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Uterine contractions at the time of embryo transfer alter pregnancy rates after in-vitro fertilization

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To investigate the possible consequences of uterine contractions (UC) as visualized by ultrasound (US) on in-vitro fertilization (IVF)–embryo transfer outcome, we studied prospectively 209 infertile women undergoing 220 cycles of controlled ovarian stimulation. Inclusion criteria were age ⩽38 years, a morphologically normal uterus, and at least three good quality embryos transferred. Just before embryo transfer, women underwent 5 min digital recordings of the uterus using US image analysis software for UC assessment. Plasma progesterone and oestradiol concentrations were measured. Four groups were defined according to UC frequency: ⩽3.0 (n = 53), 3.1–4.0 (n = 50), 4.1–5.0 (n = 43), and >5.0 (n = 74) UC/min respectively. Patients, controlled ovarian hyperstimulation and embryology characteristics were comparable in all groups. A stepwise decrease in clinical and ongoing pregnancy rates as well as in implantation rates occurred from the lowest to the highest UC frequency groups (53, 36, 21; 46, 32, 20; 23, 19, 10; and 14, 11, 4%; $P < 0.001$). Plasma progesterone and UC frequency were negatively correlated (r = –0.34, $P < 0.001$). Direction of UC did not affect embryo transfer outcome. As this study was controlled strictly for confounding variables and UC were assessed objectively by a computerized system, its results indicate that high frequency UC on the day of embryo transfer hinder IVF–embryo transfer outcome, possibly by expelling embryos out of the uterine cavity. The negative correlation between UC frequency and progesterone concentrations supports the uterine relaxing properties of progesterone.

Key words: embryo implantation/embryo transfer/in-vitro fertilization/progesterone/uterine contractions

Introduction

Embryo implantation is the factor with the greatest limitation on in-vitro fertilization (IVF) and embryo transfer. Governed by complex mechanisms (Tabibzadeh *et al.*, 1995), the interaction between embryo and endometrium depends on the quality of each (Paulson *et al.*, 1990; Tabibzadeh and Babaknia, 1995). Classically, this phenomenon has been dealt with by studies on embryo morphology (Grillo *et al.*, 1991) as well as on the histological (Navot *et al.*, 1989) and biochemical (Lessey *et al.*, 1992) characteristics of the endometrium. However, additional factors might encumber the necessary contact between embryo and endometrium, possibly altering implantation. Uterine contractility, known to affect embryo implantation in animals (Pusey *et al.*, 1980; Rogers *et al.*, 1983), has remarkably, not been examined in humans. Data exist, however, to suggest that embryo transfer may be followed by embryo expulsion, as indicated by a study of mock embryo transfer processes (Knutzen *et al.*, 1992).

Moreover, the necessary use of highly invasive tools for studying uterine contractility in non-pregnant women (Hendricks, 1966; Martinez-Gaudio *et al.*, 1973) has dissuaded extensive research on the possible consequences of UC on the human embryo implantation process. More recently, marked advances in ultrasound (US) imagery of the uterus have permitted the direct and non-invasive identification (Birnholz, 1984; Oike *et al.*, 1988) and characterization of uterine contractile activity under physiological (Abramowicz and Archer, 1990; de Vries *et al.*, 1990; Oike *et al.*, 1990; Lyons *et al.*, 1991; Chalubinski *et al.*, 1993; Fukuda and Fukuda, 1994; IJland *et al.*, 1996; IJland *et al.*, 1997a) and pathological (Salamanca and Beltran, 1995; Kunz *et al.*, 1996; Leyendecker *et al.*, 1996; IJland *et al.*, 1997b) conditions.

This spurred us to investigate the possible influences of UC as visualized on US on the outcome of embryo transfer on IVF cycles.

Materials and methods

Patient characteristics

We studied 220 consecutive controlled ovarian hyperstimulation cycles for IVF–embryo transfer undertaken in 209 infertile women (aged 23–38 years). To reduce as far as possible the interference of additional factors such as embryo quality and endometrial receptivity in the analysis of our results, we selected only women aged ⩽38 years, whose uteri were morphologically normal as confirmed by hysteroscopy and US, and who had at least three good quality embryos (defined as having blastomeres of uniform size and shape, ooplasm having no granularity and a maximum fragmentation of 10%) available for embryo transfer. Clinical indications for IVF–embryo transfer were tubal abnormalities (40%), sperm abnormalities (45%), unexplained infertility (12%), and endometriosis (3%). Informed consent was obtained from all patients and this investigation received the approval of our internal Institutional Review Board.

Protocol for controlled ovarian hyperstimulation

A single injection of a time-release gonadotrophin releasing-hormone (GnRH) agonist, leuprolide acetate (3.75 mg i.m.; Enantone, Takeda

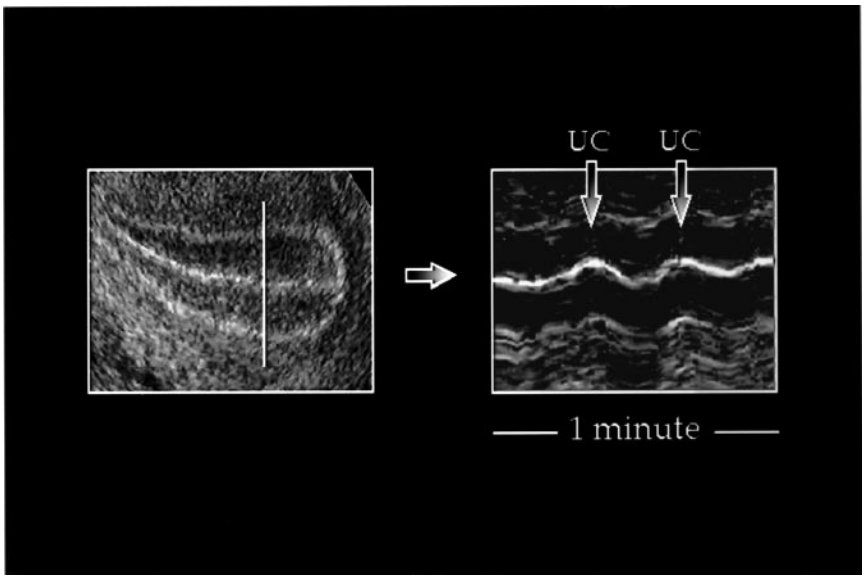

Figure 1. Computerized assessment of uterine contraction (UC) frequency. After determining the uterine section to be analysed (left panel), time-dependent changes in endo–myometrial interfaces corresponding to UC were assessed (right panel).

Pharmaceuticals, Paris, France) was administered on cycle day 2. Eighteen days later, complete pituitary desensitization was confirmed by documenting low plasma oestrogen <40 pg/ml and luteinizing hormone (LH) ⩽2 mIU/ml concentrations. Patients also underwent an US examination to exclude ovarian cysts and to verify that endometrial thickness was <5 mm. Human menopausal gonadotrophin (HMG) therapy (Humegon; Organon Pharmaceuticals, Saint-Denis, France) was then initiated at a dosage of 225 IU/day for the first 5 days of controlled ovarian hyperstimulation. Further HMG doses and the timing of human chorionic gonadotrophin (HCG; Gonadotrophine Chorionique 'Endo'; Organon Pharmaceuticals, Saint-Denis, France, 10 000 IU, i.m.) administration were decided according to the usual criteria of follicular maturation determined by US and oestrogen findings. Administration of HCG was performed when at least three follicles exceeded 17 mm in diameter and oestrogen concentrations per mature follicle (⩾17 mm in diameter) were >300 pg/ml. Oocytes were retrieved 36 h after HCG administration by transvaginal US-guided aspiration. Follicles measuring <12 mm in diameter were not aspirated. All embryo transfers were performed 2 days after oocyte retrieval using a Frydman catheter (CCD Laboratories, Paris, France). No traumatic embryo transfer, requiring the use of cervical clamps or rigid catheters, occurred. In cases of difficulty, the tip of the catheter was slightly bent to enable a slight curvature to fit that of the cervix. The luteal phase was supported with 300 mg of micronized progesterone (Utrogestan; Besins-Iscovesco Pharmaceuticals, Paris, France) administered daily (100 mg in the morning, 200 mg in the evening) by the vaginal route starting on the evening of the embryo transfer day.

Uterine contractility assessment and definition of UC frequency groups

Just before embryo transfer, all patients underwent 5 min US scans of a sagittal plane of the uterus using a 7.5 MHz transvaginal probe (Logiq 400; General Electric, Paris, France) at ~11:00 a.m. by a single operator. Environmental conditions were standardized throughout US examination. Images were digitized on-line using a rate of two images/s with a computer-assisted image analysis system (IôDP, Paris, France) that allows objective quantification of frequency of the myometrial contractile activity. As represented in Figure 1, this is based on the analysis of time-dependent variation in the endo–myometrial interfaces. Contrast enhancement and image adjustment permitted an overall improvement in image quality so that uterine contractions could be visualized and analysed adequately. Direction of UC was assessed visually at a rate of 20 images/s (10 times the normal speed) and classified arbitrarily into four types: cervix-to-fundus or retrograde, fundus-to-cervix or antegrade, antagonistic (UC starting simultaneously on the cervix and on the fundus and meeting in the middle of the uterus) and non-propagated UC (local myometrial activity). Sequences were rated by two independent observers and the assessment of inter-observer reliability showed an excellent agreement (Kappa: 0.75; $P < 0.0001$).

As displayed in Figure 2, the 220 embryo transfers studied were sorted arbitrarily into four groups according to UC frequency: ⩽3.0 UC/min ($n = 53$), 3.1–4.0 UC/min ($n = 50$), 4.1–5.0 UC/min ($n = 43$), and >5.0 UC/min ($n = 74$).

Blood samples and hormone measurement

In addition to routine hormonal monitoring of follicular development during controlled ovarian hyperstimulation, further blood samples were obtained at the time of embryo transfer for oestrogen and progesterone measurement in the women included in the protocol.

Plasma oestrogen was determined by an immunometric technique using an Estradiol-60 Amerlite kit (Ortho Clinical Diagnostics, Strasbourg, France) whose sensitivity was 14 pg/ml. Intra-assay and inter-assay coefficients of variation (CV) were 8 and 9% respectively. Plasma progesterone was measured by radioimmunoassay using a I^{125} Progesterone Coatria kit (Bio-Mérieux, Paris, France). Sensitivity was 0.05 ng/ml. Intra-assay and inter-assay CV were respectively 8 and 11%. Plasma follicle stimulating hormone (FSH) was measured by an immunometric technique using an Amerlite kit (Ortho Clinical Diagnostics, Strasbourg, France). Intra-assay and inter-assay CV were respectively 5 and 7% and sensitivity was 0.1 mIU/ml.

Statistics

Measures of central tendency used were means and measures of variability were standard errors. When data distribution was non-parametric, medians and ranges were used. Statistical assessment of our results was performed using factorial analysis of variance (ANOVA) and χ^2 tests when data distribution was normal. The Kruskall–Wallis test was used when normality of data could not be

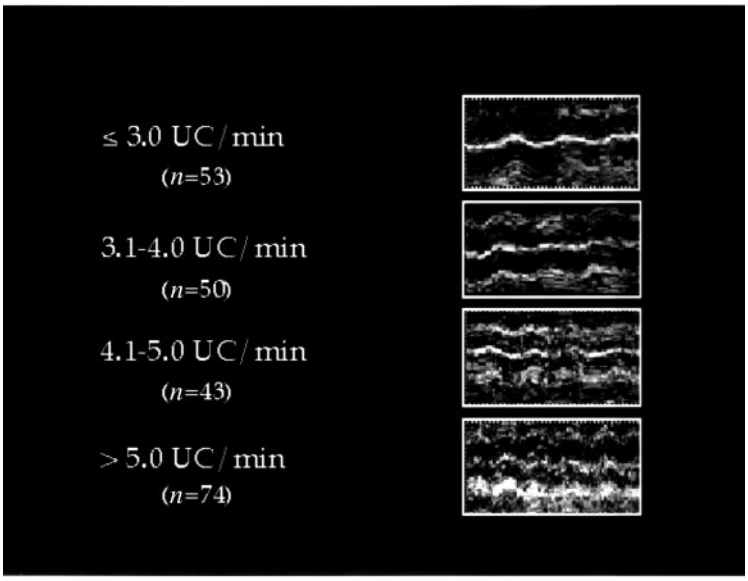

Figure 2. Definition of groups according to uterine contraction (UC) frequency.

Table I. Descriptive data on uterine contraction (UC) frequency and prevalence of each UC when classified according to rate

	Total	No. of uterine contractions/min			
		⩽3.0	3.1–4.0	4.1–5.0	>5.0
No. of embryo transfers	220	53	50	43	74
No. of UC	4766	621	899	982	2264
UC/min[a]	4.3 ± 0.1	2.4 (1.2–3.0)	3.6 (3.2–4.0)	4.6 (4.2–5.0)	6.1 (5.2–8.6)
Retrograde[b,d] (%)	55	38	54	61	64
Antegrade[c] (%)	28	31	28	24	28
Antagonistic[d] (%)	11	19	14	10	5
Non-propagated (%)	6	12	4	5	3
Total (%)	100	100	100	100	100

[a]Values are means ± SE for overall data and medians (ranges) for group data.
[b]UC starting on the cervix toward the fundus.
[c]UC starting on the fundus toward the cervix.
[d]$P < 0.001$.

confirmed. Hormonal influence on uterine contractility was assessed using simple regression. Agreement between the two independent observers was measured by Kappa statistic. A P value of <0.05 was considered statistically significant.

Results

Overall UC data

Data on UC frequency and respective prevalence of UC types in each frequency group are summarized in Table I. We observed a total of 4766 UC during the US scans performed just before embryo transfer, corresponding to an overall UC frequency of 4.3 ± 0.1 UC/min. Of all 4766 UC studied, 55% were retrograde (toward the fundus), 28% were antegrade (toward the cervix), 11% were antagonistic, and 6% were non-propagated. As presented in Table I, a progressive increase in the prevalence of retrograde UC and a progressive decrease in the prevalence of antagonistic UC occurred from the low to the high frequency groups ($P < 0.001$). However, there was no statistical difference in the prevalence of either antegrade or non-propagated UC among the four UC groups.

Patients, controlled ovarian hyperstimulation and embryology data in each frequency group

Data on patients, controlled ovarian hyperstimulation and embryology characteristics are summarized in Table II. All frequency groups were similar in regard to the age of patients, indications for IVF–embryo transfer, ovarian reserve assessment (baseline FSH and oestrogen concentrations on cycle day 3 performed during the 2 or 3 months prior to ovulation induction), number of HMG ampoules administered, duration of ovulation induction, plasma oestrogen and progesterone concentrations on the day of HCG administration, number of mature oocytes retrieved, and number of available and transferred embryos. Incidentally, endometrial thickness measured on the day of embryo transfer was comparable in the four

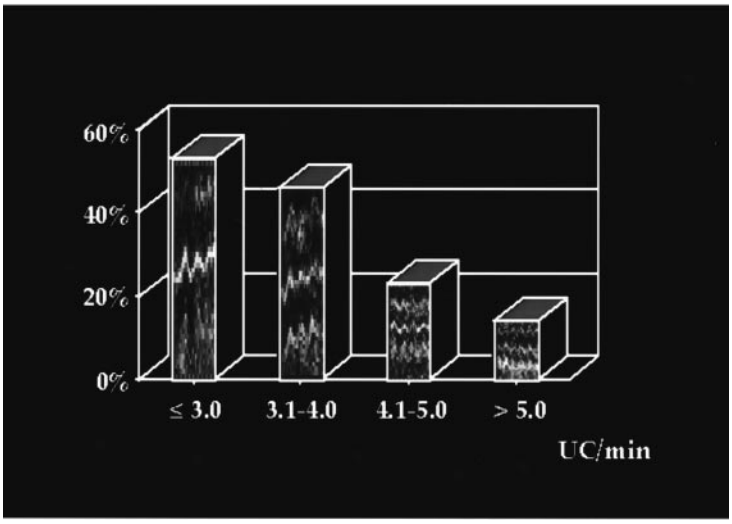

Figure 3. Stepwise decrease in clinical pregnancy rates from the lowest to the highest uterine contraction (UC) frequency groups ($P < 0.001$; ANOVA).

Table II. Patients, controlled ovarian hyperstimulation and embryology data in the uterine contraction (UC) frequency groups

	No. uterine contractions/min			
	⩽3.0 ($n = 53$)	3.1–4.0 ($n = 50$)	4.1–5.0 ($n = 43$)	>5.0 ($n = 74$)
Ages (years)[a]	31 (25–38)	33 (23–38)	31 (24–38)	32 (26–38)
Indications for IVF–embryo transfer (%)				
tubal	44	35	34	31
male	32	50	58	58
unexpl.	18	9	8	16
endom.	6	6	0	0
Plasma FSH[b] (mIU/ml)	5.0 ± 0.3	4.7 ± 0.2	4.9 ± 0.3	5.0 ± 0.2
Plasma oestradiol[b] (pg/m)	29 ± 2	33 ± 3	28 ± 2	29 ± 2
HMG ampoules	34 ± 1	33 ± 2	35 ± 2	33 ± 1
Day of HCG injection	11.4 ± 0.2	11.4 ± 0.2	11.5 ± 0.2	11.5 ± 0.2
Plasma oestradiol[c] (pg/ml)	2589 ± 138	2449 ± 153	2754 ± 177	2376 ± 112
Plasma progesterone[c] (ng/ml)	0.96 ± 0.08	0.77 ± 0.07	0.81 ± 0.10	0.74 ± 0.05
Mature oocytes	7.7 ± 0.6	8.4 ± 0.7	8.5 ± 0.7	8.0 ± 0.4
Available embryos	4.4 ± 0.4	4.9 ± 0.5	4.1 ± 0.4	4.3 ± 0.3
Transferred embryos[a]	3 (3–4)	3 (3–4)	3 (3–4)	3 (3–5)
Plasma oestradiol[d] (pg/ml)	1058 ± 132	1130 ± 123	1060 ± 120	1052 ± 76
Plasma progesterone[d] (ng/ml)	111 ± 21	91 ± 8	73 ± 8	68 ± 4

[a]Values are medians (ranges).
[b]On cycle day 3, approximately two menstrual cycles before ovulation induction.
[c]On the day of HCG administration.
[d]On the day of embryo transfer (groups statistically different for progesterone values, $P < 0.008$).
HCG = human chorionic gonadotrophin; FSH = follicle stimulating hormone; HMG = human menopausal gonadotrophin.

groups (9.8 ± 0.3, 9.2 ± 0.3, 9.4 ± 0.4 and 9.9 ± 0.3 mm respectively in the ⩽3.0, 3.1–4.0, 4.1–5.0 and >5.0 UC/min groups), and overall echogenicity patterns were consistently hyperechogenic in all groups.

In contrast to the similarity of individual and controlled ovarian hyperstimulation data among groups, we observed a marked stepwise decrease in clinical and ongoing pregnancy rates as well as in implantation rates from the lowest to the highest UC frequency group (53, 36, 21; 46, 32, 20; 23, 19, 10; and 14, 11, 4% respectively in the ⩽3.0, 3.1–4.0, 4.1–5.0 and >5.0 UC/min groups; $P < 0.001$). The marked fall in clinical pregnancy rates is displayed in Figure 3.

Further, a significant negative correlation between plasma progesterone concentrations measured just before embryo transfer and UC frequency was identified ($r = –0.34$; $P < 0.001$). Plasma progesterone concentrations decreased significantly from the lowest to the highest UC frequency group ($P < 0.008$). Conversely, no association between plasma

progesterone and oestrogen concentrations on the day of HCG administration, or between plasma oestrogen concentrations on the day of embryo transfer and UC frequency, was noticed. Plasma oestrogen concentrations on the day of embryo transfer were similar in the four frequency groups.

Additionally, we failed to observe any influence of the UC pattern (relative prevalence of retrograde, antegrade, antagonistic and non-propagated UC) on IVF–embryo transfer outcome. Patterns of UC in patients who conceived (57, 26, 9 and 7% respectively) were comparable to those observed in patients who did not conceive (49, 31, 15 and 5% respectively). No association between plasma oestrogen and progesterone concentrations on the day of HCG administration and embryo transfer and UC pattern was observed.

Discussion

The present study was conducted to investigate the possible consequences of UC as visualized by US at the time of embryo transfer on the outcome of IVF. We observed poorer rates of pregnancy and implantation in patients displaying higher UC frequency in comparison with those presenting lower UC frequency. Subjects included in this study have been controlled for age ($\leqslant$38 years), uterine abnormalities, as well as number and quality of embryos transferred ($\geqslant$3). All frequency groups were similar with regard to population and controlled ovarian hyperstimulation and embryology characteristics. Finally, the assessment of UC frequency was performed objectively using an expert analysis system. This allows us to speculate that there is a causal relationship between intense myometrial contractile activity and low pregnancy rates, most likely because normal contact between embryos and endometrium is hindered by UC.

In agreement with our results is the recent report by IJland *et al.* (1997b), which argues that overall myometrial contractile activity, assessed by US during the early, mid, and late follicular phases and early and mid-luteal phases of the menstrual cycle, is consistently and significantly lower in conceptional as compared to non-conceptional cycles. Further, Knutzen *et al.* (1992) demonstrated that UC exerted a conspicuous effect on uterine content and caused, in up to 52% of cases, antegrade or retrograde expulsion of dye boluses introduced into the uterine cavity as mock embryo transfers performed in spontaneous cycles. These authors contemplated a possible strengthening of this phenomenon under the imbalanced hormonal environment achieved during controlled ovarian hyperstimulation for IVF–embryo transfer (Knutzen *et al.*, 1992). Paradoxically, Woolcott and Stanger (1997) reported improved IVF–embryo transfer outcome when uterine contractile activity, assessed by US just after embryo transfer, was present in comparison with cases in which it was absent. These authors failed, however, to observe the presence of UC in 63% of embryo transfers, which suggests that accuracy of assessment techniques for UC was probably defective and challenges the reliability of their conclusions.

A reliable appraisal of UC effects on human embryo implantation has been hitherto impossible on account of the invasiveness of classical intrauterine pressure recordings (Hendricks, 1966; Martinez-Gaudio *et al.*, 1973). Moreover, both the improvement on US imagery allowing direct visualization of UC in US scans (Birnholz, 1984; Oike *et al.*, 1988) and the possibility of digital recording using a computer-assisted analysis of US images have offered the possibility of non-invasive and objective investigation into the consequences of UC in actual embryo transfer cycles.

The characteristics of UC as visualized by US in non-pregnant women have been assessed in several reports. The original study reported by Birnholz (1984), using a transabdominal 3.5 MHz transducer, did not allow identification of UC in up to 27% of cases. More recently, in transvaginal US scans conducted in normal menstrual cycles, UC frequency and amplitude have been described to increase progressively during the follicular phase to a maximum activity at mid-cycle (3–4 UC/min) before declining throughout the luteal phase (Abramowicz and Archer, 1990; Lyons *et al.*, 1991; IJland *et al.*, 1996). Some investigators (IJland *et al.*, 1996) found a further transitory increase in UC rate to occur from the follicular (3.3 UC/min) to the early luteal phase (3.9 UC/min). The mean UC frequency value observed in our study at the time of embryo transfer (4.3 UC/min) under ovulation induction conditions tended to exceed slightly the value observed in the early luteal phase in spontaneous cycles, which may be a result of the supraphysiological oestrogen concentrations and oestrogen/progesterone ratios induced by ovulation induction. In regard to UC direction, during the follicular phase of the menstrual cycle, a growing predominance of the retrograde UC pattern (toward the fundus) is observed (Oike *et al.*, 1990; Lyons *et al.*, 1991; IJland *et al.*, 1996). This predominance disappears progressively with the onset of the luteal phase (Lyons *et al.*, 1991), whereas the prevalence of the antagonistic UC pattern increases (IJland *et al.*, 1996). Further, an evident antegrade UC predominance has been reported during menses (Hendricks, 1966).

From a physiological standpoint, the putative role of UC at mid-cycle is to promote sperm ascension through the uterine cavity to the Fallopian tubes (Lyons *et al.*, 1991; Kunz *et al.*, 1996). After ovulation, the progressive reduction in uterine contractility (Abramowicz *et al.*, 1990; Lyons *et al.*, 1991) is deemed to propitiate the necessary contact between blastocysts and endometrium that takes place during the mid-luteal phase and may therefore assist implantation. Finally, the expulsive UC patterns observed during the menstrual phase probably help both endometrial desquamation and evacuation of menses. In conventional IVF–embryo transfer, however, at least three factors are likely to rebut some of these physiological adjustments of uterine contractility. First, embryos are prematurely replaced into the uterine cavity (2 days after fertilization) when the myometrial activity may be still too intense. Second, the supra-physiological hormonal milieu induced by controlled ovarian hyperstimulation is likely to hypersensitize the uterus to exogenous stimuli (Morizaki *et al.*, 1989), thereby favouring UC. Finally, the often considerable mechanical stimulation of the uterus as a result of the embryo transfer procedure may further invigorate the myometrial activity (Knutzen *et al.*, 1992), even though repeated embryo transfer attempts, in the

case of retention of embryos in the embryo transfer catheter, have been shown not to alter pregnancy rates (Nabi *et al.*, 1997).

The present study also focused on the possible influence of steroid hormones (oestrogen and progesterone) on myometrial contractile activity. We found a negative and significant correlation between plasma progesterone concentrations on the day of embryo transfer and UC frequency. This supports the putative uterine relaxing properties of progesterone. Moreover, although significant, the strength of the relationship between plasma progesterone concentrations and UC was relatively weak ($r = -0.34$). This may be explained by the fact that circulating progesterone concentrations do not always reflect the uterine action of progesterone (Fanchin *et al.*, 1997). Moreover, oestrogen concentrations have been reported to be directly correlated with UC frequency (Oike *et al.*, 1990), an observation that is further supported by the description of a progressive increase in UC frequency throughout the follicular phase of the menstrual cycle (Lyons *et al.*, 1991; IJland *et al.*, 1996). Yet, much to our surprise, we failed to establish any association between plasma oestrogen concentrations and UC. One possible explanation for this phenomenon is that, at the time of embryo transfer, women included in the study had supra-physiological oestrogen concentrations as a result of controlled ovarian hyperstimulation. Therefore, it is conceivable that the maximum oestrogenic effects on the uterine activity had already been reached during the follicular phase of controlled ovarian hyperstimulation and the uterus had become insensitive to further variations in oestrogen concentrations occurring during the early luteal phase.

Another issue deserving consideration is that the prevalence of retrograde (toward the fundus) UC patterns was significantly higher whereas the prevalence of antagonistic UC patterns was significantly lower in the high compared to the low frequency UC groups. Hence, it is possible that patients displaying an intense contractile activity during the early luteal phase had more UC of follicular type (retrograde), which may reflect a lack of adequate response to the growing progesterone concentrations observed at the time of embryo transfer. On the other hand, the higher prevalence of antagonistic UC patterns observed in the lower UC frequency groups at the time of embryo transfer is consonant with the physiological UC patterns observed during the early luteal phase of normal menstrual cycles (IJland *et al.*, 1996). This might indicate a more extensive action of progesterone not only on frequency but also on organization of the myometrial activity.

Finally, in contrast to previous publications, the present study employed for the first time a new software especially conceived for the analysis of UC. This system allowed objective evaluation of UC frequency and considerable acceleration of US images (10 times the normal speed) without detriment to image resolution and quality, hence rendering the analysis of UC characteristics easier and more reliable.

In conclusion, high-frequency uterine contractility at the time of embryo transfer affects adversely pregnancy and implantation rates in IVF–embryo transfer. These results impel us to investigate whether the administration of uterine relaxing substances such as progesterone, β-mimetics, anti-prostaglandins, or nitric oxide donors might reduce UC frequency, thereby improving IVF–embryo transfer outcome. Finally, in IVF–embryo transfer with prolonged embryo culture, the assessment of UC 5 or 6 days after fertilization, at the time when blastocysts are usually transferred into the uterine cavity and myometrial activity is probably reduced, may further extend our understanding of the role of UC in the embryo implantation process.

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