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GnRH agonist administration prior to embryo transfer in freeze-all cycles of patients with endometriosis or aberrant endometrial integrin expression

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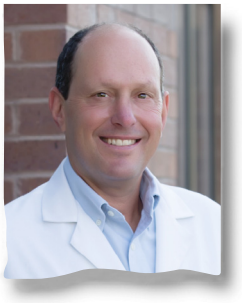

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KEY MESSAGE

A prolonged course of GnRHa after freeze-all to patients with endometriosis or aberrant endometrial integrin expression results in high implantation and ongoing pregnancy rates after embryo transfer. This avoids excessive ovarian suppression associated with agonist administration prior to fresh embryo transfer and allows for elective vitrification of all embryos.

A B S T R A C T

Prolonged gonadotrophin-releasing hormone agonist (GnRHa) administration before IVF with fresh embryo transfer to patients with endometriosis or aberrant endometrial integrin expression (-integrin) improves outcomes but may suppress ovarian response and prevents elective cryopreservation of all embryos. This retrospective cohort pilot study evaluates freeze-all cycles with subsequent prolonged GnRHa before embryo transfer in these populations. Patients from 2010 to 2015 who met inclusion criteria and received a long-acting GnRHa every 28 days twice before FET were evaluated. A subset underwent comprehensive chromosomal screening (CCS) after trophectoderm biopsy. Three groups were identified: Group 1: + CCS, +endometriosis (20 patients, 20 transfers); Group 2: +CCS, –integrin (12 patients, 13 transfers); Group 3: no CCS, +endometriosis or –integrin (10 patients, 12 transfers); Group 4: all transfers after CCS for descriptive comparison only (n = 2809). Baseline characteristics were similar among Groups 1–3 except that the mean surgery to oocyte aspiration interval was longer for Group 1 than Group 3. Implantation and ongoing pregnancy rates were statistically similar among the three groups and compared favourably to Group 4. A non-significant trend towards improved outcomes was noted in Group 1. Prolonged GnRHa after freeze-all in these patients avoids excessive ovarian suppression and results in excellent outcomes.

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Introduction

The impact of endometriosis in general on IVF outcomes is somewhat controversial, although the presence of more advanced disease (particularly in the presence of endometriomas) seems to have deleterious effects (Hamdan et al., 2015; Harb et al., 2013; Surrey, 2013). The benefit of a prolonged course of a gonadotrophin-releasing hormone agonist (GnRHa) in these patients prior to initiation of an IVF cycle with planned fresh embryo transfer has been demonstrated (Sallam et al., 2006; Surrey et al., 2002). Others have shown that this may also be beneficial in patients with recurrent implantation failure who were noted to have aberrant endometrial $\alpha v\beta_3$ integrin expression (Surrey et al., 2007).

One of the disadvantages of this approach is that prolonged pituitary down-regulation induced by the agonist may suppress ovarian response to gonadotrophin stimulation, particularly in patients with compromised ovarian reserve (Decleer et al., 2016). The duration of benefit derived from the administration of prolonged GnRHa has not been established, which may be a critical issue for patients requiring cryopreservation of all embryos, as in the case of planned comprehensive chromosomal screening (CCS) or who are at high risk of ovarian hyperstimulation syndrome. In addition, recent reports have suggested that transfer of blastocyst stage embryos after vitrification and warming may result in improved neonatal outcomes without affecting live birth rates in comparison to fresh transfers (Roy et al., 2014).

In an effort to avoid these issues, the current investigation is a pilot study that evaluates the impact of deferring administration of a prolonged course of GnRHa in these patient populations until after embryos have been vitrified and immediately prior to endometrial preparation for cryopreserved embryo transfer. To our knowledge, this is the first time that this issue has been reported upon.

Materials and methods

This is a retrospective cohort pilot trial performed in a single tertiary care assisted reproductive technology centre. All consecutive patients from 2010 to 2015 at the Colorado Center for Reproductive Medicine who underwent IVF with autologous oocytes, vitrification of all embryos and subsequent cryopreserved embryo transfer after prolonged administration of GnRHa were included. All patients had a prior surgical diagnosis of endometriosis and/or evidence of aberrant endometrial integrin expression. Patients considered to have endometriosis had received a surgical diagnosis within 10 years of initiation of their IVF cycle, although all but two patients had received a surgical diagnosis within 62 months of oocyte aspiration. Only patients with one or more of the following were offered prolonged GnRHa administration: (i) stage III or IV endometriosis (American Society for Reproductive Medicine, 1996); (ii) severe endometriosis-related symptoms; (iii) prior failed embryo transfers.

All patients underwent ovarian reserve testing including day 3 serum FSH, oestradiol and anti-Müllerian hormone (AMH) levels as well as antral follicle count determined at baseline transvaginal ultrasound examination performed in the early follicular phase. All patients were noted to have a normal uterine cavity documented at precycle office hysteroscopy. In an effort to eliminate a potential confounding variable, no patients were included who had received GnRH agonists or progestins for treatment of symptomatic endometriosis within 6 months of initiation of their IVF cycle. Only combination oral contraceptives and pain medications were permitted during this interval for those patients included in this investigation. No patients had endometriomas *in situ* that were >4.5 cm in mean diameter as measured at baseline ultrasound examination.

Endometrial biopsies to evaluate β_3 integrin expression were performed 9–11 days after documentation of an LH surge by urine ovulation induction kits. The tissue was evaluated for integrin expression using a commercial assay (Pathology Consultants, Greenville, SC) employing previously described techniques (Lessey et al., 1992). All biopsies were confirmed to be in phase ± 2 days by standard histological criteria before a decision was made to employ GnRHa if absent integrin expression was reported (Li et al., 1987). Typical indications for performing the biopsy included at least one of the following: clinically suspected endometriosis based on presenting symptoms but without prior laparoscopy and/or unexplained implantation failure as previously described (Surrey et al., 2007).

All patients underwent ovarian stimulation. The determination for the specific protocol to be used was based on age, the results of ovarian reserve testing, and prior response where appropriate. Transvaginal ultrasound-guided oocyte aspiration was performed 35 h after administration of HCG and/or GnRHa as trigger (Engmann et al., 2016; Katz-Jaffe et al., 2013). Embryos of patients who were to undergo CCS were cultured in sequential medium to the expanded blastocyst stage (days 5, 6 and/or 7 after oocyte aspiration) prior to trophectoderm biopsy as previously described (Schoolcraft et al., 2011). Blastocyst stage embryos were graded using a standardized system that has been used consistently in our centre (Gardner and Schoolcraft, 1999). Embryos from patients who were not undergoing CCS were vitrified at either the cleavage stage on day 3 or at the blastocyst stage on either days 5 or 6 after oocyte aspiration. All embryos were vitrified in Cryotops as described by Kuwayama (2007).

All patients subsequently were administered a long-lasting preparation of the GnRHa leuprolide acetate (Lupron Depot®; AbbVie, North Chicago, IL) 3.75 mg every 28 days for 56 days. The endometrium was then prepared for embryo transfer using exogenous oestradiol primarily administered by a transdermal route starting with two oestradiol 100 µg patches (Vivelle-Dot®; Novartis, Basel, Switzerland) changed every other day with doses increased at 4–6 day intervals as needed to a maximum dose of four patches to achieve adequate endometrial development (typically ≥8 mm and ≤15 mm with a triple pattern). If inadequate endometrial development was obtained, the transdermal oestradiol preparation was supplemented with orally and/or vaginally administered oestradiol 2 mg once or twice daily (Estrace®; Teva North America, North Wales, PA) and/or oestradiol valerate administered intramuscularly 25 mg twice weekly (Delestrogen®, Par Pharmaceuticals, Chestnut Ridge, NY) as needed. Once adequate endometrial development was documented, progesterone administration was initiated employing micronized progesterone 100 mg vaginally twice daily (Endometrin®, Fering Pharmaceuticals, Parsippany, NJ) and micronized progesterone in oil 25–50 mg intramuscularly every other day (West-Ward Pharmaceuticals, Eatontown, NJ). Blastocyst stage embryos were warmed and transferred on the sixth day of progesterone exposure. Cleavage stage embryos were warmed and transferred on the third day of progesterone exposure. Only embryos predicted to be euploid were transferred if CCS had been performed. Embryo transfers

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