Risk of placenta praevia is linked to endometrial thickness in a retrospective cohort study of 4537 singleton assisted reproduction technology births†

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STUDY QUESTION: Is endometrial thickness measured prior to embryo transfer associated with placenta praevia?

SUMMARY ANSWER: Following IVF, the risk of placenta praevia is increased 4-fold in women with an endometrial thickness of > 12 mm compared with women with an endometrial thickness of < 9 mm.

WHAT IS KNOWN ALREADY: Placenta praevia is a serious complication of pregnancy with adverse maternal and neonatal outcomes. Placenta praevia is 2- to 6-fold more likely to occur following IVF treatment but it remains unknown what factors contribute to that increased risk.

STUDY DESIGN, SIZE, DURATION: Retrospective cohort study involving 4007 women who had 4537 singleton assisted reproduction technology (ART) births occurring between January 2006 and June 2012 with no loss to follow-up. The primary outcome measure was the diagnosis of placenta praevia, made by the treating obstetrician on a transvaginal ultrasound in the third trimester.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women who had singleton births following single embryo transfer performed at Monash IVF in Melbourne, Australia were included. Of the 4537 cycles leading to a singleton ART birth, 2951 were stimulated cycles with fresh embryo transfers; 355 were hormone replacement therapy frozen embryo transfers and 1231 were natural cycles with frozen embryo transfers. The dataset was analysed using binary logistic general estimating equations to calculate odds ratios for placenta praevia adjusted (aOR) for known confounders.

MAIN RESULTS AND THE ROLE OF CHANCE: The study groups did not differ significantly in age, BMI and aetiologies of infertility prior to IVF treatment. When compared with stimulated cycles, placenta praevia was less common in women undergoing natural cycles with frozen embryo transfers (OR 0.44, 95% confidence interval (CI) 0.27–0.70, P < 0.01) but hormone replacement therapy frozen embryo transfer cycles were not associated with a lower risk (OR 0.89, 95% CI 0.48–1.63). After adjusting for confounders, smoking (aOR 2.58, 95% CI 1.07–6.24, P = 0.04, endometriosis (aOR 2.01, 95% CI 1.21–3.33, P < 0.01) and endometrial thickness remained statistically significant as independent risk factors for placenta praevia. Compared with women with an endometrial thickness of < 9 mm, women with an endometrial thickness of 9–12 mm had an aOR of 2.02 (95% CI 1.12–3.65, P = 0.02) and women with an endometrial thickness > 12 mm had an aOR of 3.74 (95% CI 1.90–7.34, P < 0.01). These differences remained statistically significant after performing a sensitivity analysis limited to women with no previous births.

LIMITATIONS, REASONS FOR CAUTION: The study is retrospective in nature, not all confounders may have been accounted for and details on previous intrauterine surgery, a known risk factor, were not available. In addition, ultrasound assessments were carried out by several highly trained operators measuring the endometrial thickness, the main independent variable, in a two-dimensional plane and some inter-observer variability may therefore be present.

WIDER IMPLICATIONS OF THE FINDINGS: The findings of a higher risk of placenta praevia in patients with endometriosis and in those that smoke are in agreement with the current literature on natural conception. There have so far been no reports of an association between

†The results of this study were presented in an oral communication at the 5th Congress of the Asia Pacific Initiative on Reproduction in Brisbane, Australia, from 4–6 April 2014.

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endometrial thickness and placenta praevia after ART. This novel finding warrants further study to elucidate the underlying cause of the association and to assess how to minimize harm to IVF patients and their offspring. The fact that the observed increased risk is not linked to the type of embryo transfer (fresh/frozen) but to the type of endometrial preparation, suggests that the risk of placenta praevia in ART can be reduced by considering an elective frozen embryo transfer in a natural cycle, especially given the growing evidence that this strategy also provides a number of other maternal and neonatal benefits.

**STUDY FUNDING/COMPETING INTEREST(S):** No funding was required for this study. L.R. has a minority shareholding in Monash IVF and has received unconditional research and educational grants from MSD®, Merck-Serono® and Ferring®. L.R. serves on an advisory board for MSD® and Ferring®.

**Key words:** Placenta praevia / assisted reproduction technology / endometrial thickness / endometriosis / IVF

## Introduction

Placenta praevia is a term used to describe abnormally low placentation. Placenta praevia is a significant diagnosis in pregnancy, as it is associated with important maternal and fetal complications, including antenatal and post-partum haemorrhage, placenta accreta and percreta, peripartum hysterectomy, preterm delivery, intrauterine growth restriction, malpresentation and an increase in poor neonatal outcomes (McShane et al., 1985; Stones et al., 1993). Amongst known risk factors for placenta praevia, including maternal age, multiple pregnancy, multiparity, smoking and drug use and termination of pregnancy (Parazzini et al., 1985; Stones et al., 1993), a major reason for an increasing incidence of placenta praevia may be the rising number of Caesarean sections being performed (Ananth et al., 1997; Faiz and Ananth, 2003; Declerq et al., 2011).

Another, perhaps less well-recognized, risk factor for placenta praevia is assisted reproduction technology (ART), with several large cohort studies and a meta-analysis indicating a 2- to 6-fold increased odds of placenta praevia after ART (Jackson et al., 2004; Kallen et al., 2005; Shevell et al., 2005; Romundstad et al., 2006; Poikkeus et al., 2007; Healy et al., 2010; Sazonova et al., 2011; Yang et al., 2014). Blastocyst transfer has also been associated with 2-fold increased odds of placenta praevia compared with non-blastocyst transfer in some studies (Sazonova et al., 2011; Fernando et al., 2012) but not in a very large Japanese cohort study (Ishihara et al., 2014).

A meta-analysis published by Jackson and colleagues included six studies with a combined total of only 39 cases of placenta praevia in 1610 pregnancies conceived by ART. Due to its size, this study could not determine whether the increased risk was primarily due to maternal factors (including the primary reason for infertility) or to the ART itself (Jackson et al., 2004).

A large Norwegian registry study compared the risk of placenta praevia in 7568 pregnancies conceived after ART with the risk in naturally conceived pregnancies (Romundstad et al., 2006). They also compared the risk of placenta praevia between consecutive pregnancies among 1349 women who had conceived both naturally and after ART. This study showed an almost 6-fold higher likelihood of placenta praevia in singleton pregnancies conceived by ART compared with naturally conceived pregnancies. Among mothers who had conceived both naturally and after ART, the risk of placenta praevia was nearly 3-fold higher in the pregnancy following assisted fertilization, compared with that in their naturally conceived pregnancy. The authors, therefore concluded that this increased risk may be explained by factors related to the ART procedure (Romundstad et al., 2006).

On the other hand, in a study of singleton pregnancies, patients who conceived with ART were at increased risk for several adverse obstetric and perinatal outcomes, including placenta praevia, independent of the type of ART procedure used (Hayashi et al., 2012). The authors suggest that this may indicate that adverse obstetric and perinatal outcomes following ART may be related to factors associated with infertility rather than the type of assisted reproductive technology procedure used (Hayashi et al., 2012). Such factors may include the presence of endometriosis, with some investigators finding an association between this aetiology of infertility and placenta praevia (Fernando et al., 2009; Vercellini et al., 2012).

Others have explored whether frozen embryo transfer has an effect on placenta praevia risk. In a large retrospective database study, Sazonova and colleagues found that while the rate of pre-eclampsia was higher, the adjusted odds of placenta praevia was lower in pregnancies following frozen embryo transfer cycles compared with those from fresh cycles (Sazonova et al., 2012). Others have found no association between fresh versus frozen embryo transfer and the risk of placenta praevia (Healy et al., 2010; Liu et al., 2013; Ishihara et al., 2014). The increased risk of placenta praevia following ART does not appear to be linked to socio-economic status. In a Finnish population-based study, after adjusting for cofactors including age, smoking and diabetes IVF was associated with a 5-fold higher incidence of placenta praevia (Raisanen et al., 2013).

Despite the fact that placenta praevia is significantly increased following IVF, the underlying cause is not understood. Varying theories have been developed, ranging from hormonal effects on the endometrium, effects related to the embryo transfer and altered uterine contraction wave patterns. The aim of this study was to investigate the association between endometrial thickness measured prior to embryo transfer and the relative risk of placenta praevia.

## Materials and Methods

### Study design

This was an observational study analysing data from a retrospective cohort of all women who had a singleton birth resulting from a single embryo transfer between January 2006 and June 2012 at Monash IVF in Melbourne, Australia. In this time frame, a total of 30919 IVF fresh and frozen cycles occurred. We excluded all donor recipient cycles leaving a total of 29218 cycles. Of these, 1663 had no embryo transfer and 7357 had a double embryo transfer, leaving 20198 single embryo transfers. Of these 15543 did not result in a live delivery and 118 had a multiple birth, leaving a total of 4537 singleton births originating from a single fresh or frozen embryo transfer cycle in 4007 women.
The primary outcome measure was any type of placenta praevia. In Australia, there is a regulatory requirement to report all IVF cycle outcomes, including perinatal and neonatal outcomes and complications, to the Australia and New Zealand Assisted Reproduction Database and as such there was 100% complete follow-up in this cohort. To fulfil these reporting requirements our IVF unit has a dedicated data officer who contacts the obstetrician and/or maternity hospital to obtain all the relevant medical details, including pregnancy complications such as placenta praevia. The diagnosis of placenta praevia was made by the treating obstetrician on generally accepted diagnostic criteria based on a transvaginal ultrasound in the third trimester.

The primary exposure measure was endometrial thickness, grouped into $<9$, $9–12$ and $>12$ mm. Highly trained sonographers measured the endometrial thickness in a two-dimensional plane on a Voluson E8 or a Voluson 730 Expert using intracavity probes with a frequency range of 5–9 MHz (GE Healthcare, Australia). In stimulated cycles with fresh embryo transfers (STIM), endometrial thickness was taken from the last transvaginal ultrasound (TVUS) performed before egg retrieval, typically on the day before or on the day of the hCG trigger. In hormone replacement therapy frozen embryo transfer (HRT FET) cycles, endometrial thickness was taken from the last ultrasound before starting vaginal progesterone, preferably demonstrating a measure of 6 mm or more.

Although in our unit endometrial thickness is not assessed in natural cycles with frozen embryo transfer (NAT FET) cycles, these cycles were included for some of the preliminary analyses to explore the impact of different ART treatment modalities on placenta praevia risk. All demographic data, including age, BMI, smoking data, parity and aetiology of infertility were obtained from the Monash IVF database.

**ART protocols**

Stimulation regimens were used with or without the oral contraceptive pill scheduling. The regimens all used recombinant FSH for ovarian stimulation. Down-regulation was achieved with either a GnRH agonist or a GnRH antagonist. Ovarian stimulation was monitored with serum levels of estradiol (E2), progesterone and LH and with TVUS performed by experienced sonographers supervised by a subspecialist in obstetrical and gynaecological ultrasound (Rombauts et al., 2011).

Oocyte retrievals were performed under IV sedation 38 h post hCG administration (either recombinant hCG Ovidrel (Merck Serono, Australia) at 250 µg or urinary hCG Pregnyl (MSD, Australia) at 10 000 IU). Oocytes were fertilized using either standard insemination or ICSI, and fertilization results were assessed at 16–20 h post sperm insemination. Embryos were cultured in a single 10 µl droplet in the COOK culture system (Cook Medical, Australia). Day 3 embryos were frozen at the cleavage stage using a propanediol slow freezing system and blastocysts were vitrified. Culture media and culture conditions remained unchanged throughout the study period.

A fresh single embryo transfer took place on Day 2, 3 (cleavage stage) or Day 5 (blastocyst stage). Luteal support consisted of either Cnione 8%, one pessaries 200 mg vaginally (Onion, Australia), or twice daily progesterone pessaries 200 mg vaginally (Orion, Australia).

All cryopreserved embryos were thawed on the day before transfer and cultured overnight. Frozen-thawed embryo transfer (FET) was usually performed in natural menstrual cycles with tracking of the LH surge in urine or serum without TVUS assessment of endometrial thickness. Women with oligomenorrhea or amenorrhea had artificial cycles induced with cyclical E$_2$ and TVUS assessment of the endometrial thickness. Vaginal progesterone treatment was commenced when the endometrial thickness was at least 6 mm.

All embryo transfers were performed under transabdominal ultrasound guidance and the embryos were transferred $\sim 1$ cm from the fundal endometrial surface.

**Statistical analysis**

Statistical analysis was performed using the Statistical Package for the Social Sciences v22 (IBM, Armonk, NY, USA). The primary outcome measure was the diagnosis of placenta praevia. Frequencies were compared using the Chi-square test, Fisher’s exact test or Kruskal–Wallis test. Continuous variables in multiple groups were compared with analysis of variance. The dataset contained two levels: the primary level was the treatment cycle. The secondary level was the patient, with multiple cycles per patient. These observations within the same patient may be correlated and therefore non-independent. To adjust for such within-patient correlations, generalized estimating equation (GEE) statistics were used with an independent working correlation matrix and Quasi-likelihood under the independence model criterion (QIC) and corrected Quasi-likelihood under the independence model criterion (QICC) to select the most appropriate multi-level binary logistic regression model and covariates to be retained in the final regression model. Both main effects and two-way interactions were explored. Unadjusted odds ratios (OR) and adjusted odds ratios (aOR) with their 95% confidence intervals (95% CI) are reported. A P-value of 0.05 was assumed for statistical significance.

**Regulatory approval**

This retrospective study was approved by the Human Research and Ethics Committee of the Monash Surgical Private Hospital (P07078, 25 November 2013). Written informed consent was not required.

**Results**

A total of 4007 women had 4537 singleton births, 2951 were from STIM; 355 were from HRT FET and 1231 were from NAT FET. Age, BMI and aetiologies of infertility did not differ significantly between groups (Table I). The endometrial thickness was significantly greater in the

| Table I Demographics for women with singleton births following single embryo transfer in fresh and frozen cycles.* |
|---|---|---|
| | STIM | HRT FET | NAT FET |
| | n = 2951 | n = 355 | n = 1231 |
| Age (years); mean $\pm$ SD | 34.2 $\pm$ 4.0 | 34.4 $\pm$ 3.9 | 35.0 $\pm$ 3.9 |
| Treatment cycle; median (range) | 1 (1–23) | 4 (1–23) | 3 (1–19) |
| BMI (kg/m$^2$); mean $\pm$ SD | 24.5 $\pm$ 5.0 | 24.3 $\pm$ 5.1 | 24.4 $\pm$ 4.4 |
| Previous births; median (range) | 0 (0–5) | 0 (0–3) | 0 (0–5) |
| Cigarettes per day; median (range) | 0 (0–20) | 0 (0–25) | 0 (0–25) |
| Endometriosis; n (%) | 217 (7.4) | 21 (5.9) | 78 (6.3) |
| Tubal; n (%) | 188 (6.4) | 27 (7.6) | 83 (6.7) |
| Male; n (%) | 1128 (38.2) | 132 (37.2) | 528 (42.9) |
| Unexplained; n (%) | 989 (33.5) | 91 (25.6) | 393 (31.9) |
| Other; n (%) | 368 (12.5) | 74 (20.8) | 126 (10.2) |
| Multiple causes; n (%) | 61 (2.1) | 10 (2.8) | 23 (1.9) |

*No statistically significant differences between groups.
STIM compared with the HRT FET group (P < 0.001). In this ART cohort a total of 145 women (3.2%) had placenta praevia, but the frequency was significantly lower in NAT FET cycles (Table II). The risk of placenta praevia was 1.9, 3.8, and 6.9% for women with an endometrial thickness of <9, 9–12 and >12 mm, respectively.

After univariate analysis of all patients (Table III), being a smoker (OR 2.33, 95% CI 1.01–5.36, P < 0.05) and having endometriosis (OR 2.01, 95% CI 1.27–3.19, P < 0.01), both known risk factors, were associated with a higher risk of placenta praevia. Conversely, placenta praevia was less common in women undergoing NAT FET (OR 0.44, 95% CI 0.27–0.70, P < 0.01) when compared with stimulated cycles, but interestingly, HRT FET cycles are not associated with a lower risk (OR 0.89, 95% CI 0.48–1.63), which suggests that exposure to supra-physiological levels of sex steroids may increase the risk. However, in women undergoing a STIM cycle the number of oocytes collected and maximum serum E2 levels did not have a statistically significant impact on the risk of placenta praevia. Similarly, parity and age were not associated with an increased risk of placenta praevia in this cohort.

For women in whom endometrial thickness was measured (STIM and HRT FET), we also assessed the association of endometrial thickness

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>OR 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blastocyst transfer</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cleavage stage transfer</td>
<td>0.71</td>
<td>0.47–1.08</td>
</tr>
<tr>
<td>Number of oocytes; median (range)</td>
<td>11 (1–54)</td>
<td>N/A</td>
</tr>
<tr>
<td>Blastocyst transfer; n (%)</td>
<td>2178 (73.8)</td>
<td>298 (83.9)</td>
</tr>
<tr>
<td>Endometrial thickness; mean ± SD</td>
<td>9.75 ± 2.48</td>
<td>8.07 ± 1.84</td>
</tr>
<tr>
<td>Placenta praevia; n (%)</td>
<td>112 (3.8)</td>
<td>12 (3.4)</td>
</tr>
</tbody>
</table>

E2: estradiol; N/A: not applicable.

1. P < 0.001, Kruskal–Wallis test.
2. P < 0.001, Student’s T-test.
3. P = 0.002, Chi-square test.

Table II: Main cycle characteristics (where applicable) for women with singleton births following single embryo transfer in STIM, HRT FET or NAT FET.

<table>
<thead>
<tr>
<th></th>
<th>STIM n = 2951</th>
<th>HRT FET n = 355</th>
<th>NAT FET n = 1231</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum E2; mean ± SD</td>
<td>4349 ± 3209</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Number of oocytes; median (range)</td>
<td>11 (1–54)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Blastocyst transfer; n (%)</td>
<td>2178 (73.8)</td>
<td>298 (83.9)</td>
<td>929 (75.5)</td>
</tr>
<tr>
<td>Endometrial thickness; mean ± SD</td>
<td>9.75 ± 2.48</td>
<td>8.07 ± 1.84</td>
<td>N/A</td>
</tr>
<tr>
<td>Placenta praevia; n (%)</td>
<td>112 (3.8)</td>
<td>12 (3.4)</td>
<td>21 (1.7)</td>
</tr>
</tbody>
</table>

Table III: Odds ratios of placenta praevia by univariate analysis of predictor variables based on data from all cycles (where applicable) or from subgroups.
with increased placenta praevia risk. When compared with an endometrial thickness of <9 mm (referred group), a measure of >12 mm was associated with a 4-fold risk of placenta praevia (OR 3.78, 95% CI 1.93–7.41, P < 0.01) and an endometrial thickness of 9–12 mm with a 2-fold increased risk (OR 1.99, 95% CI 1.10–3.60, P = 0.02) (Table III). Using predictors identified in the univariate analysis with P < 0.15, multivariate regression was performed in this subset (STIM and HRT FET). After adjusting for confounders, smoking, endometriosis and endometrial thickness remained statistically significant as independent risk factors for placenta praevia (Table IV).

To assess whether important explanatory variables may have been missed using this planned approach, we separately ran a multivariate analysis for the subset of women undergoing a STIM cycle including all the missed using this planned approach, we separately ran a multivariate analysis based on data from STIM and HRT FET cycles.

Table IV Adjusted ORs of placenta praevia by multivariate analysis based on data from STIM and HRT FET cycles.

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>aOR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial thickness</td>
<td>&lt;9 mm</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>9–12 mm</td>
<td>2.06</td>
<td>1.14–3.73</td>
</tr>
<tr>
<td></td>
<td>&gt;12 mm</td>
<td>3.84</td>
<td>1.95–7.56</td>
</tr>
<tr>
<td>Smoking</td>
<td>No</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2.58</td>
<td>1.07–6.24</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>No</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2.01</td>
<td>1.21–3.33</td>
</tr>
<tr>
<td>Blastocyst stage</td>
<td>I</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Cleavage stage</td>
<td>0.68</td>
<td>0.43–1.07</td>
<td>0.09</td>
</tr>
<tr>
<td>STIM</td>
<td>I</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>HRT FET</td>
<td>1.13</td>
<td>0.61–2.10</td>
<td>0.70</td>
</tr>
</tbody>
</table>

aOR, adjusted OR.

Discussion

This large retrospective cohort study of over 4000 women with >4500 singleton IVF births has found that endometrial thickness, endometriosis and smoking are all independent risk factors for developing placenta praevia after ART. Overall, age and parity were not associated with an increased risk in this cohort. For STIM cycles the number of oocytes collected or maximum E2 levels did not increase the risk, whereas NAT FET cycles were associated with a lower risk of placenta praevia.

The fact that both STIM and HRT FET were both associated with an increased risk compared with NAT FET suggests that the increased risk is not linked to the type of embryo transfer (fresh/frozen), but the type of endometrial preparation.

Perhaps the most intriguing finding from this study is that endometrial thickness appears to be a strong risk factor for developing placenta praevia after ART. To our knowledge, this is the first study to discover this association. The importance of endometrial thickness on success rates of ART on the other hand has been known for some time. A recent meta-analysis which included 22 studies of moderate quality found that clinical pregnancy rate was significantly lower when the endometrial thickness was ≤7 mm compared with when it was >7 mm (OR 0.42, 95% CI 0.27–0.67) (Kasius et al., 2014). While thicker endometrium may result in higher pregnancy rates, our study suggests that it may also be associated with an up to a 4-fold increase in placenta praevia risk. The underlying mechanism for this effect is not clear.

It may be that supra-physiological levels of sex steroids encountered during stimulation protocols may have an effect on the endometrial environment and hormonal milieu, influencing inherent endometrial function, gene expression and increasing the release of inflammatory cytokines at the time of implantation (Denison et al., 1999; Horcajadas et al., 2005). However, our study has found no significant association of E2 levels with placenta praevia risk. No data were available on luteal phase serum hormone concentrations such as progesterone, activin and inhibin, which may also have an impact on impaired placenta (Aghajanova et al., 2012; Clementi et al., 2013). However, any hormonal effects are expected to act globally on the endometrium and it is therefore difficult to understand how this would contribute to preferential implantation in the lower uterine cavity. Furthermore, Healy et al. noted that the type of luteal support (none, progesterone or luteal hCG) does not affect the relative risk of placenta praevia (Healy et al., 2010).

A thickened endometrium may also present a mechanical barrier for a smooth embryo transfer increasing the likelihood that the embryo is delivered lower in the uterine cavity. However, all the embryo transfers in this cohort were carried out in a standardized manner under transabdominal ultrasound guidance (Shamonki et al., 2005). This argument is further weakened by the observation that the risk of placenta praevia is also increased following gamete intra-Fallopian transfer treatment (Healy et al., 2010), where the embryo arrives in the uterine cavity via the natural route.

Historical reports have indicated that ‘transferred’ embryos may be found on the outside of the transfer catheter or in the cervical wash medium following transfer, indicating that embryos can be dislodged from the presumed site of transfer (Poundexter et al., 1986). In addition, it is plausible that inadvertent cervical stimulation occurs during embryo transfer which results in increased uterine peristalsis. If these peristaltic waves occur from the fundus towards the cervix (Ijland et al., 1996; Zhu et al., 2012, 2014), it is possible that a fundally placed embryo may be moved further down in the uterine cavity increasing the risk of placenta praevia. These same mechanisms, with uterine wave activity occurring in the opposite direction, may be responsible for the increased rate of ectopic pregnancy following ART (Zhu et al., 2014). There is certainly strong evidence that the frequency of the uterine contractions is...
increased following ovarian stimulation and that this lowers the chance of implantation (Zhu et al., 2012, 2014).

We also found that endometriosis was an independent risk factor for patients with placenta praevia, in line with findings from several other studies (Healy et al., 2010; Vercellini et al., 2012; Takemura et al., 2013; Carassou-Maillan et al., 2014). A study by Vercellini et al. assessed pregnancy outcomes after surgery for endometriosis and found that the incidence of placenta praevia was 25-fold increased in women with rectovaginal endometriosis, with lower rates for less severe forms of endometriosis (Vercellini et al., 2012). Previously, our group also reported that endometriosis increased the risk of placenta praevia after ART (aOR 1.7; 1.2–2.4) (Healy et al., 2010). A recently published study from France investigated women who had a singleton birth following ART, finding that women who had endometriosis had a significantly higher likelihood of placenta praevia during their pregnancy than those without endometriosis (4.9 versus 0.9%, respectively P < 0.0001) (Carassou-Maillan et al., 2014). There is again no direct evidence that explains the association between endometriosis and placenta praevia. It has, however, been shown that, here too, the presence of endometriosis can increase the irregularity of uterine wave-like contractions during the late follicular phase of the menstrual cycle, resulting in impaired movement of fluid through the uterus (Leyendecker et al., 1996; Kunz et al., 2000).

We recognize that the study has some weaknesses. The study is retrospective in nature and not all confounders have been accounted for. In particular, details on previous intrauterine surgery, a known risk factor, were not available. In the context of ART treatment there may also be as yet unknown confounders that may explain the observed association. In addition, ultrasound assessments were carried out in a two-dimensional plane by several highly trained operators measuring the endometrial thickness, the main independent variable, and some inter-observer variability may therefore be present (Martins et al., 2011).

Nevertheless, the strengths of this study are the large sample size, the fact that it was restricted to women with singleton births from single embryo transfers and that there was 100% follow-up for the primary outcome measure. No significant changes had occurred in the way embryos were cultured in the study time frame and we also accounted for the most important known confounders and performed a sensitivity analysis.

The findings are significant in that placenta praevia is a severe complication of pregnancy associated with increased risks of post-partum haemorrhage, placenta accreta and percreta, and peripartum hysterectomy. In view of the latter risk, Vercellini et al. (2012) have argued that Caesarean sections for women with endometriosis, especially those with severe disease, should be centralized in tertiary-care obstetric centres because of the increased surgical complexity associated with adhesions caused by the disease itself as well as previous surgery. If our new hypothesis is true that an increased endometrial thickness is a surrogate marker for uterine hypercontractility, it may be worthwhile exploring whether oxytocin antagonists can lower the risk of placenta praevia (Pierzynski, 2011). Clearly further studies are required to assess the validity of this approach. However, our findings also suggest that the increased risk of placenta praevia in ART can be reduced simply by considering an elective frozen embryo transfer (eFET) in a natural cycle. This strategy deserves special consideration in view of the growing evidence that eFET also provides a number of other maternal and neonatal benefits (Maheshwari and Bhattacharya, 2013; Evans et al., 2014).

In conclusion, we have presented the first study indicating that endometrial thickness in ART cycles is directly proportional to the risk of placenta praevia. Our study has also shown that this risk is independent of significant risk factors, such as smoking and endometriosis, and is not due to increased serum E2 concentrations, parity or age. We hypothesize that increased uterine peristalsis and placenta praevia may explain the observed increased risk of placenta praevia in ART and endometriosis. Further studies are needed to confirm that uterine peristalsis is increased in women with a thicker endometrium and endometriosis.

Authors’ roles
L.R. and C.M. were involved in the study design, implementation, data collection and analysis. L.R., E.B. and S.F. contributed to the preparation of the manuscript. All authors approved the final draft.

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Conflict of interest
S.F., C.M. and E.B. have no conflict of interest to declare. L.R. has a minority shareholding in Monash IVF and has received unconditional research and educational grants from MSD®, Merck-Serono® and Ferring®. He serves on an advisory board for MSD® and Ferring®.

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