Endometrial thickness as a predictor of pregnancy after in-vitro fertilization but not after intracytoplasmic sperm injection

Leonardo Rinaldi1,3, Franco Lisi1, Attilia Floccari1, Rosella Lisi1, Giampiero Pepe1 and Simon Fishel1,2

1Biogenesi, Servizio di Fisopatologia della Riproduzione, Casa di Cura Villa Europa, 27 Via Eufrate, Roma EUR, 00144, Italy and 2NURTURE (Nottingham University), Department of Obstetrics and Gynaecology, University Hospital, Queen’s Medical Centre, Nottingham NG7 2UH, UK 3To whom correspondence should be addressed

An ultrasonographic evaluation of the endometrium was performed in 158 patients undergoing ovarian stimulation for an in-vitro assisted reproduction programme. Endometrial thickness was measured on the day of human chorionic gonadotrophin (HCG) administration by longitudinal scanning of the uterus on the frozen image using electronic calipers placed at the junction of the endometrium-myometrium interface at the level of the fundus. Cases in which the endometrial thickness was ≥10 mm were included in group A; cases in which the endometrial thickness was <10 mm were assigned to group B. The age of the patients, serum 17β-oestradiol concentrations on the day of HCG administration, the length of follicular stimulation, the number of follicles, 17β-oestradiol concentrations per follicle on the day of HCG and the number of embryos transferred were analysed in each case. When comparing endometrial thickness and results in IVF and ICSI patients, an endometrium <10 mm predominated in IVF patients (27.5%) compared with those undergoing ICSI (16.7%) (P = 0.05); conversely an endometrium ≥10 mm was more frequent in ICSI than in IVF patients. The incidence of pregnancy was higher in IVF group A patients (32/79; 41%) than in IVF group B patients (5/30; 17%) (P = 0.03), whereas no significant difference was found between ICSI group A (13/42; 31%) and ICSI group B (3/7; 43%) patients. Thus, a higher percentage of IVF patients had thin endometrium when compared with ICSI patients; thin endometrium was a prognostic indicator of pregnancy only in the case of a female indication for infertility (IVF). A thin endometrium in cases of female infertility may reflect a previous or present uterine pathology, whereas in indications of male infertility (i.e. cases using ICSI), in the absence of any associated uterine pathology, the presence of a thin endometrium is not predictive.

Key words: endometrial thickness/ICSI/IVF/ultrasonography

Introduction

The use of intracytoplasmic sperm injection (ICSI) has recently resulted in a dramatic improvement of the prognosis for couples affected by severe male factor infertility (Van Steirteghem et al., 1993). In fact, in these couples the fertilization and pregnancy rates (per cycle) have almost reached those of standard in-vitro fertilization (IVF) for other indications, so that the use of ICSI has even been proposed for each case of IVF (List et al., 1995).

Endometrial receptivity is required for successful implantation in natural and IVF cycles. In the attempt to identify a non-invasive uterine predictor of implantation and pregnancy during IVF procedures, endometrial features have been widely studied by transabdominal and, more recently, transvaginal ultrasonography. Despite the large number of papers concerning this issue, the prognostic value of ultrasonographic endometrial thickness or the appearance of the endometrium, or a combination of the two, in conception and non-conception IVF cycles remains controversial (Glissant et al., 1985; Fleischer et al., 1986; Rabinowitz et al., 1989; Gonen et al., 1989; Welker et al., 1989; Sher et al., 1991; Check et al., 1991, 1993; Bergh et al., 1992; Dickey et al., 1992; Khalifa et al., 1992; Eichler et al., 1993; Oliveira et al., 1993; Coulam et al., 1994; Serafini et al., 1994; Strohmer et al., 1994; Takahashi et al., 1995).

The routine use of ICSI in male infertility has recently allowed the role of endometrial ultrasonography to be evaluated in predicting implantation in healthy women undergoing an in-vitro assisted reproduction programme for male factor infertility; moreover, these data can be compared with those obtained from women undergoing IVF for female indications.

Materials and methods

From January 1995 to April 1995, 158 patients were treated with buserelin (Suprefact; Hoechst) using the nasal spray at a dose of three inhalations per nostril every 8 h from day 21 of the previous cycle until pituitary desensitization was achieved, followed by follicle stimulating hormone (FSH; Metrodin HP; Serono) administration at a dose of two to four ampoules daily. FSH was administered at a variable dose, depending on individual response to stimulation. No statistical significance was attributed to the variable dose of gonadotrophins. Human chorionic gonadotrophin (HCG; 10 000 IU; Profasi HP; Serono) was administered to initiate ovulation 32–36 h before oocyte retrieval. The latter was performed by the transvaginal route under ultrasonic control and local anaesthesia. Oocyte fertilization and embryo culture for IVF and ICSI were performed as reported previously (Fishel and Jackson, 1986; Fishel et al., 1995). About 48 h after oocyte retrieval, a maximum of three embryos were transferred into the uterine cavity, according to availability. All
patients received 50 mg i.m. progesterone (Gestone; AMSA) daily, from the day of oocyte retrieval, to support the luteal phase.

The cause of infertility was represented by male factors alone (patients in whom male factor and female factor were associated were excluded; n = 49) or female factors (absolute tubal factor or relative tubal factor in association with endometriosis; n = 109). In female indications, conventional IVF was performed; in male indications, ICSI was the procedure of choice.

The endometrium was imaged on the day of HCG administration by transvaginal ultrasonography using a 5 MHz vaginal transducer. Each scan was performed by the same operator blinded to the hormonal response. The maximal endometrial thickness was measured by longitudinal scanning of the uterus (carefully avoiding tangential views) on the frozen image using electronic callipers placed at the junction of the endometrium—myometrium interface at the level of the fundus. No patient showed sonographic evidence of submucosal fibroids or endometrial polyps at scanning.

Endometrial thickness was assessed on the day of HCG administration in all cases. Cases in which the endometrial thickness was ≥10 mm were included in group A, cases in which the endometrial thickness was <10 mm were assigned to group B.

The following parameters were analysed: age of the patients, 17-β oestradiol concentration, as determined by a radioimmunoassay on the day of HCG administration; the length of follicular stimulation (days); the number of follicles; 17-β oestradiol concentration per follicle; and the number of embryos transferred.

Serum β-HCG concentrations were measured on day 14 after embryo transfer to diagnose all the pregnancies (including the biochemical pregnancies). Clinical pregnancies (presence of a gestational sac) were diagnosed by ultrasonography at ~6 weeks of gestation.

The data obtained were compared using Student’s t-test for unpaired results, the Fisher’s exact test, the Z-test for comparison of proportions and linear regression and correlation when necessary.

Significance was defined as $P \leq 0.05$.

Results

Age was not significantly different between patients undergoing IVF for female indication and patients undergoing ICSI for male infertility.

The pregnancy rates for IVF and ICSI were 34 (37/109) and 33% (16/49) respectively. These were not statistically different (Table I).

In all, 121 patients had an endometrial thickness ≥10 mm on the day of HCG (group A); 37 patients had an endometrial thickness <10 mm on the day of HCG (group B).

No statistical differences were noted between group A and group B patients with regard to oestradiol concentration on the day of HCG administration (8722 ± 3694 versus 10 377 ± 4872 pmol/l), the duration of follicular stimulation (12.20 ± 1.78 versus 11.90 ± 1.64 days), the number of follicles (11.10 ± 4.24 versus 12.70 ± 6.19), oestradiol concentration per follicle measured on the day of HCG (787.8 ± 206.9 versus 860.2 ± 218.6 pmol/l per follicle) and the number of embryos transferred (2.86 ± 0.41 versus 2.73 ± 0.66). The same was true when patients were subdivided according to the treatment received.

In group A, 45 pregnancies were achieved (37%); eight pregnancies were achieved in group B (22%) (not significant).

With regard to endometrial thickness, Table I shows that a higher proportion of ICSI compared with IVF patients had endometrium <10 mm thick (27.5 and 14.2% respectively) ($P = 0.05$). Conversely, a higher proportion of ICSI compared with IVF patients had endometrium ≥10 mm thick (96 and 72% respectively) (not significant).

Patients undergoing ICSI presented a higher concentration of oestradiol on the day of HCG (11 746.7 ± 4240.1 pmol/l) and a higher number of follicles (14.20 ± 4.93) when compared with patients undergoing IVF (9279.7 ± 4567.8 pmol/l and 11.30 ± 5.90 respectively) ($P = 0.005$ Student’s $t$-test), whereas the duration of follicular stimulation (12.10 ± 1.73 days in ICSI versus 11.90 ± 1.64 days in IVF), the concentration of oestradiol per follicle (839.4 ± 198.2 pmol/l per follicle in ICSI versus 841.5 ± 227.0 pmol/l per follicle in IVF) and the number of embryos transferred (2.79 ± 0.53 in ICSI versus 2.75 ± 0.65 in IVF) were similar between the two groups. No correlation was found between endometrial thickness and oestradiol concentrations, or between endometrial thickness and the number of follicles, in either ICSI or IVF patients, whereas a positive correlation ($P < 0.001$) was found between oestradiol concentration and the number of follicles in both ICSI ($n = 49$; $r = -0.846$) and IVF ($n = 109$; $r = -0.863$) patients.

The pregnancy rate was higher in IVF group A patients (32/79; 41%) than in IVF group B patients (5/30; 17%) ($P = 0.03$), whereas no significant difference was found in the pregnancy rate between ICSI group A (13/42; 31%) and ICSI group B (3/7; 43%) (Table I).

Discussion

Our data show a higher percentage of patients with thin endometrium in the IVF group when compared with the ICSI group ($P = 0.05$). Moreover, a higher pregnancy rate was observed in IVF patients with thick endometrium when compared with IVF patients with thin endometrium ($P = 0.03$), whereas no significance related to endometrial thickness was found in the pregnancy rate among groups A and B ICSI patients or when comparing pregnancy rates in groups A and
B in the whole cohort of patients (IVF plus ICSI) undergoing ovarian stimulation and embryo transfer.

We believe that the differences observed in the thickness of endometrium among the patients undergoing IVF for female indications and patients undergoing ICSI for male factor may be attributed mainly to the different pathogenesis of infertility in the two groups of patients. Tubal occlusion or stenosis is usually related to an ascendant infection that may damage the endometrium before affecting the tubes, and endometriosis, when present, is often associated with adenomyosis affecting the uterine structure and lining. On the other hand, women undergoing ICSI for male factor are usually (and in every case in our study) healthy women whose endometrium has never been exposed to any noxious agent and therefore has a physiological response to ovarian stimulation.

With regard to the higher concentration of oestradiol in ICSI patients when compared with IVF patients, we believe that this is related to the higher number of oocytes retrieved in ICSI patients, and is confirmed by the lack of correlation found between endometrial thickness and oestradiol concentration or the number of follicles and by the strong positive correlation between oestradiol concentration and the number of follicles in all the groups of patients.

We believe that the statistically significant difference found in pregnancy rate between group A and B IVF patients and the non-significant difference in pregnancy rate between group A and B ICSI patients can both be attributed to the same above-mentioned causes, i.e. patients undergoing IVF for female indications usually have a history of noxious agents affecting the endometrium, whereas women undergoing ICSI for male factors usually have no past history of endometrial diseases.

These data may have some relevance to the controversial issue of endometrial thickness as a prognostic factor for implantation. Although there are many studies concerning this issue, there is no agreement in the literature about the effectiveness of the ultrasonographic evaluation of endometrial thickness in predicting the pregnancy.

During the past 10 years some investigators have found (Glissant et al., 1985; Gonen et al., 1989; Gonen and Casper, 1990), whereas some have not found (Fleischer et al., 1986; Rabinowitz et al., 1986; Welker et al., 1989), a positive correlation between endometrial thickness and pregnancy rate. In the same way, some investigators have found (Sher et al., 1991; Dickey et al., 1992), and some have not found (Khalifa et al., 1992; Eichler et al., 1993; Oliveira et al., 1993; Noyes et al., 1995), a positive correlation between both endometrial ultrasonographic appearance and thickness and pregnancy rate. Some investigators have studied both endometrial appearance and thickness, but have only found a positive correlation between pregnancy rate and endometrial appearance (Ueno et al., 1991; Check et al., 1993; Coulam et al., 1994; Serafini et al., 1994) or between pregnancy rate and endometrial thickness (Bergh et al., 1992), but not for the other endometrial variables taken into account.

These discrepancies may be attributed to various different factors, e.g. the use of transabdominal ultrasonography (Smith et al., 1984; Glissant et al., 1985; Fleischer et al., 1986; Rabinowitz et al., 1986) versus transvaginal ultrasonography (Gonen et al., 1989; Welker et al., 1989; Gonen and Casper, 1990; Sher et al., 1991; Ueno et al., 1991; Bergh et al., 1992; Dickey et al., 1992; Khalifa et al., 1992; Check et al., 1993; Eichler et al., 1993; Oliveira et al., 1993; Coulam et al., 1994; Serafini et al., 1994; Noyes et al., 1995). Similarly, the observed differences may be in part attributed to the different stimulation protocols: clomiphene citrate plus gonadotrophin treatment alone (Smith et al., 1984; Glissant et al., 1985; Gonen et al., 1989; Gonen and Casper, 1990; Oliveira et al., 1993); the exclusive use of gonadotrophin (Fleischer et al., 1986; Rabinowitz et al., 1986); the combined use of gonadotrophin-releasing hormone (GnRH) analogues plus gonadotrophin after pituitary desensitization (Check et al., 1991; Serafini et al., 1994); the combined use of GnRH analogues plus gonadotrophin using both short and long protocols (Khalifa et al., 1992); the combined use of GnRH analogues plus gonadotrophin after pituitary desensitization and during the natural cycle (Ueno et al., 1991); clomiphene citrate plus gonadotrophin and GnRH analogues plus gonadotrophin according to the long or short protocol (Welker et al., 1989; Bergh et al., 1992; Dickey et al., 1992; Eichler et al., 1993); GnRH analogues plus gonadotrophin and gonadotrophin alone (Sher et al., 1991); or eventually GnRH analogues plus gonadotrophin, gonadotrophin alone or clomiphene citrate plus gonadotrophin (Noyes et al., 1995). The different timing of the assessment of endometrial thickness may be relevant to the explanation of the discordant findings. In fact, the endometrium has been assessed on the day of HCG (Sher et al., 1991; Dickey et al., 1992; Khalifa et al., 1992; Check et al., 1993; Eichler et al., 1993; Oliveira et al., 1993), on the day of oocyte retrieval (Welker et al., 1989; Khalifa et al., 1992), on the day before oocyte retrieval (Fleischer et al., 1986; Gonen et al., 1989; Gonen and Casper, 1990; Bergh et al., 1992; Noyes et al., 1995) and on the day before HCG (Ueno et al., 1991; Khalifa et al., 1992).

The study that is closest to the one described here is that of Check et al. (1991) who, using the same stimulation protocol at the same threshold value for endometrial thickness measured by transvaginal ultrasound (<10 versus ≥10 mm), found a statistically significant difference in the pregnancy rate between the two groups of patients. In that study, Check et al. (1991) were also able to evaluate the endometrial echogenicity and found a positive correlation between endometrial echogenicity and pregnancy rate. However, they excluded from their study nine patients who did not achieve fertilization and did not report on the percentage of patients suffering from male factor infertility included in the study.

In fact, most of the previous studies have excluded patients undergoing IVF for male factor infertility (Bergh et al., 1992; Khalifa et al., 1992; Serafini et al., 1994; Takahashi et al., 1995), or have investigated groups of patients in whom the main indications for IVF were tubal factor, endometriosis or unexplained infertility (Dickey et al., 1992; Oliveira et al., 1993), because IVF results in terms of fertilization and pregnancy rates in cases of male infertility used to be lower than those for other indications.
Only Sher et al. (1991) have considered the role of the negative impact of uterine pathologies on endometrial development, noting a higher rate of poor endometrial grades (endometrial thickness <9 mm and a homogeneous endometrial pattern, or endometrial thickness >9 mm but a heterogeneous endometrial pattern) in women with uterine pathologies; however, the impact of this finding in the ultrasonographic assessment of endometrium in the prediction of pregnancy was not fully evaluated.

Similarly, Takahashi et al. (1995) have shown that in patients with a history of ectopic pregnancy, a thinner endometrium is a predictor of poor outcome. These authors were unable to show any difference in endometrial thickness between patients who conceived and patients who did not conceive in the general population of patients undergoing IVF.

The use of ICSI, because of its high fertilization and pregnancy rates, has enabled us to compare at all levels patients undergoing assisted reproductive treatment for either female or male indications of infertility.

Our data, showing a higher percentage of thin endometrium in IVF patients when compared with ICSI patients, are in agreement with the previously reported finding (Sher et al., 1991) of a higher rate of poor endometrial lining in uterine pathologies. In addition, our results show that endometrial thickness may be taken into account as a predictor of pregnancy only in assisted reproduction treatment for female indications of infertility (IVF), in which case a thin endometrium may reflect the previous or present action of a noxious agent on the uterine lining. However, in assisted reproductive treatment for male indications of infertility (ICSI), in the absence of any associated uterine pathology, the presence of a thin endometrium does not seem to affect pregnancy and cannot be used to predict the chance of pregnancy.

Further studies are doubtless needed, and we currently have one underway to evaluate the role of endometrial appearance in addition to endometrial thickness, both in patients undergoing IVF for female indications and in patients undergoing ICSI for male indications of infertility.

References