Journal of Assisted Reproduction and Genetics (2019) 36:139–143
https://doi.org/10.1007/s10815-018-1328-9

ASSISTED REPRODUCTION TECHNOLOGIES

Sub-endometrial contractility or computer-enhanced 3-D modeling scoring of the endometrium before embryo transfer: are they better than measuring endometrial thickness?

Nivin Samara[1,2] · Robert F. Casper[1,3] · Rawad Bassil[1] · Mahvash Shere[1] · Eran Barzilay[4] · Raoul Orvieto[4,5] · Jigal Haas[1,4]

Received: 18 July 2018 / Accepted: 2 October 2018 / Published online: 25 October 2018

Abstract

Purpose Recent studies have focused on transvaginal ultrasound measurement (TVUS) of sub-endometrial contractility and computer-enhanced 3-D modeling scoring of the endometrium prior to embryo transfer (ET).The aim of this study was to compare pregnancy outcome of patients who performed the 3-D scoring or the sub-endometrial measurement prior to the ET with patients that did not perform those procedures.

Methods A single center retrospective cohort study of 635 freeze/thaw cycles of blastocysts vitrified on day 5 and transferred between January 2016 and August 2016.

Results We compared the patients who performed 3-D scoring with the control group and found comparable patients' characteristics, clinical pregnancy rates (42% vs. 44.3, p = NS, respectively), and ongoing pregnancy rates (31.7% vs. 33.9%, p = NS).We then compared the patients who performed the sub-endometrial wave measurements with the control group and found similar findings. The clinical pregnancy rate (38.2% vs. 44.3, p = NS, respectively) and the ongoing pregnancy rate (30.8% vs. 33.9%) were comparable between the two groups. We performed a regression analysis to examine the independent contribution of different variables to the ongoing pregnancy rates. Both the 3-D and the wave count procedures were not found to have any influence on the ongoing pregnancy rates.

Conclusions Although new ultrasonic methods of evaluating the endometrium have been proposed during the last years, these methods have not been shown to improve the pregnancy rates compared to the original method of assessing the endometrium by measuring the endometrial thickness.

Keywords Sub-endometrial waves · 3-D endometrial scoring · FET

Introduction

Recently, several studies comparing fresh and frozen-thawed embryo transfer (FET) cycles in normal responders demonstrated a significantly higher clinical pregnancy rate per transfer in the FET cycles versus the fresh cycles [1–4]. This improvement in pregnancy rate is thought to be due to impaired endometrial receptivity in the fresh cycles as a result of ovarian stimulation [1–4]. For a pregnancy to occur, an embryo must be implanted in a receptive endometrium during the window of implantation, which is thought to occur during a short period of time, between days 22–24 of an idealized 28-day cycle [5].

Early studies using transvaginal ultrasound (TVUS) have suggested assessing endometrial receptivity by measuring endometrial thickness as an alternative to invasive techniques, such as endometrial biopsy. Pre-ovulatory endometrial thickness of 7 mm is considered as the cutoff thickness, below which many physicians would cancel an embryo transfer [6–8]. However,

✉ Jigal Haas
jigalh@hotmail.com

1 TRIO fertility partners, 655 Bay St, Toronto, ON M5G 2K4, Canada

2 The Fertility Institute, Lis Maternity Hospital, Sourasky Medical Center, Tel- Aviv, Israel

3 Division of Reproductive Sciences, University of Toronto, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada

4 Infertility and IVF Unit, Department of Obstetrics and Gynecology, Chaim Sheba Medical Center (Tel Hashomer), Tel -Aviv University, Ramat Gan, Israel

5 Tarnesby-Tarnowski Chair for Family Planning and Fertility Regulation, Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv-Yafo, Israel

Kasius et al., in their comprehensive meta-analysis has demonstrated a low-positive predictive value for pregnancy of endometrial thickness [9].

More recent studies have focused on TVUS measurement of sub-endometrial contractility, observed as "sub-endometrial waves." Fanchin et al. observed an inverse correlation between the frequency of these waves in the luteal phase and pregnancy outcomes. Increasing progesterone exposure was shown to result in diminished wave activity and improved pregnancy rates [10].

Another recent method of evaluating the endometrium is an endometrial 2-D image scoring by computer-enhanced 3-D modeling called Matris™ (https: //matrisart.com/ what-is-matris/). Matris™ uses proprietary algorithms and specialized technologies to assess and interpret ultrasonographic images taken by the clinic. Matris™ provides a scoring system that assigns a numeric score based on what research predicts will be the quality of the endometrial lining at the time of transfer. The higher the Matris™ score, the higher the probability of pregnancy.

During the last 2 years, patients in our clinic have been offered to perform the 3-D scoring or the sub-endometrial waves measurement, 24–48 h before the planned embryo transfer, and based on those results, the decision whether to proceed to an embryo transfer or to cancel the cycle was taken.

Prompted by the aforementioned observations, we aimed to compare the pregnancy outcome of patients who performed either Matris™ scoring or the sub-endometrial waves measurement prior to the ET, to patients who underwent FET without any prior assessments.

Patients and methods

This was a single center retrospective cohort study of 635 FET cycles of blastocysts vitrified on day 5 and transferred between January 2016 and August 2016. Two hundred twenty-four patients performed the Matris™ scoring, 172 patients performed the sub-endometrial waves measurements, and 239 patients did not perform any of those procedures prior to the ET. The study was approved by the Research Ethics Board at Mount Sinai Hospital in Toronto.

Patients started on day 2–3 of the cycle with oral administration of 2 mg of micronized estradiol twice daily for endometrial preparation, which was increased by a step-up protocol to 8 mg/d. An ultrasound endometrial thickness measurement was performed about 10 days later, assessed the lining as ready for the ET procedure when the endometrial thickness was ≥ 7 mm. If not adequate, endometrial estrogen priming continued and ultrasound assessment was undertaken to further confirm the endometrial thickness. Patients with endometrial thickness < 7 mm were canceled and excluded from the analysis. Participants commenced luteal support via vaginal administration of progesterone suppositories 200 mg three times daily, and embryos were thawed and transferred on day 6 of progesterone.

Matris™ scoring

The ultrasound measurements for 3-D scoring were performed 48 h prior the ET. The images of the uterus were performed by transvaginal ultrasound in the longitudinal and transverse plane. The images were sent and evaluated by an independent company (Synergyne Imaging Technology Inc. https://matrisart.com/ about-us/) and the scores up to 10 were received within 24 h. If the score was below 7 suggesting unreceptive endometrium, the transfer was canceled and postponed to the next cycle (and the following month the Matris™ scoring was performed again).

Sub-endometrial waves measurement

The sub-endometrial wave measurement was performed 24 h prior the ET.

After the vaginal probe was inserted and a longitudinal view of the endometrial cavity was obtained, sub-endometrial wave contractions were counted over 2 min using a screen stopwatch. We intentionally delayed the wave count by 1 min after probe insertion in order to avoid possible irritation provoked by the probe itself. If no wave activity was recorded after a 3-min examination, the test was summarized as "0" wave count. Because former studies reported reduced pregnancy outcome in cases of increased sub-endometrial contractility [11, 12], our clinical protocol for a wave count ≥ 3 per minute on the fifth day of progesterone treatment was to inject two additional 50 mg of IM progesterone, one at the evening and the other in the following morning. On the morning of the 6th day of progesterone, which was the ET day, the wave count was repeated in these "hyper-contractile" cases. If the count was ≤ 2 per minute, the transfer was performed as scheduled. If the wave count was again ≥ 3, the FET cycle was canceled.

Patients with abnormal 3-D scoring, abnormal sub-endometrial wave count, or endometrium < 7 mm were excluded from the study.

The decision whether to perform Matris™ scoring, sub-endometrial wave counting, or no testing was made by the treating physicians independently.

Vitrification method used was Irvine Scientific (Irvine Scientific Santa Ana Ca, USA) "Freeze Kit" (Cat. # 90133-SO) with HSV straws.

We compared the pregnancy outcome of patients who used the Matris™ scoring or the endometrial wave measurements prior to the ET with patients who did not perform any of those procedures prior to the ET.

Clinical pregnancy was defined as a visualization of a gestational sac, while ongoing pregnancy necessitated the visualization of fetal cardiac activity on transvaginal ultrasound.

Comparison of continuous variables between the two groups was conducted using Student's *t* test. Chi-square test was used

Table 1 FET cycles comparing Matris™ scoring and controls

n	Matris™ scoring 224	Control 239	*P*
Age at the OPU	34.8 ± 3.8	35.1 ± 3.7	NS
E2 levels at the triggering day	11,574 ± 5653	11,777 ± 6282	NS
Eggs (*n*)	16 ± 7	16.4 ± 6.7	NS
M2 (*n*)	12.8 ± 6	12.7 ± 5.7	NS
Blastocysts (*n*)	5.6 ± 3.4	5.2 ± 3	NS
Transfers in the past	1.6 ± 1.5	1.6 ± 1.4	NS
Age at transfer	35.2 ± 3.7	35.1 ± 3.7	NS
Endometrial thickness (mm)	9.4 ± 2	9.3 ± 1.8	NS
Number of embryos transferred	1.2 ± 0.4	1.4 ± 1.3	NS
Pregnancy	102/224 (45.5%)	118/239 (49.3%)	NS
Clinical pregnancy	94/224 (42%)	106/239 (44.3%)	NS
Ongoing pregnancy	71/224 (31.7%)	81/239 (33.9%)	NS

for comparison of categorical variables. Logistic regression analysis was employed for multivariate analysis. Variables used in the regression model included maternal age at time of oocyte retrieval, number of transferred embryos, and 3-D scoring or endometrial wave measurements prior to the ET. Significance was accepted at $P < 0.05$. Statistical analyses were conducted using the IBM Statistical Package for the Social Sciences (IBM SPSS v.20; IBM Corporation Inc., Armonk, NY, USA).

Sample size calculation reveals that with the current sample size, we can detect a 13% difference in ongoing pregnancy rate between the study groups and the control group with a power of 80% and a *P* value of 0.05.

Results

While comparing patients who performed Matris™ scoring to the control group, no in-between group differences were found in the patients' age (34.8 vs. 35.1 years, p = NS, respectively), the number of eggs retrieved during the fresh in vitro fertilization cycle (16 vs. 16.4, p = NS), the number of fully expanded blastocysts (5.6 vs. 5.2, p = NS), the number of previous embryo transfers (1.6 vs. 1.6, p = NS), nor the endometrial thickness (9.4 vs. 9.3 mm, p = NS). The clinical pregnancy rate (42 vs. 44.3%, p = NS) and the ongoing pregnancy rate (31.7 vs. 33.9% p = NS, respectively) were comparable between the two groups (Table 1).

We then compared patients who performed the sub-endometrial wave measurements to the control group, patients' age (34.5 vs. 35.1 years, p = NS, respectively), the number of eggs retrieved (17.5 vs. 16.4, p = NS), and the endometrial thickness (9.4 vs. 9.3 mm, p = NS) were comparable between the two groups. The numbers of previous embryo transfer attempts (2.2 vs. 1.6, $p < 0.001$) and fully expanded blastocysts (6.5 vs. 5.2, $p = 0.02$) were significantly higher in the group with endometrial wave testing compared to the control group. The clinical pregnancy rate (38.2 vs. 44.3%, p = NS) and the ongoing pregnancy rate (30.8 vs.

Table 2 FET cycles comparing sub-endometrial waves and controls

n	Waves 172	Control 239	*P*
Age at the OPU	34.5 ± 3.8	35.1 ± 3.7	NS
E2 levels at the triggering day	10,307 ± 5998	11,777 ± 6282	0.03
Eggs (*n*)	17.5 ± 9	16.4 ± 6.7	NS
M2 (*n*)	14.4 ± 7.4	12.7 ± 5.7	NS
Blastocysts (*n*)	6.3 ± 5.1	5.2 ± 3	0.02
Transfers in the past	2.2 ± 1.7	1.6 ± 1.4	< 0.001
Age at transfer	35.2 ± 3.7	35.1 ± 3.7	NS
Endometrial thickness (mm)	9.4 ± 2.5	9.3 ± 1.8	NS
Number of embryos transferred	1.1 ± 0.4	1.4 ± 1.3	0.002
Pregnancy	80/172 (46.5%)	118/239 (49.3%)	NS
Clinical pregnancy	62/172 (38.2%)	106/239 (44.3%)	NS
Ongoing pregnancy	53/172 (30.8%)	81/239 (33.9%)	NS

33.9%, p = NS, respectively) were comparable between the two groups (Table 2).

We performed a regression analysis to examine the independent contribution of different variables to the ongoing pregnancy rates. Variables used in the regression model included maternal age, number of transferred embryos, number of oocytes retrieved, number of M-II oocytes, and number of blasts. Both the Matris™ scoring and the wave count procedures were not found to have any influence on the ongoing pregnancy rates.

Discussion

In the present study, we found that different ultrasonic evaluations of the endometrium prior to embryo transfer did not improve pregnancy outcome. The clinical and ongoing pregnancy rates were comparable between patients who performed Matris™ scoring or sub-endometrial wave measurements prior to the ET and patients who did not perform those procedures prior to the ET.

For many decades, the endometrial thickness has been the only tool used by clinicians in deciding whether the endometrium is appropriate for embryo transfer. Thin endometrium is related to lower implantation and pregnancy rates. Therefore, most physicians would cancel embryo transfer to a patient with thin endometrium. Pre-ovulatory endometrium of 7 mm is commonly accepted as the cutoff thickness [6–8]. However, other endometrial thickness cutoffs are common in clinical practice and they usually range between 5 and 8 mm [13–15]. A progressive correlation between endometrial thickness and pregnancy rates was reported [16]. Some studies reported a higher pregnancy rate achieved with an embryo transfer when endometrial thickness was > 9 mm [17, 18]. In donor egg recipient cycles, the pregnancy rate was higher with endometrial thickness between 9 and 10 mm [19]. Nonetheless, pregnancies were achieved in patients with endometrium as thin as 4 mm [20]. In the present study, only transfers with endometrial thickness of 7 mm and above were included and patients' thickness below 7 mm were excluded from the study.

Fanchin et al. demonstrated that multiple sub-endometrial contractions can negatively affect the pregnancy rate [21]. Uterine contractility can be spontaneous or induced by traumatic transfer. Moreover, abnormal uterine contractility might be one of the explanations for tubal pregnancy following sonographic-guided embryo transfer to the uterine midcavity [22]. It is well established that progesterone reduces uterine contractility [23]. Therefore, in cases of an overactive uterus, adding progesterone might help in achieving a reduction in contractions prior to transfer [24].

More recently, Zhu et al. demonstrated that the uterine peristaltic wave frequency before embryo transfer is inversely related to the clinical pregnancy rates in fresh and frozen-thawed embryo transfer cycles. They demonstrated a dramatic decrease in pregnancy rates with the occurrence of three waves or above per minute [25].

In the present study, only patients with less than three waves were included. The patients who had three waves or above at the morning of the ET were canceled. In the control group, none of the patients underwent sub-endometrial wave evaluation. Even without measuring the number of waves, we can assume that some of them might have had an increased number of waves and would have been canceled if they had been tested for the sub-endometrial waves. However, since the pregnancy rates were comparable in the two groups, we might assume that sub-endometrial contraction evaluation could not improve pregnancy rate.

Three-dimensional Matris™ scoring was first introduced as an abstract at the ASRM meeting in October 2012, as a novel sonographic method for evaluating the endometrial receptivity. The technique contains different proprietary algorithms developed by the company in order to optimize the endometrial receptivity evaluation. The original abstract presented data from 117 women who had 3-D scoring performed prior to ET. They demonstrated an increasing pregnancy rate with increasing 3-D scoring. When the 3-D scores were good-excellent, the ongoing pregnancy rates were between 64–100%. The authors recommended that validation of this model in a large sample of IVF/ICSI patients should be considered. Unfortunately, the data that was presented at the meeting was never published as a manuscript and a prospective study has not been performed.

Similarly to patients with abnormal sub-endometrial contractions, patients who had abnormal Matris™ scoring 48 h prior the ET were canceled. In the control group, none of the patients underwent Matris™ scoring. Since pregnancy rates were comparable between the two groups, we may assume that performing the Matris™ scoring failed to increase the pregnancy rate.

There are a few limitations to our study. The main limitation is the retrospective study design, and although the results of this study are promising, further prospective studies will be needed to confirm the findings. There are many factors that can influence the pregnancy rate, such as the physician or the embryologist performing the transfer, difficulty inserting the transfer catheter, endometrial thickness and pattern, and sub-endometrial contractions to name a few. Those factors were not controlled for in the study.

Although the patients were not randomized to the different treatments, and therefore selection bias cannot be excluded, the decisions whether to perform the 3-D scoring/sub-endometrial contraction evaluation or only endometrial thickness were made by the physician without taking into account previous fertility history. Some physicians performed Matris™ scoring on all their patients, some performed sub-endometrial contraction evaluation on all their patients, and some measured only the endometrial thickness.

We conclude that although new ultrasonic methods for evaluating the endometrium prior to ET have been proposed during the last years, according to our experience these methods have not been proven to improve pregnancy rate compared to the original method of assessing the endometrium by measuring the endometrial thickness.

Compliance with ethical standards

Ethics statement The study was approved by the Research Ethics Board at Mount Sinai Hospital in Toronto.

References

1. Shapiro BS, Daneshmand ST, Restrepo H, Garner FC, Aguirre M, Hudson C. Matched-cohort comparison of single-embryo transfers in fresh and frozen-thawed embryo transfer cycles. Fertil Steril. 2013;99:389–92.
2. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Clinical rationale for cryopreservation of entire embryo cohorts in lieu of fresh transfer. Fertil Steril. 2014;102:3–9.
3. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders. Fertil Steril. 2011;96:344–8.
4. Ozgur K, Berkkanoglu M, Bulut H, Humaidan P, Coetzee K. Perinatal outcomes after fresh versus vitrified-warmed blastocyst transfer: retrospective analysis. Fertil Steril. 2015;104:899–907 e3.
5. Bergh PA, Navot D. The impact of embryonic development and endometrial maturity on the timing of implantation. Fertil Steril. 1992;58:537–42.
6. Isaacs JD Jr, Wells CS, Williams DB, Odem RR, Gast MJ, Strickler RC. Endometrial thickness is a valid monitoring parameter in cycles of ovulation induction with menotropins alone. Fertil Steril. 1996;65:262–6.
7. 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. Fertil Steril. 1999;71:147–9.
8. Wu Y, Gao X, Lu X, Xi J, Jiang S, Sun Y, et al. Endometrial thickness affects the outcome of in vitro fertilization and embryo transfer in normal responders after GnRH antagonist administration. Reprod Biol Endocrinol. 2014;12:96.
9. Kasius A, Smit JG, Torrance HL, Eijkemans MJ, Mol BW, Opmeer BC, et al. Endometrial thickness and pregnancy rates after IVF: a systematic review and meta-analysis. Hum Reprod Update. 2014;20:530–41.
10. Fanchin R, Righini C, Olivennes F, Taylor S, de Ziegler D, Frydman R. Uterine contractions at the time of embryo transfer alter pregnancy rates after in-vitro fertilization. Hum Reprod. 1998;13:1968–74.
11. Fanchin R, Ayoubi JM, Olivennes F, Righini C, de Ziegler D, Frydman R. Hormonal influence on the uterine contractility during ovarian stimulation. Hum Reprod. 2000;15(Suppl 1):90–100.
12. Fanchin R, Ayoubi JM, Righini C, Olivennes F, Schonauer LM, Frydman R. Uterine contractility decreases at the time of blastocyst transfers. Hum Reprod. 2001;16:1115–9.
13. Bu Z, Wang K, Dai W, Sun Y. Endometrial thickness significantly affects clinical pregnancy and live birth rates in frozen-thawed embryo transfer cycles. Gynecol Endocrinol. 2016:1–5.
14. Fang R, Cai L, Xiong F, Chen J, Yang W, Zhao X. The effect of endometrial thickness on the day of hCG administration on pregnancy outcome in the first fresh IVF/ICSI cycle. Gynecol Endocrinol. 2016:1–4.
15. Lebovitz O, Orvieto R. Treating patients with "thin" endometrium - an ongoing challenge. Gynecol Endocrinol. 2014;30:409–14.
16. Al-Ghamdi A, Coskun S, Al-Hassan S, Al-Rejjal R, Awartani K. The correlation between endometrial thickness and outcome of in vitro fertilization and embryo transfer (IVF-ET) outcome. Reprod Biol Endocrinol. 2008;6:37.
17. Zhao J, Zhang Q, Li Y. The effect of endometrial thickness and pattern measured by ultrasonography on pregnancy outcomes during IVF-ET cycles. Reprod Biol Endocrinol. 2012;10:100.
18. Richter KS, Bugge KR, Bromer JG, Levy MJ. Relationship between endometrial thickness and embryo implantation, based on 1,294 cycles of in vitro fertilization with transfer of two blastocyst-stage embryos. Fertil Steril. 2007;87:53–9.
19. Dain L, Bider D, Levron J, Zinchenko V, Westler S, Dirnfeld M. Thin endometrium in donor oocyte recipients: enigma or obstacle for implantation? Fertil Steril. 2013;100:1289–95.
20. Amui J, Check JH, Cohen R. Successful twin pregnancy in a donor oocyte recipient despite a maximum endometrial thickness in the late proliferative phase of 4 mm. Clin Exp Obstet Gynecol. 2012;38:328–9.
21. Fanchin R, Righini C, Ayoubi JM, Olivennes F, de Ziegler D, Frydman R. Uterine contractions at the time of embryo transfer: a hindrance to implantation? Contracept Fertil Sex. 1998;26:498–505.
22. Lesny P, Killick SR, Tetlow RL, Robinson J, Maguiness SD. Embryo transfer–can we learn anything new from the observation of junctional zone contractions? Hum Reprod. 1998;13:1540–6.
23. Zhu L, Li Y, Xu A. Influence of controlled ovarian hyperstimulation on uterine peristalsis in infertile women. Hum Reprod. 2012;27:2684–9.
24. Casper RF, Yanushpolsky EH. Optimal endometrial preparation for frozen embryo transfer cycles: window of implantation and progesterone support. Fertil Steril. 2016;105:867–72.
25. Zhu L, Che HS, Xiao L, Li YP. Uterine peristalsis before embryo transfer affects the chance of clinical pregnancy in fresh and frozen-thawed embryo transfer cycles. Hum Reprod. 2014;29:1238–43.