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Assisted Reproduction

Cumulative Embryo Score, Not Endometrial Thickness, Is Best for Pregnancy Prediction in IVF

Cassie Laasch[1,3] and Elizabeth Puscheck[2]

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***Purpose*:** To assess the combined effect of endometrial thickness and cumulative embryo score (CES) on pregnancy rates in assisted reproduction cycles compared to the effect of each of these factors considered individually.
***Methods*:** Retrospective review of 2001 IVF pregnancy outcomes with respect to endometrial thickness and CES.
***Results*:** One hundred fifty-five IVF cycles were reviewed. Endometrial thickness ranged from 6.4 to 22 mm. CES ranged from 16 to 194. CES scores above 50 correlated with improved pregnancy rates (31%) over those less than 50 (12.5%). CES scores above 150 were correlated with a further doubling in pregnancy rates (66%). Endometrial thickness alone or in combination with cumulative embryo score did not improve the prediction of pregnancy.
***Conclusions*:** CES alone, and not combined with endometrial thickness, is a statistically significant factor in pregnancy rates that may be clinically useful in decisions regarding number of embryos transferred to ensure a better pregnancy rate.

KEY WORDS: Embryo quality; endometrial thickness; ICSI; in vitro fertilization.

INTRODUCTION

In artificial reproduction cycles, successful implantation requires both quality embryos and a receptive endometrial environment. Significant research has been done to look at the influence of these two factors on pregnancy outcomes. Most of the research has focused on each factor individually or has looked at multiple variables to determine the most predictive factor. Little data exists that correlates the cumulative effect of both embryo quality and endometrial thickness on clinical pregnancy rates.

The data is controversial regarding the role of endometrial thickness alone on pregnancy outcomes. A review of the literature by Friedler *et al.* (1) was unable to find a consistent correlation between endometrial thickness and pregnancy outcomes. There are multiple studies that have supported (2,3) or refuted (4,5) the correlation between endometrial thickness and pregnancy. Some researchers have suggested that only the extremes of endometrial thickness values (6,7) negatively impact pregnancy rates. In these studies endometrial thicknesses less than 8 mm (8) or greater than 14 mm (7) were negatively correlated with pregnancy outcomes. Bassil (4) found no correlation between endometrial thickness, width, and pattern with pregnancy rates. Controversy exists at these lower thicknesses about which cutoff is appropriate for the lower threshold. Only one paper suggests that endometrial thicknesses at the upper cutoff (greater than 14 mm) have a negative effect on pregnancy rates (7). However, most researchers concur that endometrial thicknesses less than 4 mm

[1] Department of Obstetrics and Gynecology, St. John Health System, Detroit, Michigan.
[2] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Wayne State University, Detroit, Michigan.
[3] To whom correspondence should be addressed at 22151 Moross Road, Suite 313, Detroit, Michigan 48236; e-mail: cassie.laasch@stjohn.org.

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decrease pregnancy rates significantly. Despite this general consensus, Sundstrom (9) reported a successful pregnancy with an endometrial thickness of 4 mm.

Investigators have had more success at supporting the correlation between embryo quality and IVF outcome. Embryo quality has typically been estimated on the basis of cell number, cell size, cell shape, and degree of fragmentation (10). Many studies have supported the idea that embryo quality is the best predictive factor for pregnancy in IVF cycles. Terriou *et al.* (11) examined multiple variables in IVF cycles and concluded that the most important variable is embryo quality. Schwartz *et al.* (12) compared predictive rates of embryo quality and multiple endometrial factors (thickness, doppler parameters), and they also suggested that embryo scores were most likely to predict pregnancy outcome.

In this study, we examined the correlation of embryo quality and endometrial thickness (together and individually) with pregnancy outcome. Our hypothesis was that a combination of endometrial thickness and embryo quality would improve the prediction of pregnancy.

MATERIALS AND METHODS

All cycles of IVF and ICSI during 2001 (January–December) at a university-based infertility center were reviewed.

Patients underwent stimulation protocols involving leuprolide acetate downregulation followed by administration of human menopausal gonadotropins and/or recombinant follicle stimulating hormone. Human chorionic gonadotropin (hCG; 10,000 IU) was administered when two follicles reached 20 mm and oocyte retrieval was performed 35 h after hCG administration. Ultrasound measurements of endometrial thickness were recorded on the day of hCG administration. Transvaginal ultrasound was used to measure endometrial thickness. The orientation for measurement was the maximum diameter of the endometrial stripe when viewed in the longitudinal axis. Measurements were taken by three sonographers who were within 1 mm of accuracy.

Embryos were evaluated on the third day after oocyte retrieval. Transfers were also performed on day 3. Embryo quality and cell number were recorded by concordance of two embryologists for each embryo transferred. Quality was determined by uniformity of cell size and shape and by degree of fragmentation. Embryo grades were assigned a numeric value (excellent = 5.0, very good = 4.0, good = 3.0, fair = 2.0, poor = 1.0). Embryos which were graded between categories were scored to the halfpoint. For example, an embryo graded as good/very good would receive 3.5 for quality. Cumulative embryo scores (CES) were calculated by multiplying the number of cells in each embryo transferred by the quality score of that embryo and adding the values for the embryos transferred in each patient (similar to the method used by Steer *et al.* (13)). Embryos that were classified as compacting embryos (at any stage), morulas, or blastocysts were excluded from the analysis because CES could not be calculated.

Clinical pregnancy was defined as ultrasound-confirmed fetal cardiac activity. Each cycle was considered as a separate case for statistical analysis. Data was analyzed using a SPSS statistics program utilizing the Student t test, logistic regression, and Fisher's Exact test where appropriate.

RESULTS

The mean age for all patients was 33.7 years (standard deviation 5.2 years). One hundred fifty-five cycles were reviewed. Fourteen cycles were either canceled or did not have an embryo transfer. One hundred seven patients who underwent 141 completed IVF cycles were analyzed. Twenty-six patients underwent more than one cycle during 2001. Nineteen patients had two cycles, six patients had three cycles and one patient had four cycles. Of the 141 cycles, 52 were standard IVF and 89 were ICSI. Cumulative embryo scores ranged from 16 to 194. CES could not be calculated on 13 cycles due to one or more compacting embryos or day 5 transfers. Endometrial thickness (ET) ranged from 6.4 to 22.0 mm. Eleven cycles did not have an endometrial thickness recorded on the day of hCG administration. There were 10 cycles with ET <8 mm, 100 cycles with ET between 8 and 14 mm and 20 cycles with ET >14 mm.

Comparisons of patient age, endometrial thickness, and cumulative embryo score revealed that only the CES was a statistically significant predictor for pregnancy rate (Fig. 1). The mean CES for nonpregnant patients was 75.6 and the mean CES for pregnant patients was 95.0 ($p = 0.01$). Endometrial thickness did not vary significantly in the pregnant versus the nonpregnant groups (see Table I).

Pregnancy rates were compared on the basis of CES alone. Cycles with CES values less than 50 had a pregnancy rate of 12.5%, which was significantly lower

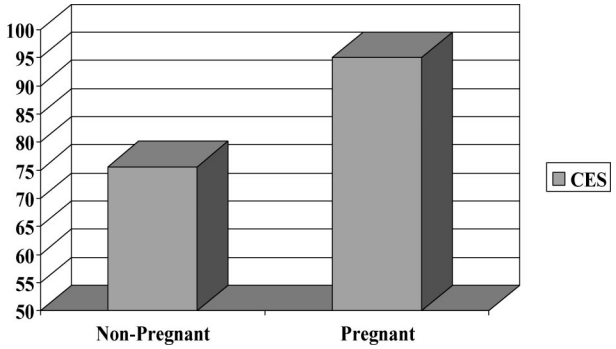

Fig. 1. Mean Cumulative Embryo Score (CES) in nonpregnant vs. pregnant outcomes. $p = 0.01$.

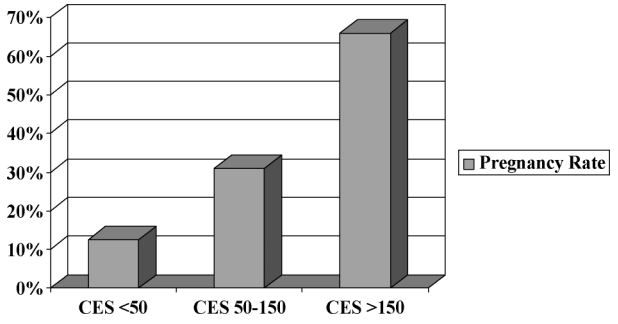

Fig. 2. Pregnancy rates based on cumulative embryo score (CES). $p < 0.05$.

than the pregnancy rates of cycles with CES above 50 (Fig. 2). Patients in cycles with CES between 51 and 150 had pregnancy rates of 31% and those patients with the cycle CES greater than 151 had pregnancy rates of 66%. Increasing CES values were significantly associated with increasing pregnancy rates ($p < 0.05$).

Logistic regression was performed to evaluate the interaction between CES and endometrial thickness in predicting pregnancy rate. Prediction of pregnancy outcome was not improved by evaluation of the CES in combination with the endometrial thickness.

Patients were then divided into subgroups based on endometrial thickness and CES. Patients were considered to have optimal endometrial thickness if values were between 8 and 14 mm. Poor endometrial thickness was considered <8 or >14 mm. Patients were considered to have optimal CES if values were greater than 50, while poor CES were those less than 50. Four groups were then considered, evaluating patients with optimal ET/good CES, optimal ET/poor CES, poor ET/good CES, and poor ET/poor CES. Fisher's Exact test was performed to evaluate the relationship between pregnant versus nonpregnant outcomes in these four groups. There was no significant relationship between the outcomes for the four groups.

Table I. Mean Age, Cumulative Embryo Score (CES), and Endometrial Thickness (ET) in Nonpregnant and Pregnant Outcomes

	Nonpregnant	Pregnant	*p* value*
Mean age	33.5	33.6	0.952
Mean CES	75.5	95.0	0.012
Mean ET	11.2	11.9	0.209

*$p < 0.05$.

DISCUSSION AND CONCLUSIONS

Our goal was to compare endometrial thickness and cumulative embryo score to determine the cumulative effect of these variables on pregnancy rates. We used a cumulative embryo score similar to the one proposed by Steer *et al.* The advantage to this system is that it takes into account the number of embryos transferred as well as the quality of each embryo. We also evaluated the use of endometrial thickness as a predictor of pregnancy rate.

Our study confirms previous reports that endometrial thickness alone does not predict pregnancy outcome. Our analysis may have been limited by the fact that there were no patients with endometrial thickness less than 6 mm. Endometrial thickness of less than or equal to 4 mm may be a significant threshold for an effect on pregnancy outcome that could not be assessed by this study. Given the fact that this potentially significant group was not present in our data, it may not be surprising that embryo quality stands out as the greater predictor.

We also concurred with previous evidence that embryo quality is correlated with pregnancy outcome, regardless of endometrial thickness. This finding may be clinically useful to consider the cumulative embryo score for each patient before making decisions regarding the number of embryos to be transferred. If the CES is less than 50, consideration may be given to transferring an additional embryo in order to increase the CES, even if it varies from national standard recommendations. Of course, the clinical impact of multiple births should also be considered.

Our data suggests that adding endometrial thickness to the cumulative embryo score does not provide additional benefit in the prediction of pregnancy outcome.

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