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ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
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ΣΥΣΤΗΜΑΤΙΚΗ ΑΝΑΣΚΟΣΚΟΠΗΣΗ ΤΗΣ ΒΙΒΛΙΟΓΡΑΦΙΑΣ

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ΤΡΙΜΕΛΗΣ ΣΥΜΒΟΥΛΕΥΤΙΚΗ ΕΠΙΤΡΟΠΗ

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**UNIVERSITY OF THESSALY
SCHOOL OF HEALTH SCIENCES
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POSTGRADUATE MASTER PROGRAMME
“PELVIC AND PERINEAL SURGERY”**



**MYOMECTOMY DURING PREGNANCY
A SYSTEMATIC REVIEW**

By

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Larisa, 2020

This thesis is dedicated to my family.
For their endless love, support and encouragement...

PREFACE

This thesis is the final work of my Master course in “Pelvic and Perineal Surgery”. It was a true learning experience, as I had to conduct a profound literature research that offered me further scientific knowledge in a field of great interest.

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ΠΕΡΙΛΗΨΗ

Στόχος: Τα ινομυώματα της μήτρας επηρεάζουν το 2-10% των εγκύων γυναικών. Αν και συνήθως ασυμπτωματικά, μπορούν να συσχετιστούν με επιπλοκές της εγκυμοσύνης. Η ινομυωματεκτομή αποφεύγεται κατά τη διάρκεια της κύησης, ωστόσο, έχει αναφερθεί σε συμπτωματικές εγκύους που δεν ανταποκρίνονται στη συντηρητική θεραπεία. Στόχος αυτής της μελέτης είναι να συνοψίσει τη δημοσιευμένη βιβλιογραφία και να παρουσιάσει τα αναφερόμενα αποτελέσματα και τους σχετικούς κινδύνους αυτής της διαδικασίας.

Σχεδιασμός Μελέτης: Μια συστηματική ανασκόπηση της βιβλιογραφίας διεξήχθη στις μηχανές αναζήτησης PubMed / MEDLINE, Scopus και Cochrane Library, συμπεριλαμβανομένων των case reports και case series, με στόχο την αριθμητική ανάλυση όλων των παραμέτρων που περιλαμβάνονται στα case reports.

Αποτελέσματα: Συνολικά, εντοπίστηκαν 54 σχετικά άρθρα, που αφορούσαν 97 ασθενείς. Η διάμεση ηλικία κύησης κατά τη διάγνωση ήταν 13 (εύρος 6-26) εβδομάδες, ενώ η διάμεση ηλικία κατά την ινομυωματεκτομή ήταν 16 (εύρος 6-26) εβδομάδες. Το κοιλιακό άλγος, μη ανταποκρινόμενο στη συντηρητική θεραπεία, ήταν η βασική ένδειξη για τη χειρουργική επέμβαση. Ο διάμεσος αριθμός ινομυωμάτων που αφαιρέθηκαν ανά ασθενή ήταν ένα (εύρος 1-5). Τα περισσότερα από αυτά ήταν μισχωτά υποορογόνια ή υποορογόνια και πυθμενικά. Αφαιρέθηκαν πρωτίστως δια λαπαροτομίας (78,4%), ωστόσο, αναφέρθηκαν και λαπαροσκοπικές και κοιλιακές επεμβάσεις. Η διάμεση διάρκεια της χειρουργικής επέμβασης ήταν 53 (εύρος 20-150) λεπτά. Η ιστολογική εξέταση των αφαιρεθέντων ινομυωμάτων ανέδειξε ως κύρια ευρήματα τη νέκρωση και τον εκφύλιση αυτών. Το περιγεννητικό αποτέλεσμα ήταν ευνοϊκό στις περισσότερες περιπτώσεις, ενώ αναφέρθηκαν μόνο λίγες επιπλοκές.

Συμπέρασμα: Με βάση τα περιορισμένα δημοσιευμένα δεδομένα, η ινομυωματεκτομή κατά τη διάρκεια της εγκυμοσύνης αποτελεί μια ασφαλή διαδικασία σε περιπτώσεις συμπτωματικών ινομυωμάτων της μήτρας που δεν ανταποκρίνονται στη συντηρητική διαχείριση και ως εκ τούτου, μπορεί να εξεταστεί μετά από κατάλληλη συμβουλευτική σχετικά με τους σχετικούς κινδύνους που εγκυμονεί ένα τέτοιο εγχείρημα.

Λέξεις-κλειδιά: ινομυωματεκτομή, εγκυμοσύνη, λαπαροσκόπηση, λαπαροτομία, συστηματική ανασκόπηση

ABSTRACT

Objective: Uterine fibroids affect 2-10% of pregnant women. Although usually asymptomatic, they may be associated with pregnancy complications. Myomectomy is preferably avoided antenatally, however, it has been reported in symptomatic cases that did not respond to conservative management. The aim of this study was to summarize the published literature and present the reported outcomes and associated risks of this procedure.

Study Design: A systematic research of the literature was conducted in PubMed/MEDLINE, Scopus and the Cochrane Library, including case reports and case series. An effort was made to numerically analyse all parameters included in the case reports.

Results: Overall, 54 relevant articles were identified, including 97 patients. The median gestational age at diagnosis was 13 (range 6-26) weeks, while the median age at myomectomy was 16 (range 6-26) weeks. Abdominal pain, not responding to medical treatment was the most common indication for surgery. The median number of fibroids removed per patient was one (range 1-5). Most of them were subserous pedunculated or subserous and fundal. Laparotomy (78.4%) was the principal surgical approach, however, laparoscopic and vaginal operations were also reported. The median duration of surgery was 53 (range 20-150) min. The histopathology revealed necrosis and degeneration as the main findings of removed fibroids. The pregnancy outcome was favourable in most of the cases, with few complications reported.

Conclusion: Based on the limited published data, myomectomy during pregnancy appears as a safe procedure in cases of symptomatic uterine fibroids not responding to conservative management and therefore it may be considered, following appropriate counselling regarding the associated risks.

Keywords: myomectomy, pregnancy, laparoscopy, laparotomy, systematic review

1. INTRODUCTION

Fibroids are the most common benign, smooth muscle uterine tumors, with a reported prevalence during pregnancy of 2-10% [1]. Although usually asymptomatic, complications may occur in about one out of ten women with myomas during the antenatal period [1, 2]. Abdominal pain and heaviness, fever and vaginal bleeding are the most common; 5-15% of pregnant women with fibroids will require hospitalisation [3]. Pain frequency increases with size, especially with fibroids >5cm in diameter [3]. This typically occurs early in pregnancy where the mean increase in fibroid volume is 12% and may be related to the rapid increase in serum human chorionic gonadotropin levels [4]. Pain may also result from degeneration or torsion of a pedunculated myoma [3]. In particular, red degeneration mostly occurs during the first and early second trimester when myomas may grow faster and receive insufficient blood supply, leading that way to ischemia and necrosis [5]. Moreover, the presence of fibroids has been associated with pregnancy complications and adverse pregnancy outcomes, such as miscarriage, placental abruption, premature rupture of membranes, placenta previa, preterm labor, fetal malpresentation, caesarean delivery and post-partum haemorrhage [3-9]. The risk of these complications is related to fibroid number, size, location and relation to the placenta [1, 3, 4, and 10].

Regarding management, myomectomy is not routinely offered during pregnancy due to the fear of associated complications, such as severe haemorrhage, uterine rupture, miscarriage and preterm labor [2, 11-15]. In cases of symptomatic myomas, conservative management is the first option, with bed rest, hydration or analgesia usually recommended [6, 7]. Nevertheless, in cases where symptoms persist after 72 hours of conservative management or torsion of a pedunculated fibroid or severe compression of other pelvic organs by large myomas is suspected, myomectomy may be considered [4, 16, and 60].

To date, few studies have been published on this issue, mostly case reports. A synthesis of available data may increase our understanding on the indications, the characteristics of the fibroids removed and the perioperative and long-term pregnancy outcomes. Therefore, the aim of this systematic review was to analyse all available data regarding myomectomy during pregnancy, with an emphasis on myomas' characteristics, surgical parameters and pregnancy outcomes.

2. MATERIALS AND METHODS

2.1 Identification and eligibility of relevant studies

A search in Medline, Scopus and the Cochrane Library (up to December 2019) was performed using various combinations of the following terms: myomectomy and pregnancy, fibroid, uterine myoma(s), pregnancy, outcomes after myomectomy, complications after myomectomy, management of fibroids during pregnancy. The search was extended to the reference lists of relevant articles. We included studies that reported myomectomy during pregnancy and excluded those that reported on caesarean myomectomy.

2.2 Data extraction

From each study, data regarding authors, journal, year of publication, country, study design and number of patients were extracted. As for the demographic characteristics, ethnicity, age and parity were recorded. We also recorded the patients' BMI and medical history, gestational age at diagnosis and at myomectomy and reported symptoms. Regarding surgical data, the type and number of removed myomas, size and weight and their relationship to the placenta were retrieved. Moreover, we documented the type of surgery and anaesthesia performed, blood loss during surgery, method of reconstruction of the uterine wall and duration of the procedure. Furthermore, histopathologic examination of the removed myomas, postoperative treatment, days of hospitalization and neonatal outcomes were noted. Data extraction was performed independently by two investigators (K.S. and I.K.). Conflicts were solved after discussion with a third author (T.D.).

3. RESULTS

Overall, 1876 abstracts were retrieved and further screened. Of these, 244 articles describing myomectomy on a pregnant uterus were recovered for full review. Relevant reviews were further screened (n=26). After excluding studies reporting myomectomy during caesarean section, 80 studies on myomectomy during pregnancy were further examined. Eight studies not in English (2 French, 1 Spanish, 1 Bulgarian, 1 Czech and 3 Italian) and 10 studies in English (3 from Italy, 2 from Nigeria, 1 from Belgium, 1 from Hungary, 1 from Croatia, 1 from Mexico and 1 from Korea) could not be retrieved. Ten studies were also excluded, because they were performed before the ultrasound era, with minimal data reported; the first was published in 1899. Thus, after a complete review, 54 studies were included in the systematic review, reporting on 97 cases [1, 2, 5-8, 11-13 and 15-59] (**Figure 1**) (Table 1).

Amongst these cases, thirteen were reported from 1985 to 2000 [7, 34, 36, 38, 52 and 56], 56 from 2001 to 2010 [2, 5, 11-13, 17, 18, 20, 24, 27-29, 31, 32, 41, 42, 44-46, 51, 53 and 57] and 28 from 2011 to 2019 [1, 6, 8, 15, 16, 19, 21-23, 25, 26, 30, 33, 35, 37, 39, 40, 43, 47-50, 54, 55, 58 and 59]. Fifty-eight patients were included in case reports, 26 patients in retrospective studies [5, 56] and 13 in a prospective cohort study [11]. The countries of the case reports are presented in Table 1.

Figure 1: Study selection process

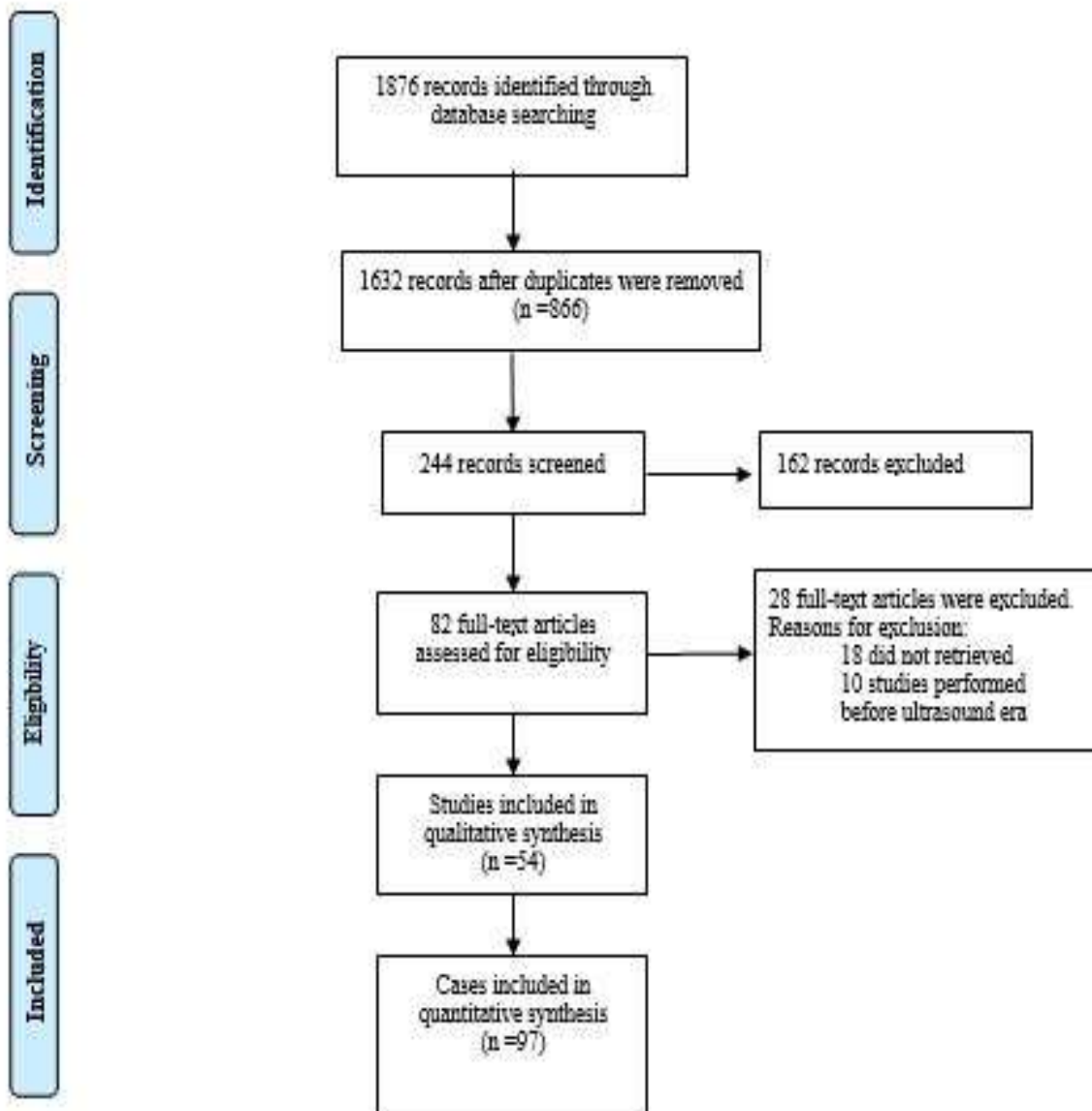


Table 1. List of articles finally included in the review

Study-Year of Publication	Type of study	Country	Number of patients	Gestational age at myomectomy	Gestational age at outcome	Mode of delivery	Pregnancy outcome (Weight, Apgar 1 and 5 min)
Burton et al., 1989	retrospective analysis	USA	8	13	40	VD	nd
				15	Miscarriage		
				nd	nd	nd	nd
				nd	40	VD	nd
				nd	40	VD	nd
				nd	40	VD	nd
				nd	40	VD	nd
				nd	40	VD	nd
Michalakis et al., 1995	case report	Greece	1	14+3	39 (PROM)	CS (myoma in lower part of uterus)	2800g
Pelosi et al., 1995	case report	USA	1	15	39 (PROM)	CS (breech)	nd
Majid et al., 1997	case report	USA	1	18	19 Fetal demise		
Luxman et al., 1998	case report	Israel	1	15	39	VD (spontaneous)	3400g
Wittich et al., 2000	case report	USA	1	16	37	CS (elective)	3275g 9/9
Danzer et al., 2001	case report	Switzerland	1	12	37	CS (twins)	3235g 9/10 2810g 9/10
De Carolis et al., 2001	retrospective analysis	Italy	18	13	39	CS	3150g 8/8
				24	38	CS	2670g 8/8
				19	36	AD	3080g 8/9
				17	38	CS	3060g 8/9
				19	19 Fetal demise		

				20	41	VD	2970g 9/9
				19	39	CS	3180g 7/9
				8	40	CS	3300g 9/9
				12	38	CS	2780g 9/10
				17	38	CS	3900g 9/9
				15	40	CS	3170g 8/10
				17	39	CS	3100g 9/10
				6	nd	nd	
				20	39	CS	
				10	40	CS	
				16	39	CS	
				13	39	CS	
				7	38	CS	
Hasbargen et al., 2002	case report	Germany	1	18	36	CS (elective)	2495g 8/9
Donnez et al., 2002	case report	Belgium	1	25	35	CS (elective)	2280g
Celik et al., 2002	case report	Turkey	5	22	38.6 (+/1.1) (mean)	CS	3200g 10/nd
				18		CS	3400g 9/nd
				20		CS	3600g 10/nd
				16		CS	3100g 8/nd
				13		CS	2800g 9/nd
Lolis et al., 2003	prospective cohort study	Greece	13	16	37	CS	3340g
				15	39	CS	3600g
				19	37	CS	2970g
				16	36	CS	3000g
				15	15 Fetal demise		
				15	37	CS	2740g
				16	38	CS	3180g
				16	39	CS	3515g

				16	39	CS	3190g
				19	38	CS	2920g
				17	38	CS	3520g
				16	38	CS	3000g
				15	29	CS (placenta previa abruption)	1606g
Sentilhes et al., 2003	case report	France	1	17	37	CS (elective, placenta accreta)	3530g nd/10
Melgrati et al., 2005	case report	Italy	1	24	39	VD (spontane ous)	9/9
Umezurike et al., 2005	case report	Nigeria	1	20	38	VD (spontane ous)	3500g 8/10
Dracea et al., 2006	case report	Romania	1	14	37	VD (spontane ous)	2600g
Santos et al., 2006	case report	Portugal	1	6	38	VD (spontane ous)	3300g
Okonkwo et al., 2007	case report	Nigeria	1	24	38	CS (elective)	2600g 8/10
Usifo et al., 2007	case report	UK	1	13	38	CS (elective)	3990g
Demirci et al., 2007	case report	Turkey	1	26	36	nd	3000g
Alanis et al., 2008	case report	USA	1	12+1	38	VD (spontane ous)	2330g
Suwandinata et al., 2008	case report	Kenya	1	18	37	CS (elective)	2950g 8/9

Vazquez Camacho et al., 2009	case report	Mexico	1	15+5	40	VD (spontaneous)	9/9
Bhatla et al., 2009	case report	India	1	19+3	38	VD (ROM)	2740g
Fanfani et al., 2010	case report	Italy	1	25	40	VD (spontaneous)	2950g
Kasum 2010	case report	Croatia	1	15	38	VD (spontaneous)	nd
Leite et al., 2010	case report	Brazil	1	17	39	CS (elective)	3315g 9/10
Kilpatrick et al., 2010	case report	USA	2	15+5 14	38 16 Fetal demise	VD (spontaneous)	2755g
Ardivino et al., 2011	case report	Italy	1	14	40	VD (spontaneous)	3216g
Leach et al., 2011	case report	USA	1	11	40+3	CS (failed induction)	4356g 9/9
Son et al., 2011	case report	Korea	1	18	39	VD	3740g
Lozza et al., 2011	case report	Italy	1	15+5	35+5	CS (ROM)	2280g 9/9
Kim TH et al., 2011	case report and review	Korea	1	12	38	CS	2640g
Doerga-Bachasingh et al., 2012	case report	The Netherlands	1	10	37	CS (partial abruption placentae)	twins

Macciò et al., 2012	case report	Italy	3	19 20 20	39 40 39	CS (malpresentation) VD (spontaneous) CS (short umbilical cord)	3150g 3310g 3050g
Tabandeh et al., 2012	case report	Iran	1	24	37	CS (elective)	nd
Shafiee et al., 2012	case report	Indonesia	1	15	38	CS (elective)	nd
Pelissier-Komorek et al., 2012	case report	France	1	13	35	VD (spontaneous)	2280g
Currie et al., 2013	case report	UK	1	11+1	nd	nd	nd
Kobayashi et al., 2013	case report	Japan	1	21+1	37	CS (elective)	2730g
Domenici et al., 2014	case report	Italy	1	16	38	CS	3250g 8/9
Zhao et al., 2014	case report and review	China	1	14	nd	VD (spontaneous)	3400g
Obara et al., 2014	case report	Japan	1	13+1	40	VD (induction due to oligohydramnios)	2755g
Saccardi et al., 2015	case report	Italy	1	15	41	CS (failed induction)	4460g
Salih et al., 2015	case report	Iraq	1	18	38	CS and hysterectomy (placenta previa abruptio)	3500gr 8/nd

Kosmidis et al., 2015	case report	Greece	1	10	nd	nd	nd
Jhalta et al., 2016	case report	India	1	13+2	39+1	VD (spontaneous)	3000g 8/10
Kim M., 2016	case report	Korea	1	10	40+1	VD	3160g
Basso et al., 2017	case report and systematic review	Italy	1	17	38+1	VD (spontaneous)	2940g 9/10
Valenti et al., 2018	case report and systematic review	Italy	1	18+1	38	CS	2180g
Allameh et al., 2019	case report	Iran	1	21+2	39+1	VD (spontaneous)	2900g
Fuchs et al., 2019	case report	Poland	1	19+1	35	CS (spontaneous labor)	2510g 10/10
Moruzzi et al., 2019	case report	Italy	1	14	nd	nd	nd
Tong et al., 2019	case report	China	1	22	32	CS (spontaneous labor)	2120g 10/10

nd: no data; VD: vaginal delivery; CS: caesarean section; PROM: prelabor rupture of membranes

3.1 Demographic characteristics

Demographic data were available in 71 of the 97 cases [1, 2, 6-8, 11-55 and 57-59]. The median maternal age was 33 years (range 22-44). In a single retrospective analysis of 18 patients, the maternal age ranged between 21 and 34 years [5]. The ethnicity was reported in only 13 cases, including eight Caucasians [1, 6, 35, 38, 40, 43, 52 and 58] and one of African [49], African-American [24], Latin-American [7], Hispanic [24] and Korean [37] origin. Parity was reported in 66 cases, of which 60 (90.9%) were primiparous [1, 2, 5-8, 12, 13, 15-23, 25-31, 33, 34, 36-45, 48, 49, 51, 52, 54, 55 and 57-59]. Data on BMI were available in only two patients (BMI: 22 kg/m² and 23.5 kg/m²) [58, 43], while in another case the patient was reported by the authors as being “morbidly obese” [16].

3.2 Medical history and symptoms before myomectomy

Ten (10.30%) women had an uneventful previous medical history [1, 24, 27, 33, 36, 38, 39, 54, 57 and 58] and eight (8.24%) were aware of the presence of the fibroid before the pregnancy [15, 20, 22, 25, 30, 42, 46, 49]. One had an adnexal mass [47] and one (1.03%) reported abdominal swelling [31]. One woman presented with brain arteriovenous malformation (AVM) and convulsions [7], one with primary infertility and multiple fibroids [51] and one was reported as a drug abuser [34]. For 74 (76, 28%) cases no relevant information was available.

Abdominal pain was the most common symptom, reported in 77 cases [1, 2, 5-8, 11-13, 15-19, 21, 22, 25-37, 39-45, 47-58]. Other commonly reported symptoms were fever (n=12) [5, 8, 17, 18, 21, 33, 36, 50 and 57], abdominal heaviness (n=10) [1, 11, 20, 38, 40, 45, 55 and 58], vomiting (n=9) [8, 12, 28, 29, 34, 36, 39, 54 and 55], constipation (n=8) [1, 6, 12, 31, 33, 34, 48 and 55] and vaginal bleeding (n=8) [5, 24, 25, 27, 40, 51 and 53]. Two patients presented with hemoperitoneum and hypovolemic shock due to excessive bleeding from the fibroids' vessels [32, 39]. A summary of the symptoms is presented in Table 2.

Table 2. Patients' symptoms before myomectomy.

Symptoms	Patients (n=97)
Abdominal pain	77
Fever	12
Abdominal heaviness	10
Vomiting	9
Constipation	8
Vaginal bleeding	8
Urine retention	6
Respiratory discomfort	5
Threatened miscarriage	4
Pedal edema	4
Cervical dilatation	3
Nausea	3
Uterine contractions	2
Hydronephrosis	2
Hypovolemic shock	2
Dehydration	2
Poor appetite	2
Weight loss	2
Diarrhea	2
Abdominal peritonitis	1
Ascite	1
Meteorism	1
Psychological disturbance	1
Weakness	1
Flush	1
Asymptomatic	1

3.3 Diagnosis

The patients were diagnosed at a median gestational age of 13 weeks (range 6-26). Relevant data were available for only 50 (51.5%) of the women. Overall, 70 (72.2%) women were diagnosed via ultrasound. Magnetic resonance imaging (MRI) was used to confirm the diagnosis in 17 (17.5%) patients. No data were available regarding an ultrasound or an MRI examination in 27 and 79 of the patients, respectively.



Figure 2 (Google search)



Figure 3 (Google search)

3.4 Management

The median age at myomectomy was 16 (range 6-26) weeks, while for six patients no relevant information was provided [56]. A single myomectomy was performed in 74 (76.28%) women [1, 7, 8, 11- 15, 17-22, 24-32, 35-39, 41-50, and 52-59], while in 23 (23.71%) patients multiple fibroids were removed [2, 5, 6, 8, 11, 13, 16, 23, 33, 34, 40 and 51]. The median number of fibroids removed from each patient was one (range 1-5). The median weight of the largest of the removed fibroids was 1,350gr (range 95-10,000) with the two largest fibroids weighing 8.9 [55] and 10 kg [28], respectively. The median largest diameter of the fibroids was 13 (range 5-40) cm.

Among single myomectomies, most of the removed fibroids were subserous pedunculated (n=33) [1, 7, 8, 11, 12, 15,17, 18, 28, 29, 35, 36, 37, 39, 41-43, 45, 49, 52 and 54-59] and subserous (n=10) [13, 20, 21, 26, 27, 30-32, 38 and 48], seven were intramural [11,50], two submucosal pedunculated [25, 44], two prolapsed endocervical [24, 53] and one prolapsed submucosal [24]. Two ovarian fibroids were also reported [22, 47]. In 17 cases, the position of the removed fibroids was not mentioned [5, 19, 46, 49 and 56]. The fibroids were mostly located at the uterine fundus (n=25) [7, 8, 11, 12, 17, 20, 21, 28, 29, 32, 35, 36, 38, 42, 43, 45, 49, 54-57 and 59], the anterior (n=10) [1, 11, 15, 18, 19, 26 and 50] and posterior wall (n=5) [27, 30, 31, 37 and 39]. Regarding their association with the placenta, one fibroid was in contact with the placenta [5], seven were described as retroplacental [5, 20, 27, 28 and 38] and 13 had no contact to the placenta [5, 22, 44 and 47]. No data were available regarding their relation to the placenta for 54 of the removed myomas. The mean size of the subserous pedunculated fibroids removed was 13.2 (\pm 9.0) cm. No relevant data were provided about the size of the intramural fibroids removed.

In multiple myomectomies, most of the fibroids were intramural (n=19) [2, 11, 13, 33, 40], subserous (n=17) [6, 11, 13, 40 and 51], subserous pedunculated (n=13) [2, 8, 11, 16, 34 and 51] and submucosal (n=2) [23, 33], while no data were available about the position of 14 removed myomas [5, 6 and 23]. Most of the fibroids were located at the uterine fundus (n=17) [11, 13, 16, 23, 40 and 51], the anterior (n=15) [11, 13, 33 and 51] and the posterior wall (n=8) [6, 11, 13, 33 and 51]. One was in contact with the placenta [5], two were retroplacental [6, 23] and three had no contact with the placenta [5]. For 59 of the removed fibroids no relevant data were available. Due to insufficient information regarding the mean size of each type of fibroid

removed during multiple myomectomy, the mean size of the largest fibroid removed was considered (11.6 ± 6.1 cm) (Table 3).

Table 3. Characteristics of removed fibroids according to the type of myomectomy (single-multiple).

Type of removed fibroids	Number of removed fibroids	
	Single myomectomy	Multiple myomectomy*
Subserous	10	17
Subserous pedunculated	33	13
Intramural	7	19
Submucosal	0	2
Submucosal pedunculated	2	0
Prolapsed submucosal	1	0
Prolapsed endocervical	2	0
Ovarian	2	0
No data	17	14
Location of the fibroids		
Fundus	25	17
Anterior	10	15
Posterior	5	8
Right wall	0	1
Left wall	0	2
Cervix	4	1
Cornual	2	2
Ovary	2	0

Isthmic	1	0
Fornix	1	0
Intraligamental	1	0
No data	23	19
Relation to the placenta		
No contact	13	3
Retroplacental	7	2
In contact	1	1
No data	54	59
Size of subserous myomas removed in single myomectomy (cm) (mean ± SD)	17.6±8.6	-
Size of subserous pedunculated myomas removed in single myomectomy (cm) (mean ± SD)	13.2±9.0	-
Size of largest myoma removed in multiple myomectomy (cm) (mean ± SD)	-	11.6±6.1

*Presentation is performed per fibroid not per patient

Laparotomy was performed in 76 (78.4%) of the cases [2, 5-7, 11-13, 16, 19-21, 23, 26, 28-34, 38-41, 45, 46, 48-51, 54-59]. Fifteen (15.5%) patients underwent laparoscopic surgery [1, 8, 15, 17, 18, 22, 35-37, 42, 43, 47 and 52], while one of them went through isobaric laparoscopy to avoid the adverse effects of carbon dioxide insufflation [17]. Furthermore, a laparoscopic salpingo-oophorectomy due to an ovarian leiomyoma was reported [22]. Vaginal myomectomy was performed in 4 patients (4.12%) [24, 25 and 44], while in one case an operative hysteroscopy was performed [53]. No data were available about the type of surgery in one patient [27].

Most of the operations were performed under general anaesthesia (n=35) [7, 8, 11, 12, 15, 16, 20, 23, 24, 28, 31, 32, 35-39, 42, 43 and 54]. Spinal anaesthesia was used in 3 cases [17, 25 and 41], while no relevant data were provided for 59 procedures [1, 2, 5, 6, 13, 18, 19, 21, 22, 26, 27, 29, 30, 33, 34, 40, 44-53 and 55-59].

Following myomectomy, reconstruction of the uterine wall was mostly performed by double-layered sutures (n=23) [2, 7, 11, 12, 30, 33, 38, 41, 50, 51 and 58], whereas one-layer

(n=2) [1, 17] or multiple layers (n=1) [6] were rarely used. During laparoscopic procedures, most surgeons used bipolar electrosurgical devices (n=8) [8, 36, 37, 42, 43, 47 and 53], while, staplers (n=2) [15, 35], bipolar/ monopolar forceps (n=1) [8], monopolar diathermy (n=1) [18] were occasionally used. In a single case report, aspiration and biopsy of the fibroid rather than myomectomy was reported [19].

For the repair of the uterine scars, Vicryl was used in most of the cases (n=29) [2, 7, 11-13, 25, 31, 39, 41, 46, 47, 49 and 51]. Chromic catgut (n= 3) [24, 30 and 38], plain catgut (n=1) [24], PDS (n=1) [1], monocryl (n=1) [58] and polysorb (n=1) [6] were alternatively used. In five cases of laparoscopic myomectomy of pedunculated myomas no suture was needed. In these cases, surgeons used bipolar electrosurgical devices (n=3) [36, 37 and 42] or staplers (n=2) [15, 35] to remove myomas. In six cases, an endoloop was used to ligate the pedicle of the fibroid for haemostasis [8, 18, 43 and 52]. No data were provided in 47 cases [5, 16, 20-23, 26-29, 32-34, 40, 44, 45, 48, 50, 54-57 and 59].

Information about the duration of surgery was available in only 20 case reports [1, 8, 13, 17, 22, 30, 36, 42, 43, 46, 47, 52, 53 and 58], with a median of 53 (range 20-150) minutes.

Finally, the estimated blood loss during surgery was reported in only 27 cases [1, 2, 6, 8, 12, 13, 17, 21, 22, 24, 25, 28-32, 36, 39, 43, 47, 50, 55 and 58] with a median of 350 (range 30-4,500) ml.

3.5 Histopathology

Regarding the histopathologic examination of removed myomas, most of them revealed necrosis (n=28) [1, 5, 8, 11, 16, 22, 24, 30, 32, 33, 37, 39, 41 and 47-49] and degeneration (n=19) [2, 5, 7, 11, 17, 34, 36 and 41]. Moreover, nine fibroids were complicated by cystic degeneration [11, 13, 19, 28, 33, 45, 54 and 55], nine by torsion [11, 15, 16, 22, 35, 42, 52 and 57], seven by red degeneration [11, 13, 26, 29 and 50] and six by hyaline degeneration [11, 12, 28 and 31]. Adhesions of the myomas either to the abdominal wall or the omentum were observed in six cases [12, 31, 34, 43, 52 and 54]. Furthermore, a case of a leiomyomatous neoplasia of uncertain malignant potential was reported [20]. Finally, in a woman that presented with fever, elevated inflammatory markers and peritonitis, a pyomyoma (suppurative leiomyoma) was diagnosed [21].

3.6 Postoperative course

Following surgery, treatment included tocolytics (n=29) [11-13, 18, 21, 28, 30, 31, 33, 34, 38, 41, 44, 51, 54, 55 and 59], antibiotics (n=19) [2, 7, 12, 13, 16, 18, 21, 25, 30, 33, 47, 48, 51, 53 and 58], progesterone (n=9) [16, 23, 30, 33, 38, 41, 47, 58 and 59], low molecular weight heparin (LMWH, n=3) [16, 33 and 58] and analgesics (n=3) [6, 48, 54]. In most cases, multiple medications were offered. Five patients needed transfusion [12, 20, 28, 31 and 39], while three patients received no treatment [1, 37 and 50]. No data were available for 49 cases [5, 8, 15, 17, 19, 22, 24, 26, 27, 29, 32, 35, 36, 40, 42, 43, 45, 46, 49, 52, 56 and 57].

The postoperative course of most patients was uneventful (n=53) [1, 7, 8, 11, 12, 15, 17, 19, 22, 24-33, 35-39, 41-48, 51-54 and 57-59], while for 34 cases no data regarding associated complications, were reported [2, 5, 13, 20, 21, 40, 50 and 56]. A woman who underwent laparoscopy for a degenerating pedunculated myoma, needed later an abdominal laparotomy due to postoperative myometrial necrosis, abscess formation, uterine rupture and exposure of the amniotic sac. In this case, a monopolar diathermy had been used [18]. Other reported complications were a moderate post-surgery vaginal bleeding [6] and a shortening of cervical length with a positive vaginal culture [16]. These events did not affected the pregnancy outcome. In one case, after surgery, a hematoma was revealed on the uterine scar, while the patient was diagnosed with adaptive and anxiety disorders that may have been triggered by her underlying medical condition [23]. Myomectomy resulted to miscarriage in five patients [5, 11, 24, 34 and 56], four of them after a single myomectomy and one after surgical removal of multiple myomas. In one of these cases, a vaginal myomectomy of a prolapsed submucosal myoma was followed by rupture of membranes two weeks later [24], while another woman suffered a miscarriage of twins, a day after surgery, due to purulent chorioamnionitis [5]. Of 97 patients, 54 were discharged from hospital after a median stay of five (range 1-14) days [1, 2, 6, 8, 11, 13, 15-17, 19, 22, 23-25, 28-31, 33-39, 41-45, 48, 52, 53, 55, 58 and 59], while for 43 women no data were reported [5, 7, 12, 18, 20, 21, 24, 26, 27, 32, 40, 46, 47 and 49-51, 54, 56 and 57].

3.7 Delivery mode and outcome

As already mentioned, of the 97 cases, five (5.2%) resulted in miscarriage. Of the 92 cases that delivered, the mean gestational age at delivery after single myomectomy was 37.2 (\pm 4.9) weeks, while for those women who went through multiple myomectomy, the mean gestational age at delivery was 36.8 (\pm 5.1) weeks. Among 74 women who underwent single myomectomy 57 delivered at term (77.0%) [1, 5, 7, 8, 11-13, 17-19, 21, 22, 24, 25, 27-32, 36-39, 41-43, 45, 48, 50 and 52-59], six (8.1%) delivered between 34 and 37 weeks of gestation (late preterm period) [5, 11, 20, 44, 46 and 49] and only two (2.7%) before 34 weeks [11, 26]. No data regarding the mode of delivery were available for five women (6.75%) that went through single myomectomy [5, 15, 35, 40 and 56], while four miscarriages (5.4%) [5, 11, 24 and 56] were also reported. Furthermore, from 23 women who underwent multiple myomectomy, 20 (86.95%) delivered at term [2, 5, 6, 8, 11, 16 and 51], while two (8.69%) delivered at the late preterm period [23, 33] and one (4.34%) suffered from a miscarriage [34]. Moreover, 57 (66.3%) women delivered by caesarean section [1, 2, 5-8, 11, 13, 18-21, 23, 26-29, 33, 36, 38, 39, 41, 46, 48, 50, 54, 55 and 58], while 29 (33.7%) women had vaginal deliveries [5, 8, 12, 16, 17, 22, 24, 25, 30-32, 37, 42, 43, 45, 47, 49, 51-53, 56, 57 and 59]. From those patients who went through single myomectomies, 38 delivered by caesarean section (51.4%), while 27 had vaginal deliveries (36.5%). On the contrary, only two women (8.7%) who had more than one fibroid removed went through spontaneous labor and delivered vaginally. Among women who delivered vaginally after single myomectomy, 18 had spontaneous labor [5, 8, 17, 22, 24, 30-32, 37, 42, 43, 45, 47, 49, 52,53, 57 and 59], one underwent induction of labor [5], one had prelabor rupture of membranes (PROM) [12] and one presented with oligohydramnios and labor was also induced [25]. No data were available for 6 patients [56]. Most of the caesarean sections were elective (n=28) [5, 7, 11, 13, 19-21, 28, 29, 41, 46, 48, 50, 54 and 58]. One woman had an unsuccessful induction of labor and delivered via caesarean section [1]. One had a caesarean section due to preterm rupture of membranes and the presence of a posterior low uterine myoma [38], while one due to preterm rupture of membranes and malpresentation [36]. There was one case each of partial abruptio placentae in a twin pregnancy [39], placenta previa [11] and placenta accreta [18]. In one case, caesarean section was performed for a short umbilical cord [8], while in another, due to contractions, to prevent uterine rupture [26]. In this case, incarceration of the gravid uterus due to a huge anterior myoma was described. In a case of a caesarean section due to placenta previa, a hysterectomy was performed in order to control the bleeding [55]. Finally, in a twin pregnancy, a caesarean section was performed due to fetal malformations [27]. Among women with multiple myomectomy, two had spontaneous labor [16, 51], while 15 went through elective

caesarean section [2, 5, 11 and 13]. One had caesarean section due to failed induction of labor [6], one due to preterm prelabor rupture of membranes (PPROM) [33], one due to uterine contractions [23] and finally, one due to malpresentation [8].

Regarding neonatal outcome, only 39 cases had available data [2, 5-7, 13, 16-18, 20, 23, 26-28, 31, 33, 41, 55 and 57-59]. An Apgar score of 9 (at 1 min) was reported in 20 cases, of which 11 after single and 9 after multiple myomectomy [5-7, 13, 16, 17, 27, 33, 41 and 57] and of 10 (in 5 min) in 16 cases (12 after single and four after multiple myomectomy) [5, 16, 18, 23, 26-28, 31, 41 and 59]. Two cases of fetal abnormalities were reported in women who went through single myomectomy. One with limb defects diagnosed at birth [20] and a case of a twin in a dichorionic diamniotic pregnancy with clubfeet, hypoplasia of the nails and hydrocephalus, revealed by ultrasound at 28 gestational weeks [27]. Moreover, between single and multiple myomectomies, no significant differences were found in delivery characteristics and complications ($p=0.26$ –Chi square test), neonatal weight ($p= 0.256$ - One Way analysis of variance) and Apgar score. (Table 4).

Table 4: Pregnancy outcomes according to the type of myomectomy (single-multiple).

	Patients (n=97)	Single myomectomy (n=74)	Multiple myomectomy (n=23)	P value
Delivery outcomes				0.033*
Vaginal delivery (VD)	29/97(29.89%)	27/74 (36.48%)	2/23 (8.69%)	
Caesarean section (CS)	57/97 (58.76%)	38/74 (51.35%)	19/23 (82.6%)	
Miscarriage	5/97 (5.15%)	4/74 (5.4%)	1/23 (4.34%)	
No data on delivery	5/97 (5.15%)	5/74 (6.75%)	0/23 (0%)	
GA at delivery (weeks)				
Term (>37)	77/97 (79.38%)	57/74 (77.02%)	20/23 (86.95%)	
Preterm (34-37)	8 (8.24%)	6/74 (8.1%)	2/23 (8.69%)	
<34)	2 (2.06%)	2/74 (2.70%)	0/23 (0%)	
Delivery characteristics and complications				0.26*
Spontaneous labor	20	18	2	
Induction of labor	2	2	0	
Elective CS	43	28	15	
Prelabor Rupture of Membranes (PROM)	3	2	1	
Failed induction of labor	2	1	1	
Uterine contractions	2	1	1	
Placenta previa	2	2	0	
Combined PROM and malpresentation	1	1	0	
Malpresentation	1	0	1	
Abruptio placentae	1	1	0	
Placenta accreta	1	1	0	
Short umbilical cord	1	1	0	
Fetal malformations	1	1	0	
No data	12	11	1	
Neonatal outcomes				
Neonatal weight (gr) (mean ± SD)		2,979±635	3,154± 476	0.256 **
Apgar Score (1 min)				0.221*
10	4	2	2	
9	20	11	9	
8	13	11	2	
7	1	1	0	
No data	54	45	9	
Apgar Score (5 min)				0.53 *
10	16	12	4	
9	15	10	5	
8	2	2	0	
No data	59	46	13	

* Chi-square test ** One Way ANOVA analysis of variance

4. DISCUSSION

This study systematically reviewed all cases of myomectomy during pregnancy. To the best of our knowledge, this is the first study that attempted to numerically analyse myomectomy during pregnancy. All numeric data from case reports were extracted and examined per patient.

Hence, the median gestational age at diagnosis was 13 weeks. The diagnosis was mainly established via ultrasound. The main symptom during the antenatal period was abdominal pain not responding to analgesics.

Regarding surgical management, the median gestational age at myomectomy was 16 weeks. Laparotomy under general anaesthesia was the most common procedure, followed by laparoscopy and vaginal myomectomy; this decision mainly depends on the location and size of the myomas. Moreover, the uterine scar was mainly closed by a 2-layer Vicryl suture and bipolar electricity was used by most surgeons during laparoscopy to minimize tissue damage.

Necrosis and degeneration were the main histopathology results of the removed myomas. In most of the cases, the postoperative course was uneventful and the patients were discharged at a median of five days.

For single myomectomies, most of the fibroids were subserous and subserous pedunculated located at the uterine fundus, with no contact with the placenta. In multiple myomectomies, most of the removed fibroids were intramural and subserous located at the fundus.

Regarding adverse outcomes, few miscarriages (5/97) and one hysterectomy at delivery were reported. The median gestational age at delivery was 38 weeks. Women mostly delivered by elective caesarean section (58.7 %), however a significant number of women went into spontaneous labor and delivered vaginally (29.9%). Only a few cases of preterm labor (10.3%) were reported and most women delivered at term with optimal neonatal outcomes. Fetal malformations were reported in only two cases, likely unrelated to the procedure. There was no increase in adverse outcomes including miscarriage, PROM or low Apgar score in multiple compared to single myomectomy.

This study has certain limitations; first the overall number of case reports and case series existing in the literature is very small and also very heterogeneous.

The data were incomplete in many of the cases. Furthermore, although very old reports (before 1985) were excluded, differences in practice may present an issue, as the review ranged over a period of 35 years. We also cannot exclude interactions with possible confounders (myomectomy technique and clinician's experience). Since the clinicians' experience is important in studies of a technical nature, we assume that the most experienced clinicians undertook the operators' role. Specifically for myomectomy technique, it is not clear whether during the fibroids' enucleation, the surgeons tried to preserve the pseudocapsule, to minimize the postoperative complications and to enhance healing [60]. Moreover, the issue of publication bias may be important, as surgeons are more likely to have reported cases with favourable outcome. Last, our search included published data from three databases (Medline/PubMed, Scopus and the Cochrane Library); however these are the most common databases used in systematic reviews.

Although myomectomy during pregnancy is reserved for a minority of cases, the small number of reported complications during this procedure is encouraging. There is a clear need of prospective contemporary studies, ideally randomized-controlled trials, in order to provide definitive conclusions regarding effectiveness and safety. Until such evidence is available, gynaecologists may discuss the option of myomectomy in cases of symptomatic fibroids in pregnancy where conservative management fails, after appropriate patient counselling regarding the scarcity of evidence on effectiveness and safety. Future case reports should implement more detailed data regarding gestational age at diagnosis, maternal demographics, symptoms and previous treatment, sonographic or MRI characteristics of the fibroids, details on the surgical procedure, post-operative course and especially pregnancy complications including preterm birth, mode of delivery and neonatal outcomes to allow more comprehensive analysis.

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