ISSN: 2472-3703 DOI: 10.6911/WSRJ.202103_7(3).0049

Thin Endometrium Is Associated with Lower Pregnancy Rate and Higher Incidence of Early Abortion in Fresh Embryo Transfer Cycles: A Retrospective Cohort Study

Jingwan Wang[1, 2], Bingchen Gong[1, 2], Yuan Yao[1, 2], Ping Sun[1, 2], Wenxin Song[1, 2], Wei Zhou[2, 3], Qingqing Guo[2, 3], Jinlong Ma[2, 3], Lingling Ding[2, 3, a, *]

[1]School of Medicine, Shandong University, Jinan, Shandong, China

[2]Center for Reproductive Medicine, Reproductive Hospital Affiliated to Shandong University, Jinan, Shandong, China

[3]National Research Center for Assisted Reproductive Technology and Reproductive Genetics, Jinan, Shandong, China

[a]Corresponding author E-mail: 18369613259@163.com

Abstract

Objective: In order to explore the relationship between endometrial thickness and pregnancy outcomes in assisted reproduction. Methods: A retrospective cohort study was conducted in a single center, we divided the women into 3 groups by endometrial thickness (EMT): EMT≤0.8cm, 0.8<EMT≤1.2cm, EMT>1.2cm. Demographic characteristics and pregnancy outcomes of patients in the 3 groups were compared. Results: Clinical pregnancy rate in Group 1 (51.0%) was significantly lower than Group 2 (64.1%) and Group 3 (63.5) (P=0.000). The incidence of early abortion in Group 1 (12.9%) was significantly higher than Group 2 (8.8%) and Group3 (8.4%) (P=0.002). The incidence of ectopic pregnancy, mid-late abortion, premature delivery among 3 groups had no statistical significance (P>0.05). The incidence of early abortion in Group 1 was 1.736 times higher than that of the Group 2, 95 confidence interval (CI) were 1.344-2.244. Age is an independent risk factor for early abortion. Conclusion: Thin endometrium is associated with lower clinical pregnancy rate and higher incidence of early abortion in fresh embryo transfer cycles.

Keywords

Thin endometrium; Pregnancy rate; Early abortion; Fresh embryo transfer; In vitro fertilization.

1. INTRODUCTION

Endometrial receptivity (ER) is one of the key factors for embryo implantation and then pregnancy in the human assisted reproductive technology (ART) cycle. Endometrial thickness (EMT) is an important index to evaluate ER(1). Thin endometrium affects ER, which is not conducive to embryo implantation. EMT represents the growth of endometrium and is the most commonly used ultrasound index in assisted reproduction(2). Thin endometrium is related to the adverse pregnancy outcome (low implantation rate and low pregnancy rate) of ART. Studies have shown that the optimal EMT for implantation is 9 to11 mm(3). Thin endometrium can be caused by many factors, the most common are inflammatory and iatrogenic factors. In terms of inflammation, acute or chronic infection can lead to the damage of the endometrial basal layer, which would lead to destruction of endometrium and contraction of uterine cavity because of

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202103_7(3).0049

fibrosis healing(4). In the iatrogenic aspect, repeated surgical operation and curettage will also destroy the basal layer of endometrium, then lead to destruction of endometrium(5,6). In the natural cycle, the incidence of thin endometrium in women under 40 years old is 5%, and that in women over 40 years old is 25%. The high incidence of thin endometrium in elderly women may be due to the decrease of vascular distribution(3,7). Among the women receiving assisted reproductive technology (ART), the incidence of thin endometrium was 1.5% to 9.1%. The difference of incidence may be related to measurement technology, ultrasound equipment, controlled ovarian hyperstimulation (COH) protocol and clinical threshold changes during transplantation(8). Vaegter and his colleagues' research shows that thin endometrium in ART is associated with low clinical pregnancy rate and live birth rate(9). The study of Von wolff showed that the pregnancy rate of the group EMT ≤7 mm was significantly lower than the group of EMT>7 mm (7.4 vs. 30.8%, P<0.05)(10), but the sample size of his study is small. Liu reported that in patients with EMT<8 mm in fresh in vitro fertilization-embryo transfer (IVF-ET) cycles and EMT<7 mm in freeze-thaw embryo transfer (FET) cycles, the clinical pregnancy rate would decrease with the decrease of endometrial thickness(11). There are also many researches show that thin endometrium has no correlation with the pregnancy outcome in ART. Zhang and Liu researches show that thin endometrium has no significant correlation with live birth rate(11,12). According to Gingold, it is the endometrial morphology that influences the pregnancy outcomes in ART but EMT(13). Kumbak(14) et al. reported that pregnancy rate increased when the maternal age less than 35 years old, the number of oocytes obtained more than 5 and the number of transplantable embryos more than 3. Researchers believe that when the number of oocytes obtained is more than 5 or the number of transplantable embryos is more than 3, even if the endometrial thickness is less than 7 mm, fresh embryo transfer also can be conducted, but it also wastes embryos to some extent. Thus, women with thin endometrium can improve the pregnancy outcomes by adjusting the number of embryos transferred. EMT may be a conditional factor affecting the pregnancy outcomes of ART, but it is not the only determinant, the number and quality of embryos transferred and the maternal age also affect the pregnancy outcome of art. At present, it is generally believed that only when the endometrium reaches at least a critical value can the embryo be successfully implanted, but this critical value has not yet been determined. Based on previous studies, this study further explored the impact of endometrial thickness on pregnancy outcomes. We routinely transfer two embryos in day 3, in this way, we can reach a balance between pregnancy rate and endometrial thickness. Therefore, we conducted this study to explore the effect of endometrial thickness on pregnancy outcomes after two cleavage stage embryos transfer, which was not covered by previous studies. This to some extent can eliminate the impact of embryos transplant days and transplant number (all women were given 2 embryos transfer on day 3) on the outcomes.

2. METHODS

Data were extracted from electronic medical records from Jan 1, 2015 to Dec 31, 2018 (all participants had given informed consent, and approved by the Institutional Review Board of hospital), then a single-center, retrospective cohort study was conducted.

All of these women had undergone their first cycle of IVF-ET or intracytoplasmic sperm injection-embryo transfer (ICSI-ET) treatment. They underwent a controlled ovarian hyperstimulation (COH) to retrieve adequate oocytes for subsequent insemination and embryo culture. After 36 to 44 hours in culture, cleavage-stage embryos were evaluated by Puissant's scoring system(15). The number and size of blastomeres and also the presence or absence of anucleate fragments were carefully recorded so that embryos could be scored as follows: 4: embryos with clear, regular blastomeres and either no fragmentation or a maximum of five small anucleate fragments; 3: embryos with few or no fragments but with unequal blastomeres

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202103_7(3).0049

(> 1/3 difference in size); 2: embryos with more fragments but over < 1/3 of the embryonic surface; 1: fragments over > 1/3 of embryonic surface. Two points are added if the embryo has reached the 4-cell stage by 48 hours after fertilization. Superior quality embryos that were 2 pronucleus (2PN) origin and involved 7-10 cells scored 3-4 points. After excluding the contraindications of fresh embryo transfer, such as ovarian hyperstimulation syndrome (OHSS), preimplantation genetic screening (PGS), 2 superior-quality cleavage-stage embryos were transferred in those women. Clinical pregnancy defined as a presence of gestational sac on ultrasound scan, or confirmation of products of conception by pathological examination after abortion or ectopic pregnancy. Early abortion defined as a miscarriage before 12th weeks (gestational age less than 11th weeks and 6 days). Mid-late abortion defined as a miscarriage after 12th weeks but no more than 28th weeks (gestational age between 12th weeks and 27th weeks and 6 days). Ectopic pregnancy defined as all gestational sac that is found not in the uterus but elsewhere (such as in the fallopian tube or peritoneal cavity). Premature delivery defined as the output of fetus after the 28th week but before the normal time (37th weeks) of delivery. Clinical pregnancy rate defined as numbers of clinical pregnancy and ectopic pregnancy / total transfer cycles. Ectopic pregnancy rate defined as the numbers of ectopic pregnancy / numbers of clinical pregnancy. Early abortion rate defined as the numbers of early abortion / numbers of clinical pregnancy. Mid-late abortion rate defined as the numbers of mid-late abortion / numbers of clinical pregnancy.

Divided the women into 3 groups by EMT in the day of injection of human chorionic gonadotropin (hCG trigger day): EMT≤0.8cm (Group 1), 0.8<EMT≤1.2cm (Group 2), EMT>1.2cm (Group 3). Demographic characteristics and pregnancy outcomes of patients in the 3 groups were compared. Numerical data included maternal age, body mass index (BMI), hormone levels on days 1 to 3 of the menstrual cycle (basal follicle-stimulating hormone [FSH], luteinizing hormone [LH], estradiol [E2]), serum thyroid-stimulating hormone (TSH) level, LH, E2 and progesterone level on hCG trigger day, the startup dosage of gonadotropin (Gn), retrieved oocytes. Categorical data included the cause of infertility (tubal factor, male factor, combinations, unexplained, or other), the type of infertility (primary or secondary), the method for assisted reproduction (IVF, ICSI), and ovary stimulation protocol (GnRH agonist long, GnRH agonist short, GnRH agonist super long, GnRH antagonist, and other protocol). pregnancy outcomes included clinical pregnancy, early abortion, mid-late abortion, ectopic pregnancy, premature delivery.

All statistical analyses were performed using SPSS 23.0 (IBM, Armonk, NY, USA). Variance analysis or non-parametric tests were used to test numerical data as indicated by the Kolmogorov-Smirnov test. Results are presented as the Median (Quartile25, Quartile75). Pearson's Chi-squared test or Fisher's exact test was used to test categorical data.

3. RESULTS

Women's demographic characteristics in the 3 groups are showed in Table 1. The maternal ages of the patients in those groups were 32 (29, 35) years, 32 (29, 35) years and 31 (28, 34) years, respectively, which showed statistical significance (P=0.000). The BMI of the patients in this 3 groups were 23.5 (21. 3, 26.4) Kg/m2, 23.7 (21.3, 26.5) Kg/m^2, and 23.8 (21.5, 26.4) Kg/m^2, respectively, showing a growing trend, while no significant differences were detected in further compared (P=0.460). LH and progesterone level on hCG trigger day, startup dosage of Gn and retrieved oocytes showed statistically significant differences (P<0.05), all the variables were selected to the crude univariate regression analysis for early abortion. Other characteristics such as basal E2 and serum TSH level, indication of ART, the type of infertility, ovary stimulation protocol, and the assisted reproductive methods, had no significant

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202103_7(3).0049

differences in our study. It can largely remove a lot of bias which would impact on subsequent analysis, and then made the results were more convincing.

Table 1. Baseline Characteristics of patients.

Characteristics	Median (Quartile25, Quartile75) or n (%)			P
	Group 1 (n=1539)	Group 2 (n=4008)	Group 3 (n=902)	
Maternal age (years)	32 (29, 35)	32 (29, 35)	31 (28, 34)	0.000*,b,c
BMI (Kg/m2)	23.5 (21.3, 26.4)	23.7 (21.3, 26.5)	23.8 (21.5, 26.4)	0.460
Basal FSH (IU/L)	6.61 (5.70, 7.80)	6.45 (5.5, 7.62)	6.38 (5.54, 7.52)	0.000*,a,b
Basic LH(IU/L)	4.57 (3.34, 6.06)	4.71 (3.45, 6.34)	4.71 (3.51, 6.41)	0.021*,a
Basal E2 (pg/ml)	35.6 (26.8, 47.0))	35.30 (26.60, 46.20)	34.45 (26.10, 45.83)	0.418
TSH (mIU/L)	2.19 (1.55, 2.92)	2.14 (1.55, 2.92)	2.12 (1.54, 3.06)	0.508
Type of infertility (n/%)				
Primary	853 (55.4)	2258 (56.3)	526 (58.3)	0.378
Secondary	686 (44.6)	1750 (43.7)	376 (41.7)	
Indication of ART (n/%)				
Tubal factor	860 (55.9)	2311 (57.7)	500 (55.4)	
Male factor	171 (11.1)	455 (11.4)	104 (11.5)	
Combinations	171 (11.1)	401 (10.0)	119 (13.2)	0.205
Unexplained	154 (10.0)	366 (9.1)	86 (9.5)	
Other	183 (11.9)	475 (11.9)	93 (10.3)	
Ovary stimulation protocol (n/%)				
GnRH agonist long	699 (45.4)	1827 (45.6)	410 (45.5)	
GnRH agonist short	445 (28.9)	1075 (26.8)	252 (27.9)	
GnRH agonist super long	122 (7.9)	407 (10.2)	93 (10.3)	0.127
GnRH antagonist	239 (15.5)	637 (15.9)	136 (15.1)	
Other protocol	34 (2.2)	62 (1.5)	11 (1.2)	
ART method(n/%)				
IVF	1108 (72.0)	2927 (73.0)	639 (70.8)	0.368
ICSI	431 (28.0)	1081 (27.0)	263 (29.2)	
Startup dosage of Gn (IU)	150 (150, 225)	150 (150, 200)	150 (150, 225)	0.025*,a
LH level on hCG trigger day (IU/L)	2.68 (1.63, 4.57)	2.54 (1.59, 4.37)	2.45 (1.55, 3.84)	0.010*,b
E2 level on hCG trigger day (pg/ml)	2641 (1898, 3529)	2713 (1928, 3488)	2771 (2004, 3530)	0.135
P level on hCG trigger day (ng/ml)	0.64 (0.43, 0.92)	0.61 (0.43, 0.85)	0.58(0.41, 0.82)	0.001*,a,b
Retrieved oocytes (n.)	9 (6, 12)	9 (6, 12)	10 (7, 13)	0.000*,a,b,c

*: The difference is significant; a Statistically significant differences between EMT≤0.8cm and 0.8<EMT≤1.2cm groups; b Statistically significant differences between EMT≤0.8cm and EMT≥1.2cm groups; c Statistically significant differences between and 0.8<EMT≤1.2cm groups and EMT≥1.2cm groups.

BMI: Body mass index; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; E2: Estrogen; TO: Testosterone; TSH: Thyroid Stimulating Hormone; ART: Assist reproductive technology; IVF: In vitro fertilization; ICSI: intracytoplasmic sperm injection; hCG: Human chorionic gonadotropin; Gn: Gonadotropin; P: Progesterone

The clinical pregnancy rate of the 3 groups were 51.0%, 64.1% and 63.5%, as shown in table 2, which were significant differences (P=0.000). Further pairwise comparison shows that statistically significant differences lied in EMT≤0.8cm and 0.8<EMT≤1.2cm groups; and EMT≤0.8cm and EMT≥1.2cm groups.

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202103_7(3).0049

Table 2. Clinical pregnancy according to endometrial thickness.

Grouping	Clinical pregnancy		P
	Yes	No	
Group 1 (n=1539), n (%)	785 (51.0)	754 (49.0)	
Group 2 (n=4008), n (%)	2569 (64.1)	1439 (35.9)	0.000*,a,b
Group 3 (n=902), n (%)	573 (63.5)	329 (36.5)	

*: The difference is significant; a Statistically significant differences between EMT≤0.8cm and 0.8<EMT≤1.2cm groups; b Statistically significant differences between EMT≤0.8cm and EMT≥1.2cm groups.

The occur of adverse pregnancy outcomes shown in Table 3. No significant between-group differences were observed in the occur of mid-late abortion (P=0.153), ectopic pregnancy (P=0.125), and premature delivery (P=0.588). Early abortion rate of the patients in this 3 Groups were 12.9%, 8.8%, and 8.4% respectively, which were significantly different (P=0.002). Further pairwise comparison shows that statistically significant differences lied in EMT≤0.8cm and 0.8<EMT≤1.2cm groups; and EMT≤0.8cm and EMT≥1.2cm groups. Thin endometrium is related to the occurrence of early abortion, while not related to the occurrence of mid-late abortion, ectopic pregnancy, and premature delivery.

Table 3. Adverse pregnancy outcomes according to endometrial thickness.

Outcomes	Group 1 (n=785)	Group 2 (n=2569)	Group 3 (n=573)	P value
Early abortion, n (%)	101 (12.9)	227 (8.8)	47 (8.4)	0.002*,a,b
Mid-late abortion, n (%)	27 (3.4)	99 (3.9)	31 (5.4)	0.153
Ectopic pregnancy, n (%)	12 (1.50)	54 (2.10)	18 (3.1)	0.125
Premature delivery, n (%)	119 (15.2)	352 (13.7)	80 (14.0)	0.588

*: The difference is significant; a Statistically significant differences between EMT≤0.8cm and 0.8<EMT≤1.2cm groups; b Statistically significant differences between EMT≤0.8cm and EMT≥1.2cm groups.

After discovering the relationship between the incidence of early abortion and EMT, we also performed univariate regression analysis of variables predicting the incidence of early abortion. Selecting age, BMI, ovary stimulation protocol, retrieved oocytes, startup dosage of Gn, estradiol, EMT and progesterone levels on the hCG trigger day in to the model, EMT was still statistically significantly associated with early abortion. LH and progesterone level on hCG trigger day, startup dosage of Gn and retrieved oocytes showed statistically significant differences in non-parametric tests, while no statistical significance in univariate regression analysis.

Compared with the women in the 8<EMT≤12 mm group, the women in the EMT≤8 mm group had an OR of 1.744 (95% CI, 1.345-2.261; P=0.000) as shown in table 4. Moreover, age was an independent predictor for early abortion in this model (OR: 1.171, 95% CI: 1.345-2.261; P=0.000).

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202103_7(3).0049

Table 4. Crude univariate regression analysis for early abortion.

Predictor variable	OR (95% CI)	P
Age	1.171	0.000*
BMI	0.994	0.715
Endometrial thickness (cm)		
EMT≤0.8	1.744 (1.345, 2.261)	0.000*
0.8<EMT≤1.2	Reference	-
EMT>1.2	0.807 (0.574, 1.133)	0.216
Ovary stimulation protocol		
GnRH agonist long	Reference	-
GnRH agonist short	1.029 (0.767, 1.38)	0.849
GnRH agonist super long	1.039 (0.705, 1.531)	0.846
GnRH antagonist	1.126 (0.807, 1.571)	0.484
Other protocol	1.632 (0.674, 3.95)	0.277
Retrieved oocytes (n.)	0.994 (0.958, 1.031)	0.744
Startup dosage of Gn (IU)	0.999 (0.997, 1.001)	0.469
E2 level on hCG trigger day	1.000 (1, 1)	0.404
P level on hCG trigger day	0.968 (0.764, 1.227)	0.787
Constant	0.001	0.000*

OR: odds ratio; CI: confidence interval; *: The difference is significant.

After adjusting for age and EMT, the early abortion rate showed significant differences (Table 5). In the final model, women in the EMT≤8 mm group were 1.736 (95% CI, 1.344-2.244; P=0.000) times more likely to have early abortion than women in the 8<EMT≤12 mm group. Age was an independent predictor, with the increase of age by 1 year the risk of early abortion increased by 17% (95% CI, 1.138-1.202; P=0.000).

Table 5. Adjusted univariate regression analysis for early abortion.

Predictor variable	OR (95% CI)	P
Age	1.171	0.000*
Endometrial thickness (cm)		
EMT≤0.8	1.736 (1.344, 2.244)	0.000*
0.8<EMT≤1.2	Reference	-
EMT>1.2	0.824 (0.591, 1.15)	0.255
Constant	0.001	0.000*

OR: odds ratio; CI: confidence interval; *: The difference is significant.

4. DISCUSSION

The main purpose of this study was to evaluate the effect of EMT on the hCG trigger day on clinical pregnancy and adverse pregnancy outcomes during fresh IVF/ICSI–ET cycles. In this study, we found a strong association between EMT and clinical pregnancy and early abortion. After adjusting for potential confounders of maternal and other important confounders. women with EMT≤8 cm still had a higher risk of early abortion than women with 0.8<EMT≤1.2cm. This

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202103_7(3).0049

result is consistent with Vaegter' (9), Von wolff's (10), and Liu' (11) results. Researchers had done a lot of researches to explore the mechanisms of thin endometrium. Miwa(16) et al. revealed that the thin endometrium was caused by glandular epithelial dysplasia, high impedance of uterine blood flow, down regulation of vascular endothelial growth factor (VEGF) gene expression. VEGF is mainly produced by epithelial cells, which can not only promote the growth of endometrium, but also promote the increase of vascular permeability in the middle of endometrial secretion, which is necessary for the successful implantation of embryos(17,18). In thin endometrium, epithelial growth is impaired, VEGF level is decreased, low VEGF leads to vascular dysplasia, which further reduces endometrial blood flow(19).

Age is an independent risk factor in our study. With the increase of maternal age, on the one hand, the peroxide increased significantly, the mitochondria in oocytes decreased which leads to the quality of oocytes decreased significantly. At the same time, the chromosome abnormalities could also increase, which can lead to embryo aneuploid rate increase. On the other hand, the sex hormone receptors in endometrium also decreased with the increase of age, which reduced the ER and increased the risk of early abortion.

We consider our study a meaningful contribution to the existing literature. First, because the research objects are fresh embryos transfer, the level of E2 in COH was high, and the growth of endometrium depends on the level of serum E2. We selected 0.8 and 1.2 cm as the lower and upper cutoff values for EMT respectively. This ensures the accuracy of the results. second, the sample size was expanded and only the fresh ET cycles were included to explore whether EMT might be associated with adverse pregnancy. Moreover, this study was conducted in only one center and the sample size in the study is large, which both minimized potential bias, such as: the measurement of EMT and laboratory conditions. Furthermore, we adjusted for confounding variables which would affect pregnancy outcomes, All patients were transferred two embryos, which eliminated the impact of the number of embryos on pregnancy outcomes.

The mechanisms of why EMT affects embryo implantation and the outcome of pregnancy are still being explored. There was hypothesis suggested that oxygen concentrations in the basal layer may increase in patients with thin endometrium(20). Such high oxygen concentrations might be harmful to embryo implantation. The growth of the fetus depended on the placenta to provide adequate nutrients and oxygen(21). At the early weeks of pregnancy, the establishment of a placenta with sufficient blood perfusion depends on remodeling of the spiral arteries. In this stage, any defects in this process might lead to adverse pregnancy outcomes. Recently, researches on etiology have increased, mainly on the maternal factors and fetal factors. Thin endometrium affects pregnancy outcome might result from a defect in spiral artery remodeling, reducing the blood supply to the placenta.

The main limitations of this study were its retrospective nature and the lack of data on maternal lifestyle factors such as smoking. Another limitation is that we did not explore the relationship between endometrial thickness and live birth rate. This study did not explore relevant molecular mechanisms.

5. CONCLUSION

Thin endometrium is associated with lower clinical pregnancy rate and higher incidence of early abortion in fresh embryo transfer cycles. Therefore, we suggest that women with a thin EMT after achieving pregnancy by IVF/ICSI treatment should receive additional prenatal care to reduce the risk of early abortion.

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202103_7(3).0049

ACKNOWLEDGEMENTS

The authors are very grateful to the attending couples in our center and every participant in initial data collection. This research was granted by National Natural Science Foundation of China (81470403,81701404).

REFERENCES

[1] Sarvi F, Arabahmadi M, Alleyassin A, Aghahosseini M, Ghasemi M. Effect of Increased Endometrial Thickness and Implantation Rate by Granulocyte Colony-Stimulating Factor on Unresponsive Thin Endometrium in Fresh In Vitro Fertilization Cycles: A Randomized Clinical Trial. Obstet Gynecol Int. 2017;2017.

[2] Sugiura T, Akiyoshi S, Inoue F, Yanagawa Y, Moriyoshi M, Tajima M, et al. Relationship between bovine endometrial thickness and plasma progesterone and estradiol concentrations in natural and induced estrus. J Reprod Dev. 2018;64(2):135–43.

[3] Ma NZ, Chen L, Dai W, Bu ZQ, Hu LL, Sun YP. Influence of endometrial thickness on treatment outcomes following in vitro fertilization/intracytoplasmic sperm injection. Reprod Biol Endocrinol [Internet]. 2017;15(1):1–7. Available from: http://dx.doi.org/10.1186/s12958-016-0222-5

[4] Türkmen IÇ, Başsüllü N, Çomunoğlu C, Bağci P, Aydin Ö, Çomunoğlu N, et al. Female genital system tuberculosis: A retrospective clinicopathological study of 1,548 cases in Turkish women. Arch Gynecol Obstet. 2012;286(2):379–84.

[5] Garcia-Velasco JA, Acevedo B, Alvarez C, Alvarez M, Bellver J, Fontes J, et al. Strategies to manage refractory endometrium: State of the art in 2016. Reprod Biomed Online [Internet]. 2016;32(5):474–89. Available from: http://dx.doi.org/10.1016/j.rbmo.2016.02.001

[6] Santamaria X, Cabanillas S, Cervelló I, Arbona C, Raga F, Ferro J, et al. Autologous cell therapy with CD133+ bone marrow-derived stem cells for refractory Asherman's syndrome and endometrial atrophy: A pilot cohort study. Hum Reprod. 2016;31(5):1087–96.

[7] Mahajan N, Sharma S. The endometrium in assisted reproductive technology: How thin is thin? J Hum Reprod Sci. 2016;9(1):3–8.

[8] Bu Z, Sun Y. The impact of endometrial thickness on the day of human chorionic gonadotrophin (hCG) administration on ongoing pregnancy rate in patients with different ovarian response. PLoS One. 2015;10(12):1–8.

[9] Vaegter KK, Lakic TG, Olovsson M, Berglund L, Brodin T, Holte J. Which factors are most predictive for live birth after in vitro fertilization and intracytoplasmic sperm injection (IVF/ICSI) treatments? Analysis of 100 prospectively recorded variables in 8,400 IVF/ICSI single-embryo transfers. Fertil Steril [Internet]. 2017;107(3):641-648.e2. Available from: http://dx.doi.org/10.1016/j.fertnstert.2016.12.005

[10] von Wolff M, Fäh M, Roumet M, Mitter V, Stute P, Griesinger G, et al. Thin Endometrium Is Also Associated With Lower Clinical Pregnancy Rate in Unstimulated Menstrual Cycles: A Study Based on Natural Cycle IVF. Front Endocrinol (Lausanne). 2018;9(December):1–6.

[11] Liu KE, Hartman M, Hartman A, Luo ZC, Mahutte N. The impact of a thin endometrial lining on fresh and frozen-thaw IVF outcomes: An analysis of over 40 000 embryo transfers. Hum Reprod. 2018;33(10):1883–8.

[12] Zhang T, Li Z, Ren X, Huang B, Zhu G, Yang W, et al. Endometrial thickness as a predictor of the reproductive outcomes in fresh and frozen embryo transfer cycles. Med (United States). 2018;97(4).

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202103_7(3).0049

[13] Gingold JA, Lee JA, Rodriguez-Purata J, Whitehouse MC, Sandler B, Grunfeld L, et al. Endometrial pattern, but not endometrial thickness, affects implantation rates in euploid embryo transfers. Fertil Steril [Internet]. 2015;104(3):620-628.e5. Available from: http://dx.doi.org/10.1016/j.fertnstert.2015.05.036

[14] Kumbak B, Erden HF, Tosun S, Akbas H, Ulug U, Bahçeci M. Outcome of assisted reproduction treatment in patients with endometrial thickness less than 7 mm. Reprod Biomed Online. 2009;18(1):79–84.

[15] Puissant F, Van Rysselberge M, Barlow P, Deweze J, Leroy F. Embryo scoring as a prognostic tool in IVF treatment. Hum Reprod. 1987;2(8):705–8.

[16] Xu B, Zhang Q, Hao J, Xu D, Li Y. Two protocols to treat thin endometrium with granulocyte colony-stimulating factor during frozen embryo transfer cycles. Reprod Biomed Online [Internet]. 2015;30(4):349–58. Available from: http://dx.doi.org/10.1016/j.rbmo.2014.12.006

[17] 1Kasius A, Smit JG, Torrance HL, Eijkemans MJC, Mol BW, Opmeer BC, et al. Endometrial thickness and pregnancy rates after IVF: A systematic review and meta-analysis. Hum Reprod Update. 2014;20(4):530–41.

[18] Gargett CE, Ye L. Endometrial reconstruction from stem cells. Fertil Steril [Internet]. 2012;98(1):11–20. Available from: http://dx.doi.org/10.1016/j.fertnstert.2012.05.004

[19] Bashiri A, Halper KI, Orvieto R. Recurrent Implantation Failure-update overview on etiology, diagnosis, treatment and future directions. Reprod Biol Endocrinol. 2018;16(1):1–18.

[20] Casper RF. It's time to pay attention to the endometrium. Fertil Steril [Internet]. 2011;96(3):519–21. Available from: http://dx.doi.org/10.1016/j.fertnstert.2011.07.1096

[21] Moffett A, Hiby SE, Sharkey AM. The role of the maternal immune system in the regulation of human birthweight. Philos Trans R Soc B Biol Sci. 2015;370(1663).