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The effect of endometrial thickness on IVF/ICSI outcome

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BACKGROUND: During the menstrual cycle the endometrium undergoes cyclic proliferative and secretory changes in preparation for implantation. If this preparation is not sufficient, then implantation will fail. The impact of endometrial thickness on the day of embryo transfer on IVF outcome was investigated in the present study. METHODS: A retrospective analysis was conducted of 1228 IVF/ICSI cycles. Stimulation was with clomiphene citrate (CC) + hMG in one-third of the cycles, and ultrashort GnRH agonist stimulation in two-thirds. Cycle parameters were compared between pregnant and non-pregnant patients. A similar comparison was made between ongoing pregnancies and those that resulted in a loss. RESULTS: There were more follicles, oocytes and embryos, the endometrium was thicker and the embryo quality was higher among women who became pregnant when compared with non-pregnant women after assisted reproduction. The pregnancy rate improved as endometrial thickness increased. No difference in cycle parameters and endometrial thickness was found between ongoing pregnancies and pregnancies that resulted in a first-trimester loss. CC had no measurable adverse endometrial effect, but the pregnancy rate was lower in CC+hMG cycles. CONCLUSIONS: Increased endometrial thickness is associated with higher pregnancy rates. However, neither attainment of pregnancy nor pregnancy outcome was predicted by endometrial thickness alone.

Key words: clomiphene citrate/endometrial thickness/gonadotrophin/IVF/pregnancy

Introduction

During the menstrual cycle the endometrium undergoes cyclic changes in preparation for implantation. In the follicular phase, the growing follicles produce increasing amounts of estradiol that will induce proliferative endometrial changes. Following ovulation, the corpus luteum produces progesterone that will initiate secretory changes. If implantation does not occur during the window of implantation, the endometrium will shed once the corpus luteum regresses.

With certain endometrial abnormalities (e.g. Asherman's syndrome) that prevent normal endometrial changes from occurring, implantation rates are low and abortion rates are high (Schenker and Margalioth, 1982).

Several studies have evaluated the effect of endometrial thickness and pattern on cycle and pregnancy outcome (Check *et al*., 1991; 1993; Dickey *et al*., 1992; Noyes *et al*., 1995; Rinaldi *et al*., 1996; Yuval *et al*., 1999; De Geyter *et al*., 2000; Bassil, 2001; Schield *et al*., 2001), but the results obtained have been controversial. For example, some authors have demonstrated a greater probability of pregnancy once the endometrium attains a threshold thickness (Check *et al*., 1991; 1993; Dickey *et al*., 1992; Noyes *et al*., 1995; Rinaldi *et al*., 1996), while others have not reproduced these findings (Yuval *et al*., 1999; De Geyter *et al*., 2000; Bassil, 2001; Schield *et al*., 2001). This variation might be due to the limited power of the smaller studies, to differences in the stimulation protocols, or to differences in patient characteristics. In the present study, an investigation was made in 1228 IVF/ICSI cycles to determine whether the method of stimulation was related to endometrial thickness, or if endometrial thickness was related to achievement of pregnancy or was predictive of first-trimester pregnancy loss.

Materials and methods

All IVF/ICSI cycles performed at the authors' centre between January 1 and September 1, 2002 were considered for the analysis (n = 1382). During the study period, several stimulation protocols were in use, but in the majority of the cycles (n = 1346) one of two methods was utilized. Since the other protocols were used only in very few cases, they were eliminated from the analysis. In two-thirds of these cycles, GnRH agonist ultrashort stimulation was used (see below; n = 964), while in the remainder clomiphene citrate (CC) in combination with gonadotrophins (n = 382) was used. The exact stimulation protocol was chosen by the primary physician according to physician and/or patient preference. For the ultrashort protocol, an oral contraceptive pill (OCP) was given from day 2 of the menstrual cycle for 3 weeks. At 5 days after the last pill, buserelin 0.5 mg s.c. was started and administered for 4 days. Gonadotrophins were started on the second day of buserelin treatment, and administered daily up to the day of hCG injection. As with the ultrashort stimulation, OCP was also administered for 3 weeks in the CC group. At 5 days after the last birth

Table I. Baseline and cycle characteristics in IVF/ICSI cycles that resulted in pregnancy and those that did not

Parameter	Pregnant (n = 402)	Non-pregnant (n = 826)
Age (years)*	32.0 ± 4.5	33.1 ± 5.0
Baseline FSH (IU/l)	7.7 ± 2.8	8.0 ± 3.1
No. of ampoules used	22.0 ± 9.0	23.2 ± 10.1
No. of follicles >14 mm*	9.0 ± 3.7	8.0 ± 3.7
No. of metaphase II oocytes*	6.6 ± 3.3	5.5 ± 3.2
No. of oocytes fertilized*	5.8 ± 2.9	4.7 ± 2.9
Embryo quality*	44.1 ± 20.0	36.8 ± 19.7
No. of embryos transferred*	2.9 ± 0.6	2.6 ± 0.9
Endometrial thickness (mm)*	10.8 ± 1.8	10.4 ± 1.7

Values are mean ± SD.
*$P < 0.05$, pregnant versus non-pregnant.

Table II. Results of the final logistic regression model

Variable	Logistic regression coefficients (B)	P*	Adjusted OR (95% CI)**
Age	–0.0354	0.0155	0.9612 (0.9343–0.9889)
Embryo score	0.0147	0.0001	1.0150 (1.0075–1.0226)
Number of embryos transferred			
2 embryos compared to 1	1.2288	0.0023	3.5372 (1.6105–7.7688)
3 embryos compared to 1	1.3471	0.0007	3.8984 (1.7915–8.4834)
4 embryos compared to 1	0.9965	0.0238	2.7190 (1.1484–6.4379)
GnRH versus CC protocol	0.4442	0.0032	1.5593 (1.1602–2.0957)
Endometrial thickness	0.1122	0.0016	1.1187 (1.0435–1.1993)

*Wald statistic test. $P < 0.05$ was considered statistically significant.
**OR (odds ratios) were adjusted for other variables in the equation.
CC = clomiphene citrate.

control pill, CC was started at 100 mg daily for 5 days. Gonadotrophins were given on days 1, 3, 5 and 7, and then daily if necessary. Three different gonadotrophin preparations were used during the study period: recombinant FSH (rFSH; Gonal-F; Serono, Italy); hMG (Merional; IBSA Switzerland); and highly purified hMG (hpHMG; Metrodin HP; Serono). Follicle growth was followed using transvaginal ultrasound. hCG (10 000 IU) was given i.m. when at least two follicles had reached 17 mm in diameter. Transvaginal oocyte retrieval was carried out at 35 h after the hCG injection. Laboratory and transfer procedures followed general laboratory protocols, and were similar in all cycles. The oocytes were fertilized on the day of retrieval, and cleavage-stage embryos were transferred on day 2 or 3 after oocyte retrieval. Embryos were qualified based on blastomere number and fragmentation (Steer *et al*., 1992). Endometrial thickness was measured in the midsagittal plane on the day of transfer using transvaginal ultrasound (Sonoline Prima 7.5 MHz, Siemens). Measurements were made from the outer edge of the endometrial–myometrial interface to the outer edge in the widest part of the endometrium. Data were collected for patient characteristics [age, baseline hormones, indication, order of treatment cycle (first versus repeat)], for stimulation characteristics [number of follicles >14 mm, number of oocytes retrieved, number of mature (metaphase II) oocytes, number of fertilized oocytes, number and quality of embryos, number of embryos transferred, endometrial thickness] and cycle outcome [pregnant (positive serum βhCG) versus not pregnant]. Pregnancies were further categorized as normal, ongoing or pathological. Any pregnancy (singleton, twins, etc.) where a heartbeat was identified on ultrasound prior to discharge to the referring obstetrician (at about 8–10 weeks gestation) was considered to be an ongoing pregnancy. Any pregnancy that resulted in a loss (spontaneous abortion, missed abortion, ectopic pregnancy, etc.) was considered to be an abnormal pregnancy. Data were collected prospectively at the authors' institution.

Statistical analysis

The Mann–Whitney U-test was used to compare continuous variables between cycles that resulted in pregnancy and those that did not. Categorical variables were compared using the chi-square test. A multiple logistic regression was used to evaluate further the association between cycle outcome and those factors that might potentially influence outcome. The independent factors studied were endometrial thickness, number of follicles, number of metaphase II oocytes, number of oocytes fertilized, embryo quality, number of embryos transferred, baseline FSH, age and type of protocol. The model of logistic regression was gained by a stepwise procedure, and specific interactions between parameters of interest were also investigated. Models were compared by the likelihood ratio test. A P-value < 0.05 was considered to be statistically significant.

Results

Among a total of 1382 IVF/ICSI cycles performed at the authors' centre during the study period, 964 GnRH agonist + gonadotrophin cycles (66%) and 382 CC + gonadotrophin cycles (26%) were identified. Complete data were available for

Table III. Pregnancy rates below and above certain endometrial thicknesses

Endometrial thickness (EM; mm)	Non-pregnant (*n*)	Pregnant (*n*)	Pregnancy rate (%) below and above EM	*P*	OR	95% CI
<6	1	1	50.0			
⩾6	825	401	32.7	0.61	0.493	0.031–7.907
<7	3	1	25.0			
⩾7	823	401	32.8	0.731	1.484	0.154–14.307
<8	21	5	19.2			
⩾8	805	397	33.0	0.13	2.103	0.787–5.617
<9	92	35	27.5			
⩾9	734	367	33.3	0.21	1.295	0.864–1.942
<10	238	94	28.3			
⩾10	588	308	34.3	0.049	1.315	1.001–1.730
<11	464	187	28.7			
⩾11	362	215	37.2	0.001	1.471	1.159–1.866
<12	615	265	30.1			
⩾12	211	137	39.3	0.002	1.506	1.164–1.949
<13	727	326	30.9			
⩾13	99	76	43.4	0.001	1.708	1.234–2.364
<14	780	370	32.0			
⩾14	46	32	41.0	0.089	1.492	0.938–2.373
<15	810	389	32.4			
⩾15	16	13	44.8	0.173	1.666	0.794–3.498
<16	821	399	33.2			
⩾16	5	3	37.5	0.789	1.216	0.289–5.115
Total	826	402				

Data indicate numbers of cycles that led to pregnancy and those that did not, when subdivided according to endometrial thickness.
OR given for achievement of pregnancy when the endometrium is thicker than the given cut-off. An improved pregnancy rate was found in cycles when endometrium was ⩾10 mm; rates further improved between 10–14 mm with additional increases in endometrial thickness.

over 90% of these cycles (874/964 in the GnRH agonist group and 354/382 in the CC group).

The overall pregnancy rate was 32.8% (*n* = 402). The clinical pregnancy rate was 35.9% in the GnRH agonist + gonadotrophin group and 26.2% in the CC + gonadotrophin cycles ($P = 0.001$). First-trimester outcome was known for 365 pregnancies; in total, 323 of the 365 pregnancies (88.5%) were normal or ongoing.

In cycles that resulted in pregnancy, the patients were younger, had more mature oocytes, had more embryos transferred, and the embryo quality was higher (Table I). Mean (± SD) endometrial thickness on the day of transfer was significantly greater in cycles where pregnancy was achieved (10.84 ± 1.8 versus 10.46 ± 1.7 mm; $P = 0.003$) (Table I). In order to compare endometrial thickness by the day of transfer (day 2 versus day 3) in addition to cycle outcome, a two-way ANOVA was performed. Mean endometrial thickness was similar between day 2 and day 3 cycles (10.5 ± 1.7 versus 10.7 ± 1.8 mm; $P = 0.079$). The proportion of cycles with day 2 or day 3 transfers was also similar for the two stimulation protocols [day 2: 623/964 (64.7%) versus 233/382 (61.0%); day 3: 341/964 (35.3%) versus 149/382 (39.0%)].

In the logistic regression model, age, embryo score, endometrial thickness and the type of stimulation protocol were significantly associated with pregnancy outcome. Pregnancy rate improved with increased endometrial thickness; the estimated odds ratio (OR) for successful pregnancy with each additional millimetre of endometrial thickness was 1.12 (95% CI 1.04–1.2; $P = 0.002$). The risk of pregnancy was significantly improved when the GnRH agonist ultrashort protocol was used (OR 1.56; 95% CI 1.2–2.1; $P = 0.003$). Age was negatively associated with pregnancy outcome, while embryo quality and the number of embryos transferred was positively associated with pregnancy outcome (Table II). The interactions between endometrial thickness and embryo quality ($\chi^2 = 0.009$, df = 1; $P = 0.924$), endometrial thickness and type of protocol ($\chi^2 = 0.165$, df = 1; $P = 0.676$), embryo score and age ($\chi^2 = 0.074$, df = 1; $P = 0.786$) and the interaction between endometrial thickness and age ($\chi^2 = 0.051$, df = 1; $P = 0.821$) were examined and tested by the likelihood ratio test. None of these interactions was significant.

Although it is difficult to identify a clear discriminating value, an attempt was made to identify an endometrial thickness cut-off above which pregnancy rates were higher. Improved pregnancy rates were found when the endometrium reached at least 10 mm [<10 mm; 94/332 (28.3%) pregnant versus ⩾10 mm; 308/896 (34.3%); OR (95% CI) 1.315 (1.001–1.73; $P < 0.05$] (Table III).

Endometrial thickness was similar with GnRH agonist ultrashort or CC + gonadotrophin stimulation (10.55 ± 1.8 versus 10.72 ± 1.84 mm; P = NS).

It was noted that 88.5% of the pregnancies were ongoing. Baseline demographic and stimulation parameters were similar between ongoing and pathological pregnancies, and endometrial thickness did not differ between ongoing and abnormal pregnancies (Table IV). The rate of pathological pregnancy

Table IV. Baseline and cycle characteristics in cycles leading normal (singleton, twins, etc.) and pathological (missed abortion, spontaneous abortion, ectopic gestation, etc.) pregnancies

Parameter	Normal pregnancy (n = 323)	Pathological pregnancy (n = 43)
Age (years)	32.0 ± 4.5	32.4 ± 4.4
Baseline FSH (IU/l)	7.7 ± 2.9	8.1 ± 2.3
No. of ampoules used	21.9 ± 8.8	23.3 ± 10.2
No. of follicles > 14 mm	8.9 ± 3.7	9.0 ± 4.0
No. of metaphase II oocytes	6.5 ± 3.2	7.5 ± 3.9
No. of oocytes fertilized	5.8 ± 2.9	4.7 ± 2.9
Embryo quality	44.2 ± 19.9	43.5 ± 20.7
No. of embryos transferred	2.9 ± 0.6	2.6 ± 0.9
Endometrial thickness (mm)	10.8 ± 1.8	10.8 ± 1.8

Values are mean ± SD.
None of the differences was statistically significant.

was similar in the GnRH agonist + gonadotrophin group when compared with the CC + gonadotrophin group (11.1 versus 7.5%; P = NS).

Discussion

An association of various cycle characteristics and treatment outcome has been evaluated since the introduction of assisted reproduction technologies. One such parameter, which has been evaluated by several groups, is that of endometrial thickness (Check *et al*., 1991; 1993; Dickey *et al*., 1992; Noyes *et al*., 1995; Rinaldi *et al*., 1996; Yuval *et al*., 1999; De Geyter *et al*., 2000; Bassil, 2001; Schield *et al*., 2001). Adequate proliferative and secretory changes are necessary for successful implantation to occur. Endometrial thickness can be regarded as a reflection of the degree of endometrial proliferation in the absence of intrauterine pathology, and is measured in the midsagittal plane during transvaginal ultrasound scan.

One group (Dickey *et al*., 1992) found that fecundity was increased when the endometrium was at least 9 mm thick, and had a triple-line appearance during IVF cycles. However, biochemical pregnancies were more frequent with a thinner endometrium (Dickey *et al*., 1992). Others (Check *et al*., 1991) demonstrated an improved pregnancy rate with a thicker endometrium, and also identified a thicker endometrium among pregnant women treated with GnRH agonist when compared to those treated with CC. In a later study, the same group reported higher pregnancy rates among donor oocyte recipients with an endometrium that was ⩾10 mm thick (9 versus 38.7%; $P < 0.01$) (Check *et al.*, 1993). Another group (Noyes *et al*., 1995) subsequently evaluated 516 IVF cycles and found pregnancy and ongoing pregnancy rates to be higher when the endometrial thickness was ⩾9 mm. Likewise, a minimum thickness of 10 mm during IVF was found to produce a higher pregnancy rate (Rinaldi *et al*., 1996).

In more recent studies, however, no significant association between endometrial thickness and pregnancy outcome was seen (Yuval *et al*., 1999; De Geyter *et al*., 2000; Bassil, 2001; Schield *et al*., 2001). It is possible that, with more advanced laboratory and stimulation methods, a small effect of endometrial thickness on outcome might become obscured or overridden. The day of measurement might also influence the association between endometrial thickness and cycle outcome. In the present study, an increased endometrial thickness was not related to improved pregnancy rates, although the measurements were made on the day of transfer—that is, at 4 or 5 days after the hCG injection. Endometrial thickness evaluated on the day of embryo transfer might be influenced by an increased luteal phase progesterone secretion, and various measurement methods (including outer edge to outer edge, or outer edge to inner edge) could further affect outcome. Differences in the analysis might also provide a further explanation for the conflicting results. Some studies evaluated cut-off values (Noyes *et al*., 1995; Rinaldi *et al*., 1996; De Geyter *et al*., 2000), while others compared mean endometrial thickness (Yuval *et al*., 1999; Schield *et al*., 2001) or compared endometrial thickness among percentile groups (De Geyter *et al*., 2000). Re-allocating the groups according to these different criteria might result in groups which contain few subjects and have only limited power to detect a small difference.

The effect of 'increased' endometrial thickness has also been evaluated. For example, one group (Weissman *et al*., 1999) reported lower implantation and pregnancy rates among women with an endometrial thickness ⩾14 mm on the day of hCG administration. However, no adverse effect of thickened (>14 mm) endometrium on implantation, pregnancy or abortion rates was identified by others (Dietterich *et al*., 2002).

In the present study, a possible association was also sought between endometrial thickness and pregnancy rate based on data from 1228 IVF cycles. The endometrium was found to be slightly but significantly thicker in cycles that resulted in pregnancy. Furthermore, pregnancy rates were shown to be higher when an endometrial thickness of at least 10 mm was achieved. While this improvement is small, the data suggest that adequate endometrial development is one of the factors that play a significant role in IVF outcome. Other variables such as age, embryo quality, number of embryos transferred and stimulation protocol were also shown to have a significant impact on treatment outcome.

In previous studies, the endometrium was found to be thinner when CC was combined with hMG (Gonen and Casper, 1990;

Check *et al*., 1991; Saito *et al*., 1991). A similar negative endometrial effect was not observed in the present CC + gonadotrophin cycles; rather, the endometrial thickness was similar to that in the ultrashort GnRH agonist cycles. It is likely that the supraphysiological estradiol level reached during CC + gonadotrophin stimulation was able to correct for the negative endometrial effects of CC alone. Estrogen supplementation during stimulation with CC has been shown to improve endometrial development and to result in thicker endometria and improved morphology (Gerli *et al*., 2000; Elkind-Hirsch *et al*., 2002).

In the present study an assessment was also made of whether endometrial thickness had an effect on pregnancy outcome. Pregnancies were followed for up to 8–10 weeks before patients were referred back to their primary provider. Once the patient was discharged from the authors' centre, it was difficult to obtain accurate follow-up information; hence, outcomes were reported only up to the time of discharge and it is possible that some pregnancies were lost during the subsequent few weeks. As no differences were observed in the loss rate up to this point, significant differences would not necessarily be expected to emerge beyond this point. As the number of abnormal pregnancies was low to start with ($n = 43$), subgroups were not created based on the exact outcome in order to avoid the comparison of subgroups with only a few cases—for example, with only six extrauterine pregnancies. Endometrial thickness on the day of transfer however, was found to be similar between ongoing and pathological pregnancies.

In conclusion, the results of the present study identified a statistically significant difference in mean endometrial thickness between cycles that resulted in pregnancy and those that did not. Adequate endometrial development is required for pregnancy to occur, and pregnancy rates were found to be higher when the endometrium reached at least 10 mm thickness. Consequently, clinicians providing IVF for infertile couples must pay close attention to endometrial development as well as to follicle growth.

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