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The effect of myomectomy on reproductive outcomes in patients with uterine fibroids: A retrospective cohort study

BIOGRAPHY

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KEY MESSAGE

Despite the recovery period and more, larger and more symptomatic fibroids in the myomectomy group, the time to live birth was not significantly different after myomectomy compared with expectant management in patients with fibroids. Additionally, fibroid-related symptoms were reduced and ART use was lower after myomectomy. This supports conducting a randomized controlled trial.

ABSTRACT

Research question: What is the effect of myomectomy in women with uterine fibroids on time to live birth and other reproductive outcomes?

Design: This was a monocentric retrospective cohort study of 311 women with fibroids, of whom 165 eventually received myomectomy and 146 remained on expectant management. To assess the primary outcome time to live birth, a Cox proportional hazards model with a time-varying covariate for myomectomy was used. In the sensitivity analyses, this was combined with an approach to account for confounders via a cloning/censoring/weighting that aimed to emulate a randomized controlled trial.

Results: Notable differences in baseline characteristics between the myomectomy and expectant management group were fibroid size (fibroid >7 cm: myomectomy 48%; expectant management 15%) and whether the patient had fibroid-related complaints (myomectomy 85%, expectant management 67%). The adjusted hazard ratio for the effect of myomectomy compared with expectant management on live birth was 1.26 (95% CI 0.87–1.81). Sensitivity analyses yielded similar results, but secondary outcomes showed that women remaining on expectant management had more often received assisted reproductive technology (63%) compared with those who eventually received myomectomy (38%).

Conclusions: The study did not find a significant difference in time to live birth after myomectomy compared with expectant management in women with fibroids and a wish to conceive, despite more, larger and more symptomatic fibroids in the myomectomy group. The results after myomectomy encourage the execution of a randomized controlled trial in women with large (symptomatic) fibroids not or minimally distorting the intrauterine cavity, and infertility or a desire to conceive.

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Declaration: Although the authors report no financial or commercial conflicts of interest relating this paper, they would like to declare the following: V.M. has received research grants from Merck, Ferring, IQ Medical and Guerbet for other projects regarding (in)fertility and endometriosis. J.A.F.H. is currently performing a randomized controlled trial that is comparing ulipristal in long–term intermittent treatment with standard surgery (hysterectomy, myomectomy and uterine artery embolization): the MYOMEX–2 trial. This is a principle investigator-initiated study, funded by NWO–ZonMW. J.A.F.H. has also received one investigator-initiated research grant from Samsung for the use of 3D power Doppler scanning in the evaluation of fibroids, and has received a research grant from NWO-TTW on contrast-enhanced ultrasonography in gynaecology. Finally, J.A.F.H. has received expenses for lectures on fibroid diagnostic methods and non-invasive therapies from Samsung Medison and Olympus.

KEY WORDS
Infertility
Live birth
Myomectomy
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INTRODUCTION

Fibroids are the most common benign tumours of the uterus. They are present in up to 40% of women of reproductive age, and by the age of 50 years the estimate rises to an incidence up to 80%. Worldwide, fibroids are the most common indication for a hysterectomy and therefore a major public health burden (*Klatsky et al., 2008*; *Parker, 2007*).

Although most women with fibroids remain fertile, studies have shown that fibroids are associated with infertility. This is partly based on the observation of fibroids in women with unexplained infertility. Of all women evaluated with infertility, 30–40% are diagnosed with unexplained infertility. Among these patients, estimates of fibroid incidence may vary from 2% to 12.6% (*Bosteels et al., 2018*; *Brady et al., 2013*; *Carranza-Mamane et al., 2015*; *Klatsky et al., 2008*). Additionally, a recent large cohort study in patients with uterine fibroids showed an increased time to first and subsequent pregnancies compared with women without fibroids (*Karlsen et al., 2020*).

Different fibroid characteristics may affect fertility in ways that are not completely understood. It is postulated that the main factor is that distortion of the uterine cavity by fibroids may alter the receptivity of the intrauterine environment. This might be additionally influenced by the changes in functionality of the myometrium. Any of these alterations can consequently disturb the implantation of the embryo and may result in adverse reproductive outcomes (*Behbehani et al., 2018*; *Brady et al., 2013*; *Christopoulos et al., 2017*).

Fibroids are heterogeneous in location, size and number. The location of fibroids in the uterus can be classified via the system of the International Federation of Gynaecology and Obstetrics (FIGO; *Munro et al., 2011*). The location of the fibroids appears to be responsible for the size of the influence on reproductive outcomes. Previous research has found that women with submucosal fibroids, compared with those with no fibroids, have higher miscarriage rates and lower rates of implantation, ongoing pregnancy and live birth. On the other hand, subserosal fibroids have no significant impact on reproductive outcomes, while the effect of intramural fibroids remains debatable because of conflicting study results (*Brady et al., 2013*; *Klatsky et al., 2008*; *Olive and Pritts, 2010*; *Pritts et al., 2009*; *Rikhraj et al., 2020*; *Somigliana et al., 2007*; *Styer et al., 2017*; *Sunkara et al., 2010*; *Tian et al., 2017*).

Oliveira and colleagues reported a poorer implantation and pregnancy rate in women with intramural fibroids larger than 4 cm compared with those with intramural fibroids smaller than 4 cm, but no difference in live birth rate was found. However, two other cohort studies did not find a relationship between fibroid size and pregnancy rate (*Klatsky et al., 2008*; *Oliveira et al., 2004*). At this point, compelling evidence of fibroid size negatively affecting fertility is lacking (*Klatsky et al., 2008*; *Oliveira et al., 2004*). In addition the influence of fibroid number on fertility has not been adequately researched, although one systematic review reported that a lower number of fibroids was associated with improved reproductive outcomes after their removal (*Orlando et al., 2020*).

Obviously, a hysterectomy as an ultimate solution for a diseased uterus is not an option for women who wish to preserve their fertility potential, but nevertheless surgical treatment is possible for these patients by performing a myomectomy. No consensual guideline is available concerning the best surgical techniques. However, compared with laparoscopic or abdominal myomectomy, hysteroscopic myomectomy avoids invasive surgery and is the gold standard for the surgical treatment of submucosal fibroids (*Thubert et al., 2016*). Previous research has shown that performing myomectomy while sparing the neurovascular bundle of the fibroid pseudocapsule improves fertility outcomes (*Tinelli et al., 2012*; *Tinelli et al., 2017*). Cold loop hysteroscopic myomectomy seems to reduce thermal injury and spares the myometrial integrity of the fibroid pseudocapsule (*Tinelli et al., 2019*).

Studies examining the effect of myomectomy on live birth are generally inconsistent with regard to the size, number and location of fibroids within the uterus. Moreover, they show a high risk of selection bias and confounding (primarily by age), and most of them are underpowered. Identical problems occur in studies focusing on early pregnancy loss, which makes the interpretation of the results strongly doubtful (*ASRM, 2017*; *Carranza-Mamane et al., 2015*; *Klatsky et al., 2008*; *Metwally et al., 2020*; *Pritts et al., 2009*). One randomized controlled trial (RCT) has studied reproductive outcomes after hysteroscopic fibroid resection (thus not laparoscopic/abdominal myomectomy) compared with a lack of surgical intervention for submucosal fibroids, and has shown a positive effect in favour of hysteroscopic resection (*Casini et al., 2006*).

A re-analysis of these data by the American Society for Reproductive Medicine (ASRM) Practice Committee and a subsequent systematic review suggested that the differences between the groups did not meet statistical significance, although the likelihood of a favourable effect on fertility could not be excluded (*Bosteels et al., 2018*; *Metwally et al., 2012*). The removal of subserosal and transmural fibroids was also studied in only one RCT and only in patients before IVF. The authors found a beneficial effect of surgical removal, although only participants with one fibroid over 5 cm in diameter and a maximum of five fibroids were enrolled in the study (*Bulletti et al., 2004*).

Previous research has not yet sufficiently determined the short- and long-term influence of fibroids on reproductive outcomes regarding location (or FIGO classification). Hence, when a woman presents with infertility but without fibroid-related symptoms, it is a unique challenge for physicians to provide evidence-based recommendations regarding treatment. This also applies to women with (severe) complaints of fibroids and a wish to preserve fertility. The aim of this retrospective cohort study was to compare the time to live birth and other reproductive outcomes after surgical treatment or lack of surgical treatment, in women with fibroids who wished to conceive, adjusting for differences between participants regarding patient and fibroid characteristics.

MATERIALS AND METHODS

Ethical approval, registration and assessment

The study was approved by the Medical Ethical Committee of the Amsterdam UMC, VU University Medical Centre (VUmc) on 16 April 2019 (number 2019.225) and was registered at the

Netherlands National Trial Register (Trial NL7990). Furthermore, the study was conducted according to STROBE guidelines (*von Elm et al., 2008*), and a Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool was used to assess the bias of the study (Appendix) (*Sterne et al., 2016*).

Study design and patient selection

Women between the age of 18 and 45 years at the time of diagnosis of uterine fibroids at the VUmc Amsterdam were included. Data were obtained from the patient medical file and one survey after obtaining informed consent. Patients were identified by electronic data extraction through screening for the diagnosis in the disease problem list, the disease label or the diagnostic code (International Classification of Diseases and Health Related Problems 10th revision) of the electronic patient file.

The search was conducted in patients who presented at the VUmc between 2004 and 2018. This time frame was selected as medical patient records were not electronic before 2004 and it was estimated that at least 2 years of follow-up after possible surgical treatment was acceptable as a time interval for women to conceive. Those with uterine defects, such as congenital uterine anomalies (excluding arcuate uterus) or severe intrauterine adhesions, were excluded. Additionally, patients with severe endometriosis (ASRM grade 4; *"Revised American Society for Reproductive Medicine classification of endometriosis: 1996," 1997*) or dominant adenomyosis (as the uterus is more affected by adenomyosis than by uterine fibroids) were excluded.

In September 2019, 1804 patients were sent a letter, the survey and an informed consent form with a stamped addressed return envelope. The letter included an overview of the study, what was expected from the participants, the possible advantages and disadvantages of participation, and the contact details of the main researchers. The informed consent form asked them to sign for whether they would or would not participate in the survey, and whether they objected to the use of their known medical data. A reminder was sent when they did not respond within 4 weeks.

The survey involved questions regarding baseline characteristics (including ethnicity), complaints of fibroids, and a diagnostic/treatment/surgery/reproductive history. Data from the patient file were collected concerning the type and number of myomectomies (hysteroscopic/laparoscopic/abdominal myomectomy) and assisted reproductive technique (ART) interventions, namely intrauterine insemination (IUI), IVF and intracytoplasmic sperm injection (ICSI). Data on fibroid characteristics such as number, size and location were also collected (the location was either immediately classified according to FIGO or, when FIGO classification information was not described but ultrasound images were stored, classified retrospectively according to FIGO). Finally, data on reproductive outcomes were stored; these included the number and outcome of pregnancies, possible pregnancy complications such as preterm birth, and possible complications of delivery, for example uterine rupture.

During a myomectomy at the VUmc the fibroid pseudocapsule is spared by using minimal coagulation, in combination with adhesion barriers and haemostatic therapy such as vasopressin. Furthermore, in the last 5 years, blood loss during myomectomy has been limited by temporary vascular occlusion using bulldog clamps on the uterine arteries and infundibulopelvic or ovarian ligament, reducing the need for additional coagulation during surgery, which allows proper suturing and approximation of the various layers. The cold loop procedure is only used in patients with large submucosal fibroids found during hysteroscopic myomectomy.

Definitions

The participants either continued expectant management or received myomectomy at some point during the follow-up; reasons for a myomectomy were infertility- and/or fibroid-related symptoms (e.g. abnormal uterine bleeding or bulky symptoms). For both treatments, the follow-up started at the diagnosis of fibroids at the authors' hospital. Follow-up for the primary outcome ended at the first live birth or the end of the study. If the woman had no wish to conceive at the time of diagnosis, follow-up started at the time she was actively trying to conceive. The primary outcome was time to live birth, defined as the time till first live birth after the start of follow-up.

For the secondary outcomes, the follow-up did not end at the first live birth, but data were collected retrospectively for all outcomes until the end of the study. Secondary outcomes were use of ART, type of ART, mode of conception, total number of live births (twin pregnancies were counted as one live birth), ongoing pregnancies, defined as a viable intrauterine pregnancy after 12 weeks of gestation, miscarriages, defined as the spontaneous loss of a clinical pregnancy before 24 weeks' gestational age, intrauterine death after 24 weeks, preterm birth before 37 weeks, mode of delivery and complications during delivery.

Potential confounders

Confounders identified a priori by expert opinion and literature were female age, duration of infertility, previous live birth, education level, smoking, body mass index (BMI), diagnosis from the fertility check-up, and physical complaints from the fibroids in addition to the number, size, location and FIGO classification of the fibroids as determined on the ultrasound at diagnosis. Non-informative confounders were removed based on the Akaike information criterion (AIC) increasing by 2 or more (*Akaike, 1998*). The AIC is a statistic that contrasts the amount of information a model comprises with the complexity of that same model. The higher the AIC, the less information it contains relative to the parameters that have been added. This study used a threshold of an increase by 2 points to indicate that the confounder was not informative.

Missing data

Primary and secondary outcome data were complete. Baseline characteristics data were missing for a total of 5.7% of cells and were accounted for using single imputation including the cumulative hazard for a live birth to incorporate the time in follow-up (*White and Royston, 2009*).

Statistical analyses

The baseline characteristics of participants who eventually underwent myomectomy during follow-up were compared with those who did not, using a table.

Because myomectomy was a procedure that occurred over time, with some participants receiving it almost immediately and some waiting years, the survival analyses had to be planned accordingly to allow for a fair comparison. To estimate the effect of myomectomy over time, a primary analysis and two sensitivity analyses using alternative methodology were chosen. For all Cox models, possible violations of the proportional hazards assumption were checked (*Grambsch and Therneau, 1994*).

Primary analysis

First, after separating the follow-up in periods of expectant management and myomectomy, a Cox proportional hazards model was fitted using left truncation and a time-varying covariate for myomectomy including all previously mentioned selected confounders for adjustment. This way, a woman who received myomectomy 1 year after diagnosis started out as a part of the 'expectant management' group, i.e. there was no myomectomy, and after that year and her procedure, her treatment status and the rest of her follow-up were changed to the 'myomectomy' group. To keep the model as simple as possible, informative confounders were selected based on AIC and this set of confounders was used for the other analyses. In addition, by adding an interaction between complaints of symptoms and myomectomy, the study investigated whether the effect of myomectomy was different for women with symptoms from their fibroids compared with those who had no symptoms.

Sensitivity analyses

The first sensitivity analysis, instead of adding confounders to the model, aimed to balance the confounders between the expectant management and myomectomy groups over time, as this is more similar to the design of an RCT with women receiving myomectomy at different points in time. To this end, an inverse probability weighting of treatment was used, in which the relationship between confounders and treatment was used to re-balance the treatment groups such that the groups were similar over time (*Cole and Hernán, 2008*).

First a Cox model with the selected confounders was fitted that predicted the probability of undergoing myomectomy over time and updated these probabilities every 2 weeks (*Dreyer et al., 2019*). Next, the probability of receiving a myomectomy in the entire cohort was divided by the individual probabilities of receiving treatment to obtain weights for balance, and this process was then repeated until the weights converged and the procedure was completed, known as iterative inverse probability weighting (*van der Wal, 2011*). Those weights were then applied in a Cox model with a time-varying covariate for myomectomy.

For the second sensitivity analysis the 'cloning' methodological approach for a treatment that is started later in time was chosen; the principle is that if the treatment decision is made at some point after diagnosis, 'strategies' to eventually treat or not treat are compared rather than assigning treatment at a fixed time point as in an RCT (*Hernán, 2018*). Initially the data from all patients for both strategies were used, and then patients were followed over time and censored, i.e. removed from analysis when they did not adhere to their assigned strategy, which here involves receiving treatment in the expectant management 'strategy' group. For example, a patient who received myomectomy at 1 year after diagnosis provided data on expectant management for both strategy groups during this year, was followed after myomectomy in the treatment strategy group but was censored at the time of myomectomy in the expectant management group. Inverse probability weighting of treatment was then applied using a priori selected confounders in logistic regression to weight and adjust for this censoring, similar to the approach described in the previous paragraph (*Cole and Hernán, 2008*; *Hernán, 2018*). Finally, adjusted weighted Kaplan–Meier curves were fitted for both groups and a log-rank test was conducted to compare the curves. What was obtained was the absolute chance of a live birth over time for both strategies, something the hazard ratio itself does not provide.

Software

Data were prepared in SPSS 26 (IBM, USA) and analysed in R version 3.6.0 (*Team, 2019*) using the *rms*, *foreign*, *mice*, *dplyr* and *prodlim* R packages.

RESULTS

Descriptive statistics

In total 526 participants were included in the study. The group of patients who had a wish to conceive at the start of follow-up consisted of 311 patients who were included in the analysis. The median time to myomectomy was 14 months, the median follow-up after the procedure was 24 months, and the median follow-up for expectant management was 18 months. Again because of the type of analysis, patients were first analysed in the expectant group and, if myomectomy was performed, from the moment of myomectomy in the group of patients whom eventually received a myomectomy. The reason for myomectomy was the presence of symptoms for 49 women (30%), a wish to conceive for 50 (30%), or both symptoms and a wish to conceive for 62 (38%), with data missing for 4 participants (2%).

The baseline characteristics of the women who remained on expectant management and those eventually receiving myomectomy are depicted in TABLE 1. Additional baseline characteristics including complaints from the fibroids, smoking status, infertility diagnosis and the surgical variables of the patients who eventually received a myomectomy are shown in the Supplementary Table. The largest differences between the groups at first glance were the largest fibroid diameter being >7 cm (in 48% of women who received myomectomy versus 15% of those continuing expectant management), and receiving a fertility check-up (56% for the myomectomy group versus 76% for expectant management). In addition the mean number of fibroids (2.0 [2.5–97.5th percentile 1.0–14.9] for the myomectomy group versus 1.0 [1.0–7.4] for expectant management) and the fibroid location (fibroid deforming the uterine cavity: 54% in the myomectomy group versus 36% for expectant management) differed between the groups.

Primary analysis

After fitting the Cox proportional hazards model with a time-varying covariate for myomectomy, the confounders of fertility check-up, smoking and fibroid FIGO location were removed for all the reported analyses, as these led to poorer statistical fits due to an increase in AIC. An adjusted hazard ratio was estimated for the effect of myomectomy compared with expectant management of 1.26 (95% confidence interval [CI] 0.87–1.81), thus showing no statistical evidence of a benefit. There was no difference in the effect of myomectomy compared with expectant management for women with or without complaints arising from their fibroids (*P* for interaction = 0.65).

TABLE 1 BASELINE CHARACTERISTICS OF THE WOMEN WHO REMAINED ON EXPECTANT MANAGEMENT AND THOSE WHO EVENTUALLY RECEIVED MYOMECTOMY

Parameter	Patients who eventually received myomectomy (*n* = 165)	Patients who remained on expectant management(*n* = 146)
Female age at diagnosis (years)	34.6 (26.0–43.9)	35.7 (28.0–43.4)
BMI (kg/m^2)	26.2 (19.2–40.9)	25.7 (19.0–35.3)
Infertile (yes versus no)	106 (64)	115 (79)
Duration of infertility at diagnosis (years), median	1.6 (0.0–10.7)	2.1 (0.0–13.3)
Primary infertility (versus secondary)	147 (89)	129 (88)
Fertility check-up (yes versus no)	93 (56)	111 (76)
Complaints from fibroids (versus no)	141 (85)	98 (67)
Number of fibroids (median)	2.0 (1.0–14.9)	1.0 (1.0–7.4)
Largest fibroid diameter		
<1 cm	3 (2)	2 (1)
1–2 cm	12 (7)	33 (23)
2–3 cm	20 (12)	26 (18)
3–4 cm	13 (8)	28 (19)
4–5 cm	11 (7)	13 (9)
5–6 cm	13 (8)	14 (10)
6–7 cm	13 (8)	8 (5)
>7 cm	80 (48)	22 (15)
Fibroid location(s)		
Only submucosal	21 (13)	9 (6)
Only transmural	21 (13)	11 (8)
Multiple locations: at least one submucosal or transmural fibroid in combination with another fibroid	35 (21)	10 (7)
Only intramural	30 (18)	47 (32)
Only subserosal	24 (15)	47 (32)
Multiple locations; only a combination of intramural and subserosal fibroids	34 (21)	22 (15)
FIGO classification[a]		
At least one FIGO type 0, 1, 2, 3 and/or 2–5 (causing deformation of the intrauterine cavity)	89 (54)	52 (36)
Only FIGO type 4, 5, 6, 7 and/or 8 (no deformation of the intrauterine cavity)	76 (46)	94 (64)

Data are mean unless indicated as median; values in brackets are percentages or the range between the 2.5th and 97.5th percentiles.

[a] The FIGO location was classified according to Munro and colleagues (*Munro et al., 2011*). When the classification was not described and ultrasound images were stored, fibroids were classified retrospectively.

BMI, body mass index.

Sensitivity analyses

Applying the survival weights, a hazard ratio of 1.15 (95% CI 0.74–1.77) we estimated, which was in agreement with the primary analysis. After applying the cloning approach and obtaining the two 'strategy' groups, a weighted Kaplan–Meier curve was produced (FIGURE 1). The log-rank test for the difference yielded a value of $P = 0.20$, again indicating a lack of statistical evidence for a clear effect of myomectomy.

Secondary outcomes

The secondary outcomes of the women who remained on expectant management and those eventually receiving myomectomy are displayed in TABLE 2. The total obstetric history is included. The largest differences were seen in total ART use and type, and the mode of conception of the first live birth. Ninety-two (63%) of the couples who remained on expectant management received ART versus 63 (38%) of the couples who eventually received myomectomy. Most conceptions that led to the first live birth in the myomectomy group occurred naturally (67%), while IVF/ICSI (45%) was the most common mode of conception in the expectant management group.

Complications during delivery arose for 14 women (14% of those who delivered at least once) in the expectant management group and 16 women (22% of those who delivered at least once) in the myomectomy group. A uterine rupture during delivery occurred for one participant (1%) in the group of patients eventually receiving myomectomy. In this case the uterine rupture occurred 2 years after the myomectomy, with no history of Caesarean section. This patient received two myomectomies in 1 year, one hysteroscopic and one laparoscopic. During the latter, two subserosal and two transmural fibroids were removed.

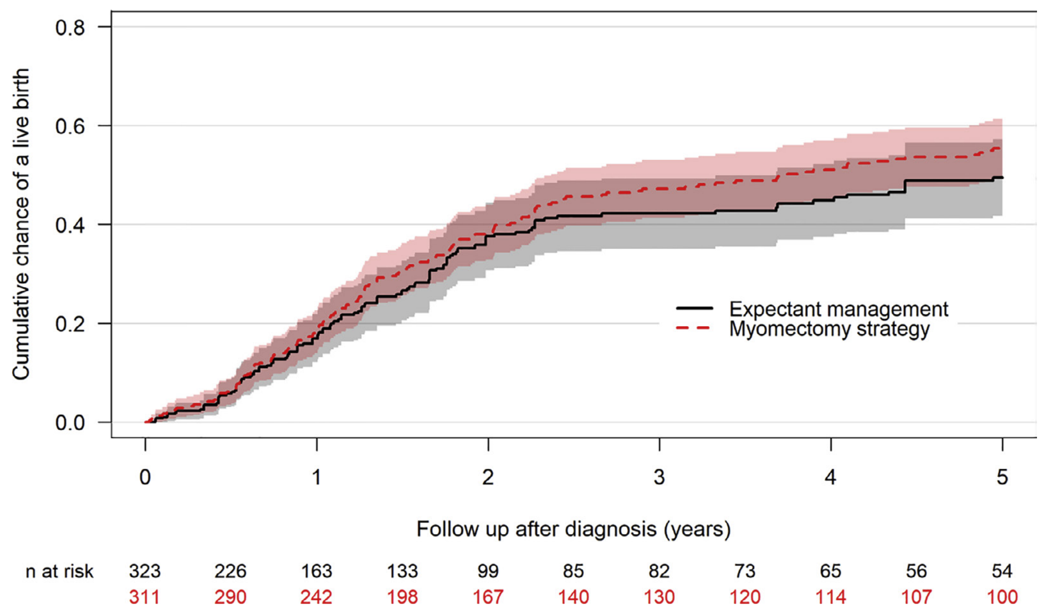

FIGURE 1 Weighted Kaplan–Meier curves for the cohort of women adhering to a strategy of expectant management or eventually receiving myomectomy.

The largest fibroid was 5 cm and was removed by entering the uterine cavity; therefore an elective Caesarean section was advised. However, labour started spontaneously with contractions at 35 + 3 weeks of pregnancy, after which the uterine rupture occurred. A Caesarean section was then performed and a healthy child was delivered.

DISCUSSION

No significant difference was found in the time to live birth between the myomectomy and expectant management groups (adjusted hazard ratio 1.26, 95% CI 0.87–1.81). The secondary outcomes showed no clear differences in other obstetric outcomes between the women in the myomectomy or expectant management group. When looking at ART and mode of conception, participants who eventually received myomectomy underwent ART considerably less often and, consequently, more frequently conceived naturally compared with those who continued expectant management. In addition, if they did receive ART, they were likely to skip IUI and start with IVF/ICSI. Because of the retrospective nature of the study, the characteristics of the participants differed between groups, most notably in terms of fibroid size (fibroid >7 cm: myomectomy group 48%, expectant management group 15%), fibroid number (myomectomy group 2 [1.0–14.9], expectant management 1 [1.0–7.4]) and fibroid type (fibroid type causing deformation of the intrauterine cavity: myomectomy group 54%, expectant management group 36%).

In accordance with these results, previous studies have demonstrated that a clear effect of myomectomy has not been proven (Bosteels et al., 2018; Brady et al., 2013; Fernandez et al., 2001; Khaw et al., 2020; Klatsky et al., 2008; Metwally et al., 2020; Orlando et al., 2020; Pritts et al., 2009). However, these studies all show that a myomectomy does not decrease fertility rates either and tends to show (non-significant) positive effects of surgical treatment.

The current study also included women who received myomectomy primarily because of symptom complaints, and not infertility. Although the duration of trying to conceive at diagnosis was accounted for, this could have diluted the results because some fibroids can give complaints without deforming the uterine cavity, affecting myometrial contractions or influencing endometrial angiogenesis, which are depicted as important factors negatively influencing fertility (Brady et al., 2013).

In addition, dyspareunia caused by fibroids, in turn leading to a low exposure to intercourse, can negatively affect fertility. Although sexual complaints were experienced in both groups (myomectomy group 22%, expectant management group 14%, as depicted in the Supplementary Table) and this was included in the complaints assigned as a confounder, it is interesting that 1 year after myomectomy only 9% (15 patients) of women were experiencing sexual complaints and natural conception was higher after myomectomy (67%, versus 36% in the expectant management group).

This is the first retrospective study to examine the difference in reproductive outcomes between participants after myomectomy or expectant management that includes all types of fibroids and has categorized them (retrospectively) according to their FIGO location. A strenghts of the study is that both the general gynaecological population and the population after ART were included in this study. This provides an insight into which type of patient is more likely to receive a myomectomy and to assess the effect of the myomectomy on reproductive outcomes. Also, the participants provided information via a survey as an addition to the information available in the patient medical file, which resulted in low amounts of missing data. Another strenght of the study is that by using statistical techniques to adjust for confounding and triangulating this approach using three methods in total, this retrospective study aimed to make a most equitable comparison between groups (Hernán, 2018). Different advantages of these contemporary

TABLE 2 SECONDARY OUTCOMES OF THE WOMEN WHO REMAINED ON EXPECTANT MANAGEMENT AND THOSE WHO EVENTUALLY RECEIVED MYOMECTOMY

Parameter	Patients who eventually received myomectomy (*n* = 165)	Patients who remained on expectant management (*n* = 146)
Mode of conception leading to first live birth		
Total	73	100
Natural conception	49 (67)	36 (36)
Ovulation induction	1 (1)	3 (3)
IUI (with and without stimulation)	3 (4)	17 (17)
IVF/ICSI	20 (27)	45 (45)
Total ART	63 (38)	92 (63)
Number of ART cycles[a]		
IUI (with and without stimulation)	156	334
IVF/ICSI	82	158
Total live births	115[a]	159[a]
Total ongoing pregnancies	301[a]	306[a]
Total miscarriages under 24 weeks	105[a]	100[a]
Total intrauterine fetal deaths after 24 weeks	1[a]	6[a]
Total preterm birth at 24–37 weeks	15[a]	15[a]
Total deliveries		
Total	115[a]	159[a]
Vaginal	42	96
Assisted delivery	3	10
Primary Caesarean section	49	22
Secondary Caesarean section	21	31
Complication of (at least one) delivery	16/73 (22)	14/100 (14)
Total uterine rupture	1 (1)	0

Data are *n* or *n/N* (%).

[a] Some participants had more than one pregnancy during the follow-up, and all pregnancies were included.

ART, assisted reproductive technology; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination.

methods were the simplicity (the confounders in the model), the induction of balance over time (inverse probability weighting over time) and the comparison of strategies as in a trial and the estimation of the absolute chances of a live birth (cloning/censoring/weighting) (*Hernán, 2018*; *Hernán et al., 2008*; *Hernán and Robins, 2016*).

However, the study also has some limitations. Information on the date that the ART was ended was missing, such that ART usage could not be adjusted for over time. This is expected to dilute the estimated effect of myomectomy due to more ART usage in the expectant management group. In addition, due to the observational nature of the study, there could be residual confounding due to other factors that were not accounted for. A third limitation is selection bias that occurred because some specific patients could be more prone to reject participation in this study. For instance, it was seen that women who had an obstetric history with multiple adverse outcomes were less likely to participate, but this is inherent to the design. Despite this, after comparing the baseline characteristics of non-responders and responders, the study found no significant differences in total live birth ($P = 0.998$), ethnicity ($P = 0.068$) or BMI ($P = 0.888$). There was, however, a difference in age (38.5 versus 35.1 years; $P = 0.001$). Furthermore, the number of participants included was too low to stratify for specific fibroid characteristics, such as the FIGO location, in relation to reproductive outcomes.

In addition, Figure 2 shows that the cumulative chance of a live birth is below 40% in both study groups. The probability of conception in healthy people is around 95% after 2 years, so compared with this number, the cumulative conception in this study is much lower (*Taylor, 2003*). However, a selected group of people were analysed. In the Netherlands there is a tendency to be very conservative in relation to uterine fibroids, and in most centres expectant management is proposed unless severe symptoms occur. The women who visit the authors' uterine repair centre are mostly tertiary referrals because of complexity or visit the hospital in a very late stage after the failure of various other therapies; as a consequence they have a lower probability of a live birth. This is underlined by the baseline characteristics reported in TABLE 1. In total 64% in of the women in the myomectomy group and 79% in the expectant management group were infertile. Moreover, the median age of the participants was around 35 years (TABLE 1), indicating age as an important factor negatively influencing the conception rates in this study – it is known that the cumulative probabilities of conception decline with age because of a diminished ovarian reserve (*Taylor, 2003*). Additionally, the fertility of women with fibroids is influenced by changes in the endometrial environment, pressure complaints in the tube(s) and/or endometrium, and changes in myometrial contractility, negatively influencing conception and implantation (*Navarro et al., 2021*).

After a woman has undergone myomectomy, she has a recovery time of up to 6 months in which she is advised not to conceive. Despite this inherent negative effect on the time to live birth, no clear negative effect of myomectomy was found. There was thus more evidence in this study that any negative effect due to waiting after the procedure could have been offset by a possible positive effect of myomectomy, which, in addition to reducing symptoms, provides arguments to perform a myomectomy.

CONCLUSION

Comparing the two study groups, no significant difference was found in the time to live birth, although this comparison regarding live birth is limited due to the waiting period of patients before and after the myomectomy procedure. Given that after myomectomy the time to live birth rate is similar to that of expectant management, despite the waiting period, and considering the other advantages of myomectomy in terms of reducing symptoms, the logical next step after this study and reviewing the accumulated evidence is to conduct an RCT. This should include infertile women or those with an actual desire to conceive who have fibroids that are not, or are minimally distorting, the uterine cavity. To unravel the effect of specific fibroid characteristics on reproductive outcomes, it is important that future results are stratified by the size, number and FIGO location of the fibroids. This is essential to research the effect of myomectomy free of confounding and selection and, in addition, to further determine which specific patients, with regards to fibroid characteristics, obtain the most benefit from surgical treatment.

Providing patient-specific care for women with fibroids and infertility remains a challenge. Additional to the evaluation of fibroid characteristics, ovarian reserve is an important factor to assess. Because this study shows no negative effect on fertility after myomectomy, it provides clinicians with support to advise myomectomy in women with fibroid-related symptoms and a wish to conceive.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2022.05.025.

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