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The changing pattern of uterine contractions before and after fresh embryo transfer and its relation to clinical outcome

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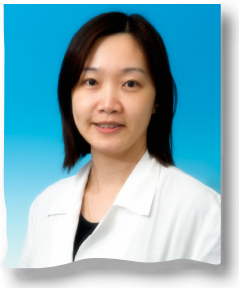

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A B S T R A C T

In this prospective cohort study of 286 women undergoing fresh embryo transfer after IVF, uterine contraction frequency and direction were measured before (–5 min), 5 min after (+5 min) and 60 min after (+60 min) embryo transfer. Mean ± SD uterine contraction frequency at –5 min was 1.8 ± 1.1 contractions per min, increasing significantly ($P < 0.05$) to 2.0 ± 1.1 at +5 min, and returning back to baseline 1.8 ± 1.1 at +60 min. At –5 min, the proportion of women the with retrograde, antegrade, indeterminate direction and absent contractions were 33%, 44%, 17% and 6%; at +5 min, 40%, 42%, 13% and 5%, and at +60 min, 42%, 38%, 14% and 6%. No significant change was observed in the proportion of direction at these three time points. Logistic regression analysis showed live birth rate was significantly reduced in older women ($P = 0.035$) and in those with higher uterine contraction frequency at +5 min ($P = 0.006$). Frequency of uterine contraction immediately after embryo transfer (+5 min) seemed to be a significant predictor of IVF outcome and may help to identify women who could benefit from the use of muscle relaxant therapy to improve outcome.

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Introduction

Several studies have suggested that excessive uterine contractions at the time of embryo transfer are associated with a reduced chance of successful implantation in natural (Ijland et al., 1997) and stimulated (Fanchin et al., 1998; Zhu et al., 2014a) cycles. In natural cycles, Ijland et al. (1997) found that endometrial activity in conception cycles was less than that of non-conception cycles. In stimulated cycles, Fanchin et al. (1998) observed that uterine contraction frequency immediately before embryo transfer was inversely related to implantation rate and clinical pregnancy rate. The latter finding was confirmed by a subsequent study involving both fresh and frozen embryo cycles (Zhu et al., 2014a), in which uterine contraction frequencies in women who conceived were significantly lower than that of women who did not conceive.

Little, however, is known about how uterine contraction frequency and direction change after embryo transfer and to what extent these changes affect clinical outcome. In this prospective cohort study, the effect of an embryo transfer procedure on both the frequency and direction of uterine contractions was examined at 5 min and 60 min after the procedure and to relate the results to live birth rate (LBR) in women undergoing fresh embryo transfer after IVF treatment.

Materials and methods

Patients

Women undergoing IVF between July 2011 and August 2013 in the Assisted Reproductive unit of Prince of Wales Hospital, Chinese University of Hong Kong, were invited to participate in this study. Women were recruited during their treatment cycle and the enrolment was confirmed on the day of embryo transfer. Exclusion criteria for recruitment included women aged 40 years or over; congenital uterine anomaly or acquired uterine pathology such as myoma, adenomyosis or endometrial polyp; presence of a hydrosalpinx; and repeated implantation failure (failed to conceive after three or more embryo transfer cycles with good-quality embryos). Congenital uterine anomaly and acquired uterine pathology were excluded by two-dimensional ultrasound scan in all cases, and one or more additional investigations, including hysterosalpingogram, three-dimensional ultrasound scan, two- and three-dimensional saline-infusion-sonography, hysteroscopy and laparoscopy in selected cases. Women with a history of mid-trimester loss or recurrent pregnancy loss were routinely offered three-dimensional saline-infusion-sonography. The study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee on 23 July 2011 (registration number CRE 2011.303) and all patients completed a written informed consent before enrolment. We previously reported on the migration of the embryo flash (air bubble) after embryo transfer in this cohort (Saravelos et al., 2016).

Ovarian stimulation cycle

Pituitary suppression was achieved either by long (luteal) GnRHa or antagonist protocol. For long down-regulation protocol, Buserelin nasal spray (Suprecur, Hoechst, Germany) 600 µg daily was administered for at least 14 days starting from the mid-luteal phase of the preceding cycle. In the antagonist protocol, Cetrorelix (Cetrotide, Merck Serono, Germany) or Ganirelix (Orgalutran, MSD, Ireland) was started once oestradiol was greater than 800 pmol/l or the leading follicle was greater than 14 mm. Ovarian stimulation was started using HMG (Pergonal, Serono, Aubonne/Switzerland) or recombinant FSH (Gonal-F, Serono, Aubonne/Switzerland; or Puregon, Organon, Holland) ranging from 150 to 450 IU/day according to patients' age, ovarian reserve test and ovarian response. Ovarian response was monitored by transvaginal ultrasonography and serum oestradiol measurements from stimulation day 6 onwards. An injection of 5000 IU of HCG was given once three or more mature follicles were 18 mm or wider in diameter and transvaginal oocyte retrieval was carried out 36 h later. Embryo transfer was carried out 3 days after oocyte retrieval and surplus embryos were cryopreserved.

Serum LH and oestradiol were measured on the day of ovulation trigger whereas oestradiol and progesterone level were measured on the day of embryo transfer. Vaginal progesterone (Crinone gel 8% daily, Merck Serono, or Endometrin 100 mg BD, Ferring) was given as luteal phase support after the embryo transfer until the day of the pregnancy test (16 days after oocyte retrieval). If the pregnancy test was positive, transvaginal ultrasonography was carried out 2 weeks later to determine the number of gestational sacs as well as fetal viability. Clinical pregnancy was defined as the presence of one or more intrauterine gestational sacs 4 weeks after oocyte retrieval. Miscarriage was defined as a non-viable pregnancy after ultrasonographic visualization of an intrauterine gestational sac before 24 weeks of gestation. Live birth was defined as a viable delivery at or after 24 weeks of gestation.

Embryo transfer

After the first 3-min transabdominal ultrasound scan to measure the frequency and direction of any uterine contractions, patients were placed in a lithotomy position. A bivalve speculum was inserted into the vagina to expose the cervix, and the cervical mucus was cleared using a moist cotton wool stick. One or two embryos were loaded into an atraumatic Cook Sydney embryo transfer catheter (Cook Medical, Indiana, USA) by the embryologist and then transferred transcervically to the middle of the uterine cavity aiming for a distance of 15 mm from the fundus by one of the three experienced reproductive medicine subspecialists under ultrasound guidance. The total duration of the inner and outer catheter insertion, along with the difficulty in transfer and the subjective feeling about the urge of micturition (mild, moderate and severe) at the time of embryo transfer were recorded.

Uterine contraction measurement

On the day of embryo transfer, all recruited women underwent transabdominal ultrasonography with the use of a General Electric Voluson 730 Expert series ultrasound machine and a RAB4-8L, 4.0–8.0 MHz 3D/4D probe (GE Medical Systems Kretztechnik GmbH & Co, Austria), which was connected to a dedicated monitor and DVD player for recording in live time. To reduce bias and variability, all examinations were carried out using the same machine and by a single operator (CPSC). Uterine contraction measurements were assessed at three different time points: 5 min before (–5 min), 5 min after (+5 min), and 1 h after (+60 min) the embryo transfer procedure. A mid-sagittal plane of uterine image was taken and a video of the live ultrasound image was recorded for at least 3 min. This was then subsequently analysed for both uterine contraction frequency and uterine contraction di-

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