The effect of small intramural uterine fibroids on the cumulative outcome of assisted conception

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BACKGROUND: This study aimed to evaluate the effect of small intramural fibroids on the cumulative pregnancy, ongoing pregnancy, live birth and implantation rates after three IVF/ICSI attempts. METHODS: The first three treatment cycles of women enrolled for IVF/ICSI over a 12-month period were analysed. Only patients with small (≤5 cm) intramural fibroids not encroaching upon the endometrial cavity were included in the fibroid group. Cox’s hazards regression was used to estimate the hazard ratio (HR) associated with the presence of intramural fibroids. RESULTS: During the study period, 322 women without fibroids (control group) and 112 women with fibroids (study group) underwent 606 IVF/ICSI cycles. The pregnancy, ongoing pregnancy and live birth rates in the study group were 23.6, 18.8 and 14.8% compared with 32.9, 28.5 and 24% in the control group, respectively (P < 0.05). Cox regression analysis showed that the pregnancy rate at each cycle was reduced by 39% (HR = 0.61, 95% CI = 0.39–0.95, P = 0.029) in the study group compared with the control group. The cumulative ongoing pregnancy rate was reduced by 43% (HR = 0.57, 95% CI = 0.35–0.91, P = 0.018), and the cumulative live birth rate was reduced by 47% (HR = 0.53, 95% CI = 0.32–0.87, P = 0.013) in the study group. After adjusting for confounding variables, the presence of fibroids was found to significantly reduce the ongoing pregnancy rate at each cycle of IVF/ICSI by 40% (HR = 0.60, 95% CI = 0.36–0.99, P = 0.048) and the live birth rate at each cycle by 45% (HR = 0.55, 95% CI = 0.32–0.95, P = 0.03). CONCLUSION: Small intramural fibroids are associated with a significant reduction in the cumulative pregnancy, ongoing pregnancy and live birth rates after three IVF/ICSI cycles.

Key words: ART/fibroids/hazard regression analysis/live birth/pregnancy

Introduction

Uterine fibroids can occur in up to 80% of women by the age of 50 years and are more common in certain ethnic populations (Cramer and Patel, 1990; Vollenhoven et al., 1990; Verkauf, 1992). Although most women affected with fibroids are fertile, fibroids may interfere with fertility secondary to anatomical distortion and alterations to the uterine environment (Hasan et al., 1990; Verkauf, 1992), with the effect being dictated largely by the location and size of the fibroid (Ubaldi et al., 1995; Rackow and Arici, 2005).

With respect to IVF treatment, fibroids have been implicated in reduced treatment outcome (Stovall et al., 1998; Bernard et al., 2000; Hart et al., 2001) as well as increased risk of pregnancy loss (Buttram and Reiter, 1981; Li et al., 1999). Indeed, it has been shown that submucosal fibroids can adversely affect implantation rate and pregnancy outcome in assisted reproduction cycles (Farhi et al., 1995; Eldar-Geva et al., 1998; Pritts, 2001) and that IVF outcome is markedly improved in women with submucosal fibroids following myomectomy (Narayan and Goswamy, 1994; Hart et al., 1999; Varasteh et al., 1999; Bernard et al., 2000; Surrey et al., 2005).

However, the effect of fibroids not encroaching on the uterine cavity (i.e. intramural or subserosal) on the outcome of IVF treatment remains controversial, and the means by which they might affect fertility are less obvious (Bajekal and Li, 2000; Surrey, 2003). Eldar-Geva et al. (1998) showed that pregnancy and implantation rates were significantly lower in women with intramural, but not subserosal, fibroids. Likewise, Stovall et al. (1998), Bernard et al. (2000), Surrey et al. (2001) and Benecke et al. (2005) found a significant decrease in implantation and/or delivery rates in those with intramural fibroids undergoing IVF/ICSI compared with age-matched controls. On the contrary, Ramzy et al. (1998) reported that fibroids <7 cm in diameter that did not encroach on the uterine cavity had no effect on implantation or miscarriage rates in IVF/ICSI cycles. Dietterich et al. (2000), Jun et al. (2001), Ng and Ho (2002) and Yarali and Bukulmez (2002) also found that IVF/ICSI outcome was not affected by the presence of intramural or subserosal fibroids. Check and colleagues
Demographic data before starting the first cycle of treatment

More recently, Oliveira et al. (2004) showed that women with small subserosal or intramural fibroids not encroaching on the cavity had similar pregnancy, implantation and miscarriage rates compared with matched controls. However, most of these studies were retrospective, made little distinction between intramural and subserosal fibroids and assessed patient performance during one treatment cycle only.

The aim of the current study was to evaluate the effect of small intramural fibroids on the cumulative pregnancy, ongoing pregnancy, live birth and implantation rates after three fresh IVF/ICSI attempts in a controlled setting. This follows our initial prospective study (Hart et al., 2001), where we studied the effect of intramural fibroids of ≤5 cm (mean size 2.3 cm) on the outcome of one cycle of IVF/ICSI.

**Materials and methods**

**Study population**

All women enrolled in our previous study (Hart et al., 2001) were included in the current study, according to the protocol previously described (Hart et al., 2001). Table I summarizes the causes of infertility in the study population. Their first three IVF/ICSI treatment cycles from the date of enrolment (between 1 August 1999 and 31 July 2000) to November 2003 were analysed.

**Uterine evaluation**

All patients underwent transvaginal ultrasound evaluation before IVF/ICSI treatment. Patients in whom a uterine fibroid was reported were further evaluated for its exact position. If it appeared in proximity to the endometrial cavity, saline hysterosonography or hysteroscopy was performed as previously described (Hart et al., 2001). Only patients with intramural fibroids not encroaching on the endometrial cavity were included in the study. Submucosal fibroids were found, patients were referred for hysteroscopic resection and excluded from the study.

A fibroid was considered to be subserosal if >50% of its volume protruded from the serosal surface of the uterus, as previously described (Li et al., 1999). The mean number of fibroids in the study group was 1.8 ± 0.8 and mean size of the largest fibroid was 2.3 ± 1.1 cm. None of the patients underwent myomectomy during the study or follow-up period.

**IVF/ICSI and embryo transfer**

Ovarian stimulation and IVF/ICSI protocols were performed as described previously (Hart et al., 2001). Between one and three embryos were replaced 2–3 days after oocyte retrieval using an Edwards-Wallace embryo replacement catheter (Sims Portex Ltd, Hythe, Kent, UK) replacing the best grade cleavage-stage embryos under abdominal ultrasound control.

**Cycle outcome**

Pregnancy was diagnosed by a positive urine test for hCG approximately 14 days after embryo transfer. A clinical pregnancy was defined as the observation on ultrasound scanning of a gestational sac with fetal heart beat between 4 and 5 weeks after the positive pregnancy test. All pregnancies were followed to delivery. Implantation rate was defined as the number of gestational sacs observed on ultrasound compared with the number of embryos transferred.

**Statistical analysis**

The study results were analysed using survival analysis, with the discrete time-variable being the cycle number. Women were included in the study until the first live birth or until the third cycle. Certain co-variates changed with each cycle such as patient age, number of oocytes retrieved, number of embryos available for replacement and number of embryos replaced.

Cox’s proportional hazards regression was used to estimate the hazard ratio (HR) associated with each predictor of interest, adjusted for confounding by multiple regression analysis. In this study, HR represents the relative degree to which the pregnancy rate is reduced on average at each cycle. The implantation rate per embryo transferred was considered using logistic regression, giving equal weight to each cycle. Standard errors were adjusted for clustering by woman.

All analyses were carried out using the statistical software package Stata version 8.2 (StataCorp, College Station, Texas, USA). All results were presented as estimates, with 95% confidence intervals (CI). A P-value of <0.05 was considered significant when ‘no effect’ (i.e. difference in means = 0 or HR = 1) was not in the interval.

**Results**

During the study period, 322 women without fibroids (control group) and 112 women with intramural fibroids (study group) were treated. The first, second and third cycles of treatment completed by women following enrolment in the study were included in the final analysis—a total of 606 fresh IVF/ICSI cycles.

Demographic characteristics at the time of the first cycle showed that both groups were similar in terms of duration of infertility, number of previous treatment cycles and FSH concentration before the first cycle of treatment was started (Table I). Age was significantly different at the time of enrolment between the two groups, being on average 1.8 years greater in the study group (36.4 versus 34.6 years, P < 0.01).

The pregnancy, ongoing pregnancy and live birth rates in the study group were 23.6, 18.8 and 14.8% compared with 32.9, 28.5 and 24% in the control group, respectively (P < 0.05). Using Cox regression analysis, the pregnancy rate at each cycle was reduced by 40% in the study group compared with the control group (HR = 0.60, CI = 0.38–0.93, P = 0.022). This effect was also seen in the cumulative ongoing pregnancy rate, which was reduced by 43% (HR = 0.57, CI = 0.35–0.91, P = 0.018), and the live birth rate, which was reduced by 47% (HR = 0.53, CI = 0.32–0.87, P = 0.013) in the study group.

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**Table I. Demographic data before starting the first cycle of treatment**

<table>
<thead>
<tr>
<th></th>
<th>Fibroids group (n = 112)</th>
<th>Control group (n = 322)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at start of treatment (years)</strong></td>
<td>36.4 ± 3.9</td>
<td>34.6 ± 3.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Duration of infertility (years)</strong></td>
<td>3.6 ± 3.5</td>
<td>3.2 ± 3.7</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Number of previous IVF/ICSI cycles</strong></td>
<td>0.6 ± 1.2</td>
<td>0.7 ± 1.1</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Pretreatment basal FSH (IU/l)</strong></td>
<td>7.6 ± 10.7</td>
<td>7.9 ± 10.8</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Cause of infertility, number (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male factor</td>
<td>39 (34.8)</td>
<td>126 (39)</td>
<td>0.42</td>
</tr>
<tr>
<td>Tubal damage</td>
<td>34 (30.4)</td>
<td>78 (24.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Unexplained</td>
<td>19 (17)</td>
<td>64 (19.8)</td>
<td>0.50</td>
</tr>
<tr>
<td>Other^</td>
<td>20 (17.8)</td>
<td>54 (17.7)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

^Anovulation, endometriosis or not recorded. Data are given as mean ± SD or as indicated.
Cox regression analysis was then performed to study the influence of fibroids on the outcome of IVF/ICSI treatment after controlling for confounders. Variables analysed included the presence of an intramural fibroid, age as a continuous variable (i.e. the effect of each additional year of age on outcome), number of oocytes collected and number of embryos available for transfer and replaced. As data from the previous study showed that the effect of age was largely limited to a reduced chance of pregnancy in women over 40 years of age (Hart et al., 2001), age ≥40 years was also included in the Cox regression analysis as a possible confounder.

When age (as a continuous variable), age ≥40 years, number of oocytes collected, number of embryos available for transfer, number of embryos replaced and the presence of intramural fibroids were controlled for, the number of embryos available for transfer and presence of fibroid remained as significant variables influencing pregnancy rate, with the presence of intramural fibroids showing a trend towards reduction in the pregnancy rate at each cycle (HR = 0.66, CI = 0.41–1.06, \( P = 0.08 \) ) (Figure 1).

Likewise, when Cox regression was carried out for ongoing pregnancy and live birth rates, and after controlling for age (as a continuous variable), number of oocytes collected and number of embryos available for transfer and replaced, intramural fibroids were found to reduce significantly the ongoing pregnancy rate at each cycle of IVF/ICSI by a factor of 40% (HR = 0.60, CI = 0.36–0.99, \( P = 0.048 \) ) (Table II, Figure 2) and the live birth rate at each cycle by a factor of 45% (HR = 0.55, CI = 0.32–0.95, \( P = 0.030 \) ) (Table II, Figure 3). Similarly, when age ≥40 years was controlled for, there was a significant reduction in the ongoing pregnancy rate in the fibroid group by 42% (HR = 0.58, CI = 0.36–0.93, \( P = 0.024 \) ) and in the live birth rate in the fibroid group by 45% (HR = 0.55, CI = 0.33–0.92, \( P = 0.022 \) ).

Binomial regression was then used to analyse the effect of intramural fibroids on implantation rate (Table III). This

| Table II. Hazard ratios (HR) by Cox regression analysis for the chance of an ongoing pregnancy or a live birth in women with an intramural fibroid = 5 cm in size, adjusted for the number of embryos available for transfer and age or age = 40 years |
|------------------|------------------|------------------|
|                  | HR   | 95% CI        | \( P \)-value |
| Uncontrolled effect of the presence of fibroids |
| Ongoing pregnancy | 0.57 | 0.35–0.91     | 0.018          |
| Live birth       | 0.53 | 0.32–0.87     | 0.013          |
| Effect of fibroids adjusted for the number of embryos available and age |
| Ongoing pregnancy | 0.60 | 0.36–0.99     | 0.048          |
| Live birth       | 0.55 | 0.32–0.95     | 0.030          |
| Effect of fibroids adjusted for number of embryos available and age ≥40 years |
| Ongoing pregnancy | 0.58 | 0.36–0.93     | 0.024          |
| Live birth       | 0.55 | 0.33–0.92     | 0.022          |

CI, confidence interval.

Figure 2. Kaplan–Meier survival analysis of the effect of the presence of fibroids on the proportion of women achieving an ongoing pregnancy.

Figure 3. Kaplan–Meier survival analysis of the effect of the presence of fibroids on the proportion of women achieving a live birth.
Logistic regression analysis for implantation rate in women with intramural fibroids ≤5 cm in size

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled effect of the fibroid</td>
<td>0.73</td>
<td>0.47–1.11</td>
<td>NS</td>
</tr>
<tr>
<td>Controlled for embryos available and age as a continuous variable</td>
<td>0.74</td>
<td>0.47–1.17</td>
<td>NS</td>
</tr>
<tr>
<td>Controlled for embryos available and age ≥40 years</td>
<td>0.74</td>
<td>0.47–1.15</td>
<td>NS</td>
</tr>
</tbody>
</table>

CI, confidence interval; NS, non-significant.

Table III.

showed a trend towards a reduction in the implantation rate in the study group after controlling for the confounders, although this did not reach significance at the 95th CI.

The miscarriage rate was also studied and found to be 28.9% (57/197). The difference between the miscarriage rate in the study group (36.1%, 13/36) and that in the control group (27.3%, 44/161) was not statistically significant (P = 0.29).

Finally, during the study period 86 frozen embryo transfers took place: 22 transfers in the study group and 64 in the control group. Although the pregnancy rate in the study group was 45% lower than that in the control group (18 versus 33%), that difference did not reach statistical significance (P = 0.1) probably due to the small number of patients who had a frozen embryo transfer in the study.

Discussion

This is the first large prospective controlled study of the influence of small intramural fibroids on the cumulative outcome of up to three attempts of IVF/ICSI treatment (Wang et al., 2001). Results show that small intramural fibroids reduce the pregnancy rate at each IVF/ICSI cycle by 40%, the cumulative ongoing pregnancy rate by 45% and the cumulative live birth rate by 49%.

These findings are in agreement with those from our first study (Hart et al., 2001), which showed that small intramural fibroids have a negative effect on the outcome of one IVF/ICSI cycle, reducing the chance of achieving an ongoing pregnancy after controlling for confounding variables. The results also complement those of the only other two prospective matched controlled studies conducted so far (Stovall et al., 1998; Check et al., 2002), which observed lower live birth rates in women with small (≤5 cm) intramural fibroids undergoing IVF.

This study also lends support to retrospective reports highlighting the impact of intramural fibroids on the outcome of assisted conception. Healy (2000) found that women with intramural and subserosal fibroids with no cavity distortion had significantly lower clinical pregnancy rates than women with no fibroids. Likewise, the clinical pregnancy rate following IVF/ICSI treatment was found to be significantly reduced in women with intramural fibroids compared with controls and those with only subserosal fibroids (Eldar-Geva et al., 1998). Gianaroli et al. (2005) studied the impact of the presence of small fibroids in 75 patients undergoing 129 IVF/ICSI cycles compared with a control group of 127 women without fibroids. Lower implantation rate was found in the fibroid group, although no distinction was made in the study between intramural and submucosal fibroids.

The mechanisms by which small intramural fibroids exert their adverse effect on the success rate of IVF are unclear but may include altered myometrial contractility, uterine vascular distortion (Ng et al., 2005), endometrial inflammation, thinning and atrophy (Verkauf, 1992) as well as exerting an adverse effect on gamete migration (Donnez and Jadoul, 2002; Nishino et al., 2005). Recently, alterations in gene expression (particularly those regulating retinoid synthesis and insulin-like growth factors metabolism) were found in myoma tissue compared with adjacent normal myometrium (Arslan et al., 2005). Because the same genes are involved in implantation (Zheng et al., 2000; Tamura et al., 2004) and post-implantation embryonic development (Glabowski et al., 2005), these findings may provide a link between the presence of fibroids and adverse reproductive outcome (Surrey, 2003).

Despite the growing body of evidence in favour of a negative impact of intramural fibroids on IVF/ICSI outcome, it is unclear whether this impact can be reversed by myomectomy (Pritts, 2001; Check et al., 2002). Whereas women with large subserosal or intramural fibroids have been shown to have increased pregnancy and delivery rates and decreased miscarriage rates after myomectomy (Dubuisson et al., 1996; Li et al., 1999; Bajekal and Li, 2000; Campo et al., 2003; Bulletti et al., 2004; Marchionni et al., 2004), exposure of women with small intramural fibroids to the risks of myomectomy with the sole aim of improving reproductive performance remains controversial (Seoud et al., 1999; Surrey, 2003). With such lack of definitive data, patients with intramural fibroids are left to embark on repeated IVF attempts in order to achieve similar outcome to those with no fibroids, as previously suggested (Gianaroli et al., 2005). Our results can help to counsel these women regarding the reduced cumulative outcome after up to three IVF attempts.

Finally, future research into the reproductive performance of women with small intramural fibroids following myomectomy should also consider the influence of other factors, such as female age and duration of infertility, on reproductive outcome after surgery (Vercellini et al., 1999; Marchionni et al., 2004; Kumakiri et al., 2005).

In conclusion, small intramural fibroids are associated with a significant reduction in the cumulative pregnancy, ongoing pregnancy and live birth rates in women undergoing three cycles of IVF/ICSI compared with controls. This can have important implications, particularly for women failing to conceive after their first IVF cycle and considering further treatment attempts.

References


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