Human Reproduction, Vol.26, No.12 pp. 3274–3279, 2011
Advanced Access publication on September 27, 2011 doi:10.1093/humrep/der293

human reproduction

ORIGINAL ARTICLE *Early pregnancy*

The prevalence and impact of fibroids and their treatment on the outcome of pregnancy in women with recurrent miscarriage

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Submitted on June 22, 2011; resubmitted on July 17, 2011; accepted on August 9, 2011

BACKGROUND: Although uterine fibroids have been associated with spontaneous miscarriage, to our knowledge there have been no studies in the literature assessing their role in the recurrent miscarriage (RM) population. The aims of this study are to examine the impact of different types of fibroids on the pregnancy outcome of women with RM and to investigate to what extent resection of fibroids distorting the uterine cavity affects the outcome of a future pregnancy.

METHODS: The study analysed retrospective and prospective data from a large tertiary referral RM clinic. Couples were investigated as per an established protocol. Fibroids were diagnosed using combined transvaginal ultrasound and hysterosalpingography. Fibroids distorting the uterine cavity were resected via hysteroscopy. Two study groups were subsequently examined: women with cavity-distorting fibroids who underwent surgery ($n = 25$) and women with fibroids not distorting the cavity who did not undergo any intervention ($n = 54$). The latter was compared with a control group of women with unexplained RM ($n = 285$).

RESULTS: The prevalence of fibroids was found to be 8.2% (79/966). In total, 264 pregnancies of women with fibroids and 936 pregnancies of women with unexplained RM were analysed. Women with intracavitary distortion and undergoing myomectomy significantly reduced their mid-trimester miscarriage rates in subsequent pregnancies from 21.7 to 0% ($P < 0.01$). This translated to an increase in the live birth rate from 23.3 to 52.0% ($P < 0.05$). Women with fibroids not distorting the cavity behaved similarly to women with unexplained RM achieving a 70.4% live birth rate in their subsequent pregnancies without any intervention.

CONCLUSIONS: Fibroids are associated with increased mid-trimester losses amongst women with RM. Resection of fibroids distorting the uterine cavity can eliminate the mid-trimester losses and double the live birth rate in subsequent pregnancies. Women with fibroids not distorting the uterine cavity can achieve high live birth rates without intervention.

Key words: fibroids / myomectomy / recurrent miscarriage / pregnancy outcome

Introduction

Recurrent miscarriage (RM) affects ~1% of couples and may be defined as three or more consecutive pregnancy losses at <24 weeks of gestation (Rai and Regan, 2006). RM is largely a heterogeneous condition thought to be caused by chromosomal, thrombotic, uterine, hormonal and immunological abnormalities (Christiansen *et al.*, 2005). However, following thorough investigation, it is estimated that ~50% of patients have no cause identified and are therefore classified as having unexplained RM (Li *et al.*, 2002).

The prevalence of fibroids is difficult to determine, as their incidence increases with age. In the general population, it is estimated that the prevalence ranges 3–10% for women of reproductive age (Borgfeldt and Andolf, 2000; Laughlin *et al.*, 2009). In the infertile population, the prevalence has been reported to be 1–2.4% (Buttram and Reiter, 1981; Verkauf, 1992). The prevalence in the RM population is not known, as to our knowledge there have been no studies reporting it in the literature. As a result, the epidemiological association between fibroids and RM is unclear.

Whilst fibroids may contribute to miscarriage (Lumbiganon *et al.*, 1996; Benson *et al.*, 2001; Sheiner *et al.*, 2004), it is recognized that

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different types of fibroid may affect the reproductive outcome to a different degree. Specifically, it is generally accepted that submucosal, intramural and subserosal fibroids interfere with fertility in a decreasing order of importance (Bajekal and Li, 2000; Somigliana *et al.*, 2007). However, whilst a number of meta-analyses have recently been published to address the relationship between uterine fibroids and infertility (Bajekal and Li, 2000; Donnez and Jadoul, 2002; Pritts *et al.*, 2009), the relationship between fibroids and RM has not previously been examined.

The finding of a fibroid in women with RM raises two specific questions: First, is the fibroid the cause of the repeated miscarriage or an incidental finding? Secondly, is removal of the fibroid necessary to improve the outcome? In this retrospective cohort study involving a group of women with RM, we attempt to compare patterns of miscarriage and the results of expectant versus surgical treatment between women with and without uterine fibroids, with a view to understanding whether the relationship of fibroids and RM is a casual or causal one.

Materials and Methods

Recruitment

All the women included in the study ($n = 364$) attended the Sheffield RM Clinic (Jessop Hospital, Sheffield, UK). This is a tertiary referral centre for women suffering three or more consecutive miscarriages up to 24 weeks of gestational age. A detailed history was taken to include comprehensive details of previous pregnancy losses and to establish potential risk factors in the preconception period. All patients subsequently underwent investigations according to an established protocol (Li, 1998), which included karyotyping of both partners, thrombophilia screening, autoimmune testing, endocrine studies and investigations for uterine anomalies.

Diagnosis and treatment

Patients were first screened for uterine anomalies using a combined transvaginal two-dimensional ultrasound (2D US) and hysterosalpingography approach. Fibroids were diagnosed and grouped according to a classification previously described in the literature (Bajekal and Li, 2000). Fibroids were classified as submucosal if they distorted the uterine cavity, intramural if they did not distort the cavity and had <50% protrusion into the serosal surface, and subserosal if they did not distort the cavity and had >50% protrusion out of the serosal surface. It has been the policy of the unit to offer hysteroscopic surgery to all women with submucosal fibroids, while intramural and subserosal fibroids are not routinely operated on. Occasionally, large intramural fibroids >50 mm may be considered for abdominal resection, but this is considered on an individual basis, while taking into account the reproductive history. In the present study, fibroids were resected from 22 patients via hysteroscopy alone, while 3 patients required laparoscopy/laparotomy for resection of multiple large fibroids that had a significant submucosal component. All operations were performed or supervised by the senior author (T.-C.L.) ensuring homogeneity in the surgical technique for all patients.

Fibroid details

Details were retrieved for all patients from a purpose-designed database of the Sheffield RM Clinic. Trained staff systematically update the database on every patient visit and following every investigation and intervention. In this study, notes for each patient were additionally reviewed by two investigators (S.H.S. and H.R.) to include detailed information on fibroid type, size and location. With regard to fibroid size, dimensions were recorded across three axes (x, y and z), while for analysis purposes the largest recorded diameter was considered.

Study and control groups

This trial included two study groups and one matched control group.

(i) A study group of women with fibroids distorting the uterine cavity who underwent myomectomy. This group did not have a control group for comparison.
(ii) A study group of women with fibroids not distorting the uterine cavity who did not undergo any intervention. This group was matched to a control group of women with unexplained RM who also did not undergo any intervention.

Pregnancy outcomes

Rather than using the traditional miscarriage versus live birth outcomes, detailed outcomes of all pregnancies were established, to help better describe the timing at which the pregnancies were compromised. This was achieved through a comprehensive review of patient records and antenatal US findings, and correspondence with referring clinicians and hospitals where necessary. As a result, the following pregnancy outcomes were analysed:

(i) Biochemical loss: occurring before the sixth week of gestation with no US evidence of an intrauterine pregnancy.
(ii) Early first trimester loss (<6 weeks): occurring after US evidence of a gestational sac with or without a fetal pole, but with fetal heart beats never having been demonstrated.
(iii) Late first trimester loss (6–12 weeks): occurring in the first trimester after the detection of fetal heart beats.
(iv) Mid-trimester loss: occurring between 13 and 24 weeks of gestation.
(v) Live birth: viable fetus after 24 weeks of gestation.

To reduce bias, only the first pregnancies occurring following referral were analysed. Stillbirths, ectopic pregnancies and terminations were excluded from the analysis as the numbers were negligible.

Statistical analysis

All data on patient demographics and pregnancy outcomes were entered and analysed in SPSS for Windows (Version 19.0, SPSS Inc., IL, USA). Continuous variables were assessed for equality of variance using Levene's test and subsequently analysed using the Student's t-test. Discrete variables were analysed using Pearson's χ^2 test and Fisher's exact test. Statistical significance was determined at $P < 0.05$.

Results

Following investigations, 8.2% (79/966) of women were found to have fibroids. The incidence of submucosal fibroids was 2.6% (25/966), whilst the incidence for intramural/subserosal fibroids was 5.6% (54/966). In total, 264 pregnancies of women with fibroids and 936 pregnancies of women with unexplained RM were analysed.

Patient characteristics

The patient demographics were similar in all three groups apart from the patient age. The average age for women with fibroids was 36.0 (range 24–42), versus 31.4 (range 20–48) for women with unexplained RM ($P < 0.05$). Patients with fibroids that distorted the uterine cavity and were resected had either only submucosal or mixed submucosal/intramural fibroids (64.0 and 36.0%, respectively).

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Patients with fibroids that did not distort the cavity and were therefore not resected had either intramural, subserosal or mixed intramural/subserosal fibroids (42.6, 35.2 and 22.2%, respectively). The fibroid number and size was not significantly different between the two groups. The patient characteristics are presented in Table I.

In women with submucosal fibroids, 16% reported dysmenorrhoea and 32% reported heavy bleeding prior to myomectomy, which subsequently improved following surgery. The average haemoglobin level did not change significantly from the preoperative assessment period until 12 months following surgery (13.1 versus 12.9 g/dl, respectively).

Comparison of outcome prior to referral

Prior to referral, women with fibroids distorting the uterine cavity showed a total miscarriage rate of 76.7% (46/60) and a live birth rate of 23.3% (14/60). In terms of pregnancy losses, mid-trimester miscarriage rates were significantly increased compared with the group of women with unexplained RM (21.7 versus 8.0%; $P < 0.01$) (Table II).

For women with fibroids not distorting the uterine cavity, the total miscarriage rate was 79.4% (100/125) and the live birth rate was 20.6% (25/125) prior to referral. These women also showed a significantly higher rate of mid-trimester miscarriages compared with the control group, although to a lesser extent (17.6 versus 8.0%, respectively; $P < 0.01$). They were also found to have a significantly lower early first trimester miscarriage rate (28.8 versus 39.0%; $P < 0.05$) (Table III).

Comparison of outcome after referral

Women with fibroids distorting the uterine cavity conceived after a mean of 6.4 months (range 2–18 months) following myomectomy. In the first pregnancy for each woman following surgery, the mid-trimester loss rate dropped from 21.7 to 0.0% ($P < 0.01$). This translated into a significant increase in the live birth rate from 23.3 to 52.0% ($P < 0.05$) (Table II).

In women with fibroids not distorting the uterine cavity, the live birth rate after referral reached 70.4% with no intervention. This was similar to the live birth rate observed for women with unexplained RM after referral (70.4 versus 71.9%), respectively. This result did not change significantly when analysing women with intramural and subserosal fibroids separately, with the post-referral live birth rates reaching 73.9% (17/23) and 78.9% (15/19), respectively. Following referral, the types of pregnancy loss, including mid-trimester miscarriages, were also similar to that of the control group (Table III).

Table I Patient demographics in different patient groups.

	Unexplained RM ($n = 285$)	Fibroids distorting the cavity ($n = 25$)	Fibroids not distorting the cavity ($n = 54$)
Age (years)	31.4 (20–48)	36.4* (24–42)	35.8** (28–41)
BMI	25.4 (18.1–26.6)	24.6 (20.2–29.7)	23.9 (19.2–30.7)
Cycle length (days)	28.7 (21–39)	27.1 (21–29)	30.2 (27–37)
Fibroid diameter (mm)		19.9 (7–56)	22.6 (8–78)
Fibroid number		2.6 (1–8)	1.5 (1–5)
Fibroid type (distribution)			
Submucosal		64.0%	0.0%
Intramural		0.0%	42.6%
Subserosal		0.0%	35.2%
Mixed		36.0%	22.2%

Continuous variables expressed in mean (range).
Discrete variables expressed in percentage.
*$P < 0.05$.
**$P < 0.01$.

Table II Pregnancy outcome in women with fibroids distorting the uterine cavity.

Pregnancies	Biochemical loss	First trimester loss		Mid-trimester loss	Live birth
		Early	Late		
Prior resection ($n = 60$)	8 (13.3%)	19 (31.7%)	6 (10.0%)	13 (21.7%)	14 (23.3%)
First post-resection ($n = 25$)	2 (8.0%)	7 (28.0%)	3 (12.0%)	0 (0.0%)*	13 (52.0%)**

Expressed in n (%).
*$P < 0.01$.
**$P < 0.05$.

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Table III Pregnancy outcome in women with fibroids not distorting the uterine cavity.

Pregnancies	Biochemical loss	First trimester loss		Mid-trimester loss	Live birth
		Early	Late		
Prereferral					
Unexplained RM ($n = 651$)	137 (21.0%)	254 (39.0%)	74 (11.4%)	52 (8.0%)	134 (20.6%)
Extracavitary fibroids ($n = 125$)	25 (20.0%)	36 (28.8%)*	17 (13.6%)	22 (17.6%)**	25 (20.0%)
First post-referral					
Unexplained RM ($n = 285$)	13 (4.6%)	34 (11.9%)	28 (9.8%)	5 (1.8%)	205 (71.9%)
Extracavitary fibroids ($n = 54$)	4 (7.4%)	6 (11.1%)	6 (11.1%)	0 (0.0%)	38 (70.4%)

Expressed in *n* (%).
*$P < 0.05$.
**$P < 0.01$.

Discussion

For over a decade, there has been great interest in the role of uterine fibroids in infertility, with several systematic reviews concluding that submucosal, intramural and subserosal fibroids may cause infertility in a decreasing order of importance (Bajekal and Li, 2000; Mukhopadhaya *et al.*, 2007; Somigliana *et al.*, 2007; Pritts *et al.*, 2009). However, although a link between fibroids and spontaneous miscarriage has been described, it has not been established to what extent these benign tumours may cause pregnancy loss in women who have no significant problem conceiving.

Fibroids as a cause for miscarriage

To date, only a few studies have reported a link between fibroids and spontaneous miscarriage in the general population (Lumbiganon *et al.*, 1996; Benson *et al.*, 2001; Sheiner *et al.*, 2004). Interestingly, the overwhelming majority of studies in the literature reporting an increase in spontaneous miscarriage rates involve women undergoing IVF. Unfortunately, their main outcome measures have been focusing more on pregnancy rates rather than miscarriage rates, while only a few have made a distinction between different types of fibroids. A recent systematic review found the spontaneous miscarriage rate to be higher in women with submucosal and intramural fibroids (in descending order) undergoing IVF, compared with women with no fibroids; however, only 11 controlled studies were analysed (Klatsky *et al.*, 2008). Another systematic review found three controlled studies reporting on pregnancy outcomes of women with subserosal fibroids undergoing IVF, reporting overall pregnancy and delivery rates similar to those of women with no fibroids (Somigliana *et al.*, 2007). Consequently, it would appear that submucosal, intramural and subserosal fibroids may also cause spontaneous miscarriage in a decreasing order of importance, although there is a definite need for further well-designed studies to delineate this.

Perhaps the most convincing evidence that fibroids may cause spontaneous miscarriage stems from studies that have reported a significant reduction in miscarriage rates following abdominal myomectomy. A prominent review over 30 years ago first showed that spontaneous miscarriage rates decreased from 41 to 19% post-myomectomy (Buttram and Reiter, 1981). Further relatively small studies have more recently reinforced this finding, showing reductions in miscarriage rates following abdominal myomectomy in the order of 40–60% (Li *et al.*, 1999; Vercellini *et al.*, 1999a; Campo *et al.*, 2003; Marchionni *et al.*, 2004). In terms of hysteroscopic resection of submucosal fibroids, the data are more sparse. Shokeir (2005) in a study of 29 women compared pre- and post-hysteroscopy miscarriage rates and found a reduction from 73.1 to 26%. Other studies have reported only post-operative miscarriage rates and have found them to be in the order of 8–32% (Giatras *et al.*, 1999; Varasteh *et al.*, 1999; Vercellini *et al.*, 1999b; Bernard *et al.*, 2000).

Unfortunately, all the studies so far concerning hysteroscopic and abdominal myomectomy have not had a control group of women with fibroids not undergoing surgery. As a result, definitive conclusions on the impact of myomectomy on the pregnancy outcomes cannot be drawn.

Fibroids and RM

To our knowledge, there are no studies in the literature describing the pregnancy outcomes of women with RM and fibroids, whether treated or untreated. We feel this is an area that requires urgent attention for three main reasons. First, other anomalies of the uterus, such as congenital abnormalities have been found to be strongly associated with RM (Grimbizis *et al.*, 2001; Saravelos *et al.*, 2008). Secondly, fibroids have been associated with spontaneous miscarriages. Thirdly, myomectomy has been shown to reduce spontaneous miscarriage rates in the general population and in women with infertility. As a result, women with fibroids and RM may benefit the most if effective evidenced-based treatment is established.

Fibroids distorting the cavity have been shown to have the largest impact on fertility, implantation and possibly pregnancy loss and can be corrected safely via hysteroscopy, a minimally invasive procedure. For this reason, in our centre we offer hysteroscopy to all women with submucosal fibroids and RM in a 'see and treat' manner. We do not routinely perform myomectomy for intramural and subserosal fibroids that do not distort the uterine cavity, although occasionally laparoscopy/laparotomy may be performed for large or multiple intramural fibroids >50 mm.

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Insights from the study and clinical implications

In the present study, it was shown that the prevalence of fibroids in an RM population is ~8.2%, higher than that reported for women with infertility.

For women with fibroids distorting the uterine cavity, results show that, prior to referral, one in five pregnancies end in a mid-trimester loss, significantly higher than that observed in women with no uterine anomalies. As a result, any woman presenting with a previous history of mid-trimester loss should undergo thorough investigation for the presence of a fibroid. Our data show that following myomectomy, the mid-trimester losses may be eliminated and translated into an equivalent increase in the live births. The rates of first trimester miscarriages remain the same post-myomectomy, suggesting that the intervention specifically resolved the problem of mid-trimester miscarriage. As a result, we would recommend offering hysteroscopic surgery to all women with a history of one or more mid-trimester pregnancy losses. In women with a history of first trimester losses only, the role of surgery is debatable.

With regard to women with fibroids not distorting the uterine cavity, our results demonstrate that prior to referral they also suffer from a higher rate of mid-trimester miscarriages compared with women with unexplained RM. This may indicate a tendency for a similar pathology to the fibroids distorting the cavity. However, following referral, these women show favourable pregnancy outcomes, with live birth rates similar to the women with unexplained RM. As a result, we would advise not to operate on women with RM and intramural and/or subserosal fibroids. These women should be counselled that they have a high chance of subsequent live birth and should be classed as having unexplained RM.

It is important to note that in this trial the fibroid size and numbers were not different in the two study groups. This is of significance, as it demonstrates that even women with large or multiple fibroids not distorting the cavity can have favourable pregnancy outcomes. An example is the case of a patient with a 78 mm intramural/subserosal fibroid who achieved two live births following referral to the RM clinic.

Limitations

The main limitation of this study is the lack of a control group for the women who underwent myomectomy. Although outcomes seem favourable, it is not possible to be sure how the patients would have responded had they not undergone surgery. Women with fibroids not distorting the uterine cavity had a drop in their mid-trimester losses following referral without the need for any intervention. This begs the question of whether women with fibroids distorting the cavity would have behaved similarly had they not been operated on. Women with unexplained RM have been known to achieve high live birth rates with supportive care alone (Stray-Pedersen and Stray-Pedersen, 1984; Clifford *et al.*, 1997). We were able to demonstrate this for women with fibroids not distorting the uterine cavity, but unfortunately we could not assess this effect for women with fibroids distorting the cavity as they all underwent surgery. Another important limitation of this study is the relatively small numbers of patients with submucosal fibroids ($n = 25$). Having estimated the incidence of submucosal fibroids in women with RM (only 2.6%), it can be appreciated why this is the case. Nevertheless, we have attempted to control for confounding factors and bias, and have analysed the pregnancy outcomes in the clearest possible way.

Future studies

This study highlights the need to perform a randomized controlled trial (RCT) to assess the value of myomectomy versus no surgery on women with RM and fibroids distorting the uterine cavity. To show a beneficial increase of 25% in the live birth rate, a power calculation indicates that 58 patients per arm would be required to take part in such a trial ($\alpha = 0.05$, power = 0.80). A similar RCT does not seem necessary or practical for women with fibroids not distorting the cavity. Our findings indicate that without intervention, these women achieve live birth rates of over 70%. As a result, the same power calculation indicates that 294 patients per treatment arm would be required to show a 10% increment in live births. Given that these types of fibroids are present in ~5% of the RM population, over 10 000 patients with RM would have to be examined in total.

In the present study, we have based our classification and treatment according to whether the fibroids distort the uterine cavity. However, different levels of distortion may play a different role in fertility and pregnancy loss. Quantitative analyses may help clarify this more accurately; one way is to assess the distance between the fibroids and the myometrial junctional zone. As advanced imaging modalities such as magnetic resonance imaging become readily available, measurements like this may become more widely adopted and possibly form the basis for new classifications. This may ultimately help delineate the role of different fibroid types, sizes and locations in reproductive failure.

Authors' roles

S.H.S. contributed to the conception of the project, performed data collection, analysis and interpretation and drafted the manuscript. J.Y. and H.R. assisted with the data collection, analysis and interpretation and drafting of the manuscript. T.-C.L. conceptualized the project, interpreted the data analysis, approved the final draft and supervised the overall project.

Acknowledgements

The authors would like to thank staff nurses Barbara Anstie and Kathryn Wood for their invaluable contribution in the collection of the clinical data.

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