Significance of Increased Endometrial Thickness in Assisted Reproduction Technology Treatments

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Purpose: The purpose of this study was to evaluate the relationship between thick endometrium and both implantation and pregnancy rates in ART treatments.

Methods: The study group was composed of consecutive women undergoing ultrasonographic evaluation on the day of hCG administration in our ART unit. Endometrial thickness was measured at the thickest part of the midsagittal plane. On the basis of the findings, patients were divided into two groups: A—endometrial thickness >14 mm (above the 95th percentile) and B—endometrial thickness 7–14 mm (between the 5th and 95th percentiles). Patients with a thickness of less than 7 mm were excluded from the study.

Results: In all, 1218 cycles were included in the study (50 in Group A and 1168 in Group B). There was no significant difference between the groups in mean patient or mean number of embryos transferred. Similar pregnancy and implantation rates were noted in Group A (24 and 11.3%, respectively) and Group B (27.7 and 14.7%, respectively). Endometrial thickness was found to have a significant positive correlation with the duration of follicular stimulation, and an inverse correlation with woman's age.

Conclusions: Increased endometrial thickness (>14 mm) is not associated with decreased implantation or pregnancy rates in assisted reproduction.

KEY WORDS: Implantation and pregnancy rates; thick endometrium; ultrasound.

INTRODUCTION

Endometrial receptivity is one of the key factors determining the likelihood of success in assisted reproduction technology (ART) treatments. It is widely accepted that a thin endometrial stripe on transvaginal ultrasound scan is associated with a poor pregnancy rate (1–3). However, the possible effect of increased endometrial thickness remains unclear. Some authors have found that it decreases the chances of success (4), whereas others (5) failed to confirm this finding. The purpose of the present study was to further evaluate the possible role of increased endometrial thickness on the outcome of ART treatments.

MATERIALS AND METHODS

The study group was composed of consecutive women enrolled in our ART unit between 1998 and 2000. The unit's ovarian stimulation protocols, ultrasound and hormonal surveillance methods, timing of human chorionic gonadotropin (hCG) administration, and oocyte retrieval and sperm processing techniques are detailed elsewhere (6). In brief, women treated by either the long or the short protocols utilizing either follicle-stimulating hormone (FSH; Metrodin, Tevapharma, Natanya, Israel) or human menopausal gonadotropin (HMG; Pergonal, Serono, Herzelya, Israel) for follicular stimulation. FSH or HMG was administered in variable doses depending on the individual response. hCG (10,000 IU; Chorigon, Tevapharma, Natanya, Israel) was administered to initiate ovulation when at least two follicles of >17 mm were identified by transvaginal scan

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and serum E2 levels were appropriate. On the day of hCG administration (as well as for all previous surveillance examinations), the endometrium was imaged by transvaginal ultrasound equipped with a 4–7-MHz vaginal transducer (General Electric Ultrasound Division, Atlit, Israel). The scans were performed by either of two experienced sonographers who were blinded to the hormonal response. Endometrial thickness was measured at the thickest part of the midsagittal section: after the proper view was identified, the image was frozen and electronic calipers were placed at the junction of the endometrium–myometrium interface (junction between the stratum basalis of the endometrium and the inner myometrium); the total thickness from one side to the other was recorded. On the basis of these findings, the patients were divided into two groups: (A) endometrial thickness >14 mm (above the 95th percentile); (B) endometrial thickness 7–14 mm (between the 5th and 95th percentiles). The endometrial width was not a factor in the timing of hCG administration. All patients had a normal uterine cavity as evidenced by a normal hysterosalpingography or hysteroscopy performed during the year preceding the current cycle.

Oocytes were fertilized conventionally or by ICSI according to criteria published before (6). Embryo quality was graded before embryo transfer: embryos with equal-sized blastomeres, ideal cleavage rate (four cells on day 2 or eight cells on day 3), and $\leq 10\%$ fragmentation were defined as Grade A; similar embryos but with $\leq 20\%$ fragmentation were defined as Grade A₁. The total number of embryos transferred was based on the individual woman's age and cycle number, according to our unit's policy. Embryos were transferred gently to the lower uterine cavity with soft-pass catheters, either Cook (Cook OB/GYN, Spencer, Indiana) or Wallace (Simcare Ltd., Lancing, West Sussex, England), depending on their availability in the unit. For luteal phase support patients received either 50-mg IM progesterone (Gestone, Ferring, Lapidot, Natanya, Israel) daily or 600-mg micronized progesterone soft gel vaginal capsules (Utrogestan, Besins, Iscovesco, C.T.S. Petah Tikva, Israel) in three divided doses daily. *Clinical pregnancy* was defined as the presence of a gestational sac by transvaginal ultrasonography in association with rising β -hCG levels.

All pertinent clinical data were collected prospectively on a computerized database and evaluated at the end of the study. Patients who met the following criteria were excluded from the analysis: 1)

endometrial thickness less than 7 mm (below the 5th percentile); 2) sonographic identification of an intrauterine polyp or submucosal fibroids; 3) no embryo transfer performed in the same cycle; 4) blastocyst transfer performed in the same cycle; 5) natural cycle—in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI); 6) zygote intrafallopian transfer (ZIFT); 7) age > 40 years at the time of the study; 8) data not recorded prospectively (for technical reasons). The following variables were assessed: patient age, duration of follicular stimulation and number of gonadotropin ampoules consumed, hCG-day estrogen and progesterone levels, number of follicles measuring >14 mm in diameter on the same day, number of oocytes retrieved, fertilization and cleavage rates, number of embryos transferred, and pregnancy and implantation rates.

Because measurement of endometrial thickness is done routinely in our program, Institutional Review Board approval for the study protocol was not necessary. All patients signed our standard ART informed consent form prior to initiation of therapy.

Power analysis demonstrated that to find a 15% difference in pregnancy rate between the study and control groups with a power of 0.8, we needed at least 50 cycles in the study group.

For statistical analysis, Student's *t* test, chi-square test, and Fisher's exact test were used as appropriate. Correlations and regression analyses were performed utilizing SPSS software (SPSS 9.0 for Windows). A *p* value of less than 0.05 was considered significant.

RESULTS

A total of 1278 cycles (performed in 808 women) were available for the initial analysis. On the day of hCG administration, endometrial thickness ranged between 2 and 19 mm (mean 9.9 ± 2.3 mm). There was no significant difference in mean endometrial thickness between IVF cycles and ICSI cycles conducted for severe male factor infertility (9.8 ± 2.4 and 10.0 ± 2.2 mm, respectively). The 5th and 95th percentiles were 7 and 14 mm, respectively. After excluding the patients with an endometrial thickness of less than 7 mm, 1218 cycles (783 women) remained for analysis: 50 in Group A (endometrial thickness >14 mm) and 1168 in Group B (endometrial thickness 7–14 mm).

The clinical data for both groups are summarized in Table I. There were no significant differences between Groups A and B for the following parameters: patient age, E2 and progesterone levels on the day of

Table 1. Pertinent Clinical Data of Group A (Endometrial Thickness >14 mm) and Group B (Endometrial Thickness 7–14 mm)

	Group A (N = 50)	Group B (N = 1168)	p value (Student's t- test)
Age (years)	31.9 ± 4.6	32.9 ± 4.7	ns
No. of ampoules	37.1 ± 17.0	31.3 ± 14.2	<0.01
No. of stimulation days	10.4 ± 2.3	9.3 ± 2.8	<0.01
Peak E2 level (pmol/L)	4630 ± 1917	4891 ± 3929	ns
Progesterone level on hCG day (nmol/L)	4.3 ± 3.1	4.3 ± 2.3	ns
No. of follicles >14 mm	6.6 ± 2.8	6.7 ± 3.4	ns
No. of oocytes retrieved	9.8 ± 5.4	9.6 ± 6.0	ns
Fertilization rate (%)	56.2 ± 25.9	61.0 ± 29.2	ns
Cleavage rate (%)	94.2 ± 36.8	93.3 ± 42.2	ns
No. of Grade A embryos transferred	0.9 ± 1.2	1.1 ± 1.2	ns
No. of Grade A ₁ embryos transferred	1.0 ± 1.2	1.3 ± 1.3	ns
Total no. of embryos transferred	2.8 ± 0.9	2.9 ± 1.1	ns

Note. Figures are provided as mean ± standard deviation. ns – not significant.

hCG administration, number of follicles >14 mm in diameter, number of oocytes retrieved, fertilization and cleavage rates, number of Grades A and A₁ embryos transferred and total number of embryos transferred. The women with a thick endometrium (Group A) had received significantly more gonadotropin ampoules (37.1 ± 17.0 vs. 31.3 ± 14.2 , respectively, $p < 0.01$) and were stimulated for a significantly longer period (10.4 ± 2.3 days vs. 9.3 ± 2.8 days, respectively, $p < 0.01$).

The results indicated similar pregnancy and implantation rates for both groups (27.7 and 14.7%, and 24 and 11.3% for Groups A and B, respectively). Similar results were obtained when the data for standard IVF cycles and ICSI cycles conducted for severe male factor infertility were analyzed separately. There were no between-group differences with regard to pregnancy and implantation rates for long and short protocols (data not provided). The proportion of IVF and ICSI cycles and of short and long protocols was similar in Groups A and B.

Endometrial thickness showed a significant inverse correlation with patient's age ($R = -0.1$, $p < 0.01$), and a significant positive correlation with the duration of follicular stimulation ($R = 0.11$, $p < 0.01$). No significant correlation was found between endometrial thickness and number of gonadotropin ampoules consumed, hCG-day E2 and progesterone levels, number of follicles >14 mm on the same day, and number of oocytes retrieved.

A stepwise regression analysis was carried out wherein endometrial thickness served as the dependent variable and all the other parameters as the independent variables. Both the duration of follicular stimulation and patient age were found to have a significant influence on endometrial width ($r^2 = 0.03$, $p = 0.002$, and $r^2 = 0.037$, $p = 0.036$, respectively).

DISCUSSION

The main rate-limiting step that determines the likelihood of success of ART treatment is the implantation stage. Implantation depends largely on two factors: embryo quality and uterine receptivity. Uterine receptivity, in turn, depends on many variables, one of which is known to be the endometrial lining.

The time of administration of hCG in fresh ART stimulation protocols is based mainly on the diameter of the leading follicles, and in part on the peripheral estrogen level. The thickness of the endometrium is not considered a relevant factor in this decision. Thus, by the nature of the procedure, patients are subject to a wide range of exposure to gonadotropin (in both duration and number of ampoules)—and its unopposed hyperestrogenic effect—resulting in a wide range of endometrial thickness (2–19 mm in this study). By contrast, in the ovum donation program, endometrial thickness is the sole parameter that determines readiness of the uterus for implantation and the beginning of progesterone supplementation. As a result, the range of endometrial thickness in ovum receivers is much narrower and the implantation rate usually higher than in fresh cycles (7, 8). These observations imply that there might be a point at which a “too-thick” (i.e., >95th percentile) as well as “too-thin” endometrial lining can have a detrimental effect on the implantation process. To test this hypothesis, we conducted this study in a large (1218) sample of cycles.

A minimal endometrial thickness (usually >6 mm) as a prerequisite for implantation, although widely accepted, is still controversial. Specifically, there is no agreement in the literature concerning the effectiveness of ultrasonographic evaluation (both thickness and appearance) of the endometrium as a predictor for success (9–13). In a recent large study of De Geyter *et al.* (9) on the role of the endometrium in various fertility treatments, the endometrium was found to be significantly thicker in women treated by the long protocol for IVF than in women given the natural or ultrashort protocols for intrauterine insemination. This observation is concordant with our findings of

a correlation between the endometrial thickness and the duration of follicular stimulation (which is known to be longer in long protocols). Interestingly, while the odds ratio for achieving pregnancy in the study of De Geyter *et al.* (9) was affected only marginally by the degree of endometrial proliferation, the odds ratio for singleton pregnancies was higher in the presence of a thin endometrium, indicating a lower implantation rate in these cycles. Moreover, their study group included only 12 IVF/ICSI cycles (out of 1061) with an endometrial thickness below 6.9 mm. Therefore, their conclusions, which oppose those of other studies (14–17), that the likelihood of pregnancy is influenced only marginally by a reduced endometrial thickness and that treatment should not be canceled because of inadequate endometrial thickness need to be viewed with caution until more supportive data become available.

In our series, similar pregnancy and implantation rates were achieved in patients with an endometrial thickness of 7–14 mm and patients with an endometrial thickness of >14 mm (24 and 11.3%, and 27.7 and 14.7%, respectively). These results indicate that an endometrial thickness above the 95th percentile on the day of hCG administration does not interfere with the likelihood for success.

Regarding an increased endometrial thickness, Weissman *et al.* (4), using a design similar to ours, reported that an endometrial thickness of >14 mm has a detrimental effect on implantation and pregnancy rates. It should be noted, however, that the group with the thick endometrium was composed of significantly older women, which is the single most important factor influencing pregnancy rates in ART treatments. It is not clear from their results whether any attempt was made to statistically control for this major confounding factor. One advantage of this study was the similar mean patient age in the two groups (Table I). However, in other studies, an endometrial thickness of ≥ 14 mm, noted in 9.6% of the patients (10) and of ≥ 15 mm, noted in 11.6% of the patients (2), was associated with a normal pregnancy rate (42.8 and 48.39%, respectively). The implantation rate documented in the second study was also high (24.8%). Similar findings were recently described by Dietterich *et al.* (5).

Rinaldi *et al.* (18) found that endometrial thickness was a predictor of pregnancy after IVF but not after ICSI. However, their 10-mm cutoff does not seem to identify those with either a thin or a thick endometrium. They suggested that the significantly thinner endometrium in the IVF patients compared to the ICSI patients probably represents an adverse

Table II. Correlations of Endometrial Thickness with Different Variables According to Different Studies

Refs.	Age	Stimulation length	No. of gonadotropin ampoules	Peak E2 level
(10)	NT	↑	NT	NT
(2)	↓	NT	NT	↑
(18)	NT	NT	NT	↔
(7)	NT	NT	NT	↑
(4)	NT	↔	NT	↔
(9)	↔	NT	NT	↑
Present study	↓	↑	↑	↔

Note. NT – not tested.

affect of a previous noxious agent on the uterine lining in at least some cases. Our study does not support this statement, being no significant difference in mean endometrial thickness between IVF and ICSI cycles.

The inverse correlation between endometrial thickness and patient age observed in this study, and the significant contribution of patient age to endometrial thickness on regression analysis, are concordant with our previous reports (19, 20), and with that of Noyes *et al.* (2). These findings imply that the thinner endometrium may contribute to the decline in implantation efficiency with advancing age. Although De Geyter *et al.* (9) failed to demonstrate a correlation between endometrial thickness and patient age, they did note a correlation of endometrial thickness with the E2 concentration on the day of hCG administration, which in turn correlated inversely with patient age. A similar negative correlation between E2 levels and patient age was demonstrated by our data ($r = -0.14$, $p < 0.01$). The various correlations reported by different authors are summarized in Table II. It is noteworthy that although differences exist among the studies, there are no contrary findings for any of the parameters evaluated.

A histological study is still needed, which can be carried out in an ovum donor program, to shed light on the question of whether endometrial thickness >95th percentile is associated with an abnormal histological structure.

Although it may be argued that the endometrial thickness measurement is not sufficiently accurate, recent reports (9,21) documented acceptable intraobserver and interobserver variability.

A limitation of our study is that the pattern of the endometrium (triple-line vs. homogeneous) was not recorded and therefore could not be analyzed. In conclusion, increased endometrial thickness (>14 mm) is apparently not associated with decreased implantation and pregnancy rates in IVF/ICSI treatments. The

endometrial thickness correlates positively with the duration of follicular stimulation and inversely with patient age.

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