos grown in vitro. BJOG: An International Journal of Obstetrics & Gynaecology. 1980 Sep;87(9):757-68.

3- Templeton AA, Morris JK,Parslow W. Factors that affect the outcome of in-vitro fertilization treatment. Lancet 1996;348:1402-6.

4- Denker HW. Implantation: a cell biological paradox. Journal of Experimental Zoology. 1993 Sep 1;266(6):541-58.

5- Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. New England Journal of Medicine. 1999 Jun 10;340(23):1796-9

6- Bergh PA,Navot D. The impact of embryonic development and endometrial maturity on the timing of implantation. Fertil. Steril 1992;58:537-42.

7- Fanchin R. Assessing uterine receptivity in 2001:ultrasonographic glances at the new millennium. Ann NY Acad Sci 2001;943:185-202.

8- Simon A, Hurwitz A, Zentner BS, Bdolah Y, Laufer N. Transfer of frozen-thawed embryos in artificially prepared cycles with and without prior gonadotrophin-releasing hormone agonist suppression: a prospective randomized study. Hum Reprod 1998;13:2712–17

9- Oehninger S,Veeck L, Lanzendroft S, Maloney M, Toner J, Muasher S. Intracytoplasmic sperm injection:Achievement of high pregnancy rate in groups with sever male factor infertility is dependent primarily upon femal and not male factors. Fertil Steril 1995;64:977-4

11- de Ziegler D, Frydman R. Different implantation rates after transfers of cryopreserved embryos originating from donated oocytes or from regular in vitro fertilization. Fertile Steril 1990;54:682-8

12- Brus L, Rogers PAW, Danielsson KG, Maccolini A. Specific gonadotrophin-releasing hormone

analogue binding predominantly in human luteinized follicular aspirates and not in human preovulatory follicles. Hum Reprod 1997;12:769-73

13- Gonen Y, and Casper RF. Prediction of implantation by the sonographic appearance of the endometrium during controlled ovaran stimulation for vitro fertilization. J in-vitro Fertil Embryo Transfer 1990;7:14

14- Cao C, Tulac S. Global gene profiling in human endometrium during window of implantation. Endocrinol 2002;143:2119-38.

15- Friedler S, Schenker JG, Herman A, Lewin A: The role of ultrasonography in the evaluation on endometrial receptivity following assisted reproductive treatments: a critical review. Hum Reprod Update 1996, 2: 323-334.

16- Weissman A, Gotlieb L, Casper RF: The detrimental effect of increased endometrial thickness on implantation and pregnancy rates and outcome in an in vitro fertilization program. Fetril Steril 1999, 71: 147-149.

17- Rashidi BH, Sadeghi M, Jafarabadi M, Nejad ES. Relationships between pregnancy rates following in vitro fertilization or intracytoplasmic sperm injection and endometrial thickness and pattern. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2005 Jun 1;120(2):179-84.

18- Kuc P, Kuczynska A, Topczewska M, Tadejko P, Kuczynski W. The dynamic of endometrial growth and the triple layer appearance in three different controlled ovarian hyperstimulation protocols and their influence on IVF outcome. Gyencol Endocrinol 2011; 27(11): 867-73.

19- Okohue JE, Onuh SO, Ebeigbe P, Shaibu I, Wada I, Ikimalo JI, et al. The effect of endometrial thickness on in vitro fertilization outcome. Afr. J Reprpd Health 2009;13(1):113-21.

20- Traub ML, Van Arsdale A, Pal L Jindal S, Santoro N. Endometrial thickness , Caucasin ethnicity, and age predict clinical pregnancy following fresh embryo transfer:a retrospective cohort. Reprod Biol Endocrinol 2009;27(7):33.

21- Chen S, Wu F, Luo C, Chen X, Shi Xheng h et al. combined analysis of endometrial thickness and pattern in predicting outcome of in vitro fertiliztion And embryo transfer: a retrospective cohort study. Reprod Biol Endocrinol 2010;8:30-6