

Aus der
Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe
der Ludwig-Maximilians-Universität München
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**Conservative Medical vs. Surgical Therapy Management of High Risk
Pregnancies, Complicated by Large Uterine Fibroids**

A Single German University Center Experience at the University Clinic Großhadern
from 1996-2007

Dissertation
zum Erwerb des Doktorgrades der Medizin
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

vorgelegt von

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Athen

2018

Mit Genehmigung der Medizinischen Fakultät
der Universität München

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Tag der mündlichen Prüfung: 12.07.2018

For my family:

Christian, Ariadne, Elina & Manuel

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List of Abbreviations:

Pt.#	Patient number
GA Deliv	Gestational Age at Delivery
Dur.Adm	Duration of hospital admission
Birthweight	Newborn Weight at Birth in grams
GP	Gravity/parity
Di. Di.Twins	Dichorionic-Diamniotic Twins
GW	Gestational Week Patient was first seen
GA Adm.	Gestational Age on Admission
Len. Adm.	Length of hospital Admission
Prior OP	If Patient had a prior gynaecological operation
Fibr@Deliv	Fibroid size at Delivery
Fibr remov	Whether Fibroid was removed at Delivery - or in the cases with the gestational age written in –the fibroid was removed during the pregnancy at the corresponding gestational week
Op	gestational week at which patient underwent myomectomy
Mode Deliv.	Mode of Delivery
prim. Cesa.	Primary Caesarean
Sek. Cesa	secondary Caesarean
spont.	Spontaneous vaginal delivery
Vacuum	spontaneous vaginal delivery assisted via vacuum
conserv.	Conservative medical therapy
LSK diagn.	Diagnostic Laparoscopy
LSKM	Laparoscopic Myomectomy
LapM	Myomectomy via Laparotomy
CRP	elevated C-Reactive protein
HE	Hysterectomy
Complica	Complication following Delivery
Prem. Cxs.	Premature Contractions
Vag. Bleeding	Vaginal Bleeding
Hydron.	Hydronephrosis
Abd. Pain	Abdominal pain
Reop	Reoperation
Postp.fever	postpartum fever

1. Introduction

Uterine fibroids are found in approximately 2-4% of pregnant women, making them the most common solid pelvic tumour encountered during pregnancy. [Burton et al., Katz et al. 1989] Sixty percent of these pregnancies usually remain asymptomatic whereas in approximately ten to forty percent of patients, complications may arise either during pregnancy or during postpartum [Burton et al. 1989, Exacoustos et al. 1993]. The most common complications arising from fibroids in pregnancy include an increased frequency of spontaneous abortion, placental abruption, premature rupture of membranes, premature labour, postpartum haemorrhage and postpartum sepsis [Rice et al. 1988, Exacoustos et al. 1993, Katz et al. 1989, Coronado et al. 2000].

The clinical management of uterine fibroids during pregnancy is primarily medical, but in cases of failed medical treatment, surgical intervention via myomectomy should be considered.

The goal of our study was to observe the possible complications that may arise from large uterine fibroids in pregnancy, the effectiveness of medical vs. surgical therapy, and the ability to determine the appropriate modality for the appropriate patient.

In this study we present the pregnancy outcomes in our obstetrics department of **12** medically treated patients with large uterine fibroids. From these **12** patients **3** were carefully selected and surgically treated, undergoing a myomectomy during their pregnancy.

2. Materials and Methods

Nineteen pregnant patients, all with large uterine fibroids (>8cm) presenting at Klinikum Grosshadern, a German university clinic and tertiary referral centre,

between 1996 and 2007, either for routine pregnancy ultrasound or admitted with pregnancy complications, were retrospectively followed throughout their pregnancy, delivery and postpartum. Data was collected via confidential patient charts as well as labour and delivery log, the ultrasound Viewpoint program from General Electric, and the confidential clinical data base of the university clinic Grosshadern. In cases of lost follow up, patients or their treating gynaecologists were contacted via telephone for details up to and including delivery. All patients received an initial ultrasound documenting the number, size and position of their fibroids as well as follow up ultrasounds documenting their potential growth, as well as growth of the fetus. All ultrasounds were performed by obstetricians/gynaecologists with special training in obstetrical sonography. 8(42%) Patients received a pelvic MRI in addition to Ultrasound. These were Patients with rather large fibroids with documented central necrosis and growth of the fibroid during pregnancy.

The 19 Patients had a mean age of 35 years, ranging from 26 to 42 years of age, 12 (63%) were nulliparous vs. 7(37%) multiparous. The fibroids were evaluated for size, number, position, and location in relationship to the placenta and sonographic echotexture (important in the evaluation of degenerating fibroids). Ultrasonographic confirmation of the myoma was based on the criteria described by Muram and Colleagues [Muram et al. 1980]: 1) spherical mass with a diameter equal to or greater than - in our study population 8cm 2) distortion of the myometrial contour by the mass, and 3) differentiation of the mass from the myometrium by different variations in echogenicity as seen by ultrasonography [Muram et al. 1980, Rosati et al. 1992]. The classification of the fibroids was based on Benson`s described criteria (Benson et al., 2001) and subdivided into 1) submucosal: protrusion of a part of the fibroid into the uterine cavity, 2) intramural: fibroid growing within the uterine myometrium and 3) subserosal: fibroids extending externally to the serosa.

Patients who underwent myomectomy during pregnancy were more likely to have symptoms resistant to medical therapy. The criteria for deciding which

patients underwent myomectomy during their pregnancy were: 1) persistent symptoms resistant to conservative medical therapy (listed below), 2) rapid growth of the fibroid during pregnancy (documented via ultrasound or MRI), 3) retroplacental location of fibroid, and 4) signs of fibroid myxoid degeneration or central necrosis. Conservative medical therapy consisted of ice pack cooling, thrombosis prophylaxis with Heparin (due to strict bed rest), tocolytics (magnesium sulfate, 1µg/min Fenoterol (β-sympathomimetic; Partusisten®, Boehringer Ingelheim Pharma, Ingelheim, Germany) analgesics (Buscopan, Boehringer, Paracetamol), in cases of increased CRP and presumed infection (Augmentan®, SmithKline Beecham Pharma, Munich, Germany), intravenous fluid and prostaglandin inhibitors (Ibuprofen), as well as (Betamethason - Celestan®, Essex Pharma, Munich; Germany) for induction of lung maturation when deemed appropriate. All patients underwent fetal vitality monitoring via ultrasound, as well as cardiotokographic documentation of contractions.

All myomectomies were performed in the second trimester (19th week and 21st week of pregnancy) following informed consent via laparotomy and with the use of a cell-saver to minimise blood loss. Postoperative fetal monitoring via ultrasound and tocolysis (magnesium sulfate and Partusisten, Boering) assured fetal well being. All patients were compared as to their complaints leading to hospital admission, length of admission prior to delivery, length of pregnancy as well as fetal outcome and occurrence of postpartum complications.

3. Description of Patients

Patient 1

40 year old G1P0-was admitted repeatedly in a different hospital between the 7th and 14th week of pregnancy with vaginal bleeding. The patient was finally transferred to Klinikum Großhadern in the 14th week, following an on/off admission time of 4 weeks at the initial hospital, with the question of myomectomy vs. continuous conservative therapy. At the time of admission, the patient had light intermittent vaginal bleeding, but no abdominal pain or other symptoms. A single cervical transmural fibroid measured 12cm x 10cm x 9cm on admission (ultrasound and MRI) which within 3 weeks had increased to 17cm x 18cm x 12cm. A second smaller cervical fibroid measured 3,5cm x 5x4cm. On MRI the fibroid showed an inhomogeneous signal which indicated a subacute earlier blood clot. The edge of the placenta contacted the two fibroids, and the two cervical fibroids distorted the natural birth canal. Interestingly enough there always seemed to be a two week discrepancy between the size of the fetus and the gestational age based on ultrasound.

The patient received conservative management during her admission over the span of roughly a week and was discharged after remaining asymptomatic and without any further vaginal bleeding, to outpatient control every two weeks. The patient delivered a 2820 gram healthy male fetus via primary caesarean (due to the distortion of the birth canal), in the 39th week. APGAR (neonatal assessment score named after Virginia Apgar) were 9 at 5 minutes and 10 following 10 minutes. The main cervical fibroid at the time of delivery was over 20cm and was left in place. The patient was discharged a week after delivery without any postpartum complications.

Patient 2

37 year old G1P0 who was admitted in the 14th week of pregnancy because of abdominal pain. A 12cm x 12cm transmural posterior wall fibroid without signs of necrosis was documented via ultrasound. In addition a 6,5cm subserosal right sided and 3,5cm subserosal fundal fibroid were documented. The patient was conservatively managed and was discharged after 2 weeks. The fibroids showed minimal growth throughout the pregnancy. No MRI was performed in this patient. The patient delivered a healthy 3100g female infant (APGAR 9 and 10) at a different hospital in the 41st week via secondary caesarean, following premature rupture of membranes and arrest in the second phase of labour. At the time of caesarean, the patient had an 8x8cm intramural right sided fibroid. The placenta was anterior. No complications postpartum were noted. The patient was discharged with the recommendation to have a myomectomy prior to future pregnancy.

Patient 3

33 year old G1P0 who was admitted in the 21st week of pregnancy with abdominal pain, fever and increased infection parameters in blood. The patient had a 15cm x 12cm intramural fundal fibroid (Image 1) and was treated conservatively with antibiotics, cooling, pain medication and anticoagulation over a period of 13 weeks. In the 26th week the patient had nausea, and right upper quadrant abdominal pain despite non rising infection as well as liver enzyme parameters. An examination of the gallbladder was within normal limits. The patient continued to be managed conservatively, and remained stable up until the 32nd week where she again started complaining of right upper quadrant abdominal pain, most likely attributed to the growing fibroid and possibly its inner necrosis. In the 34th week (33+2) following RDS prophylaxis, and due to premature labour and an increase of the fibroid size to 25cm, the patient was delivered via caesarean, without removal of the fibroid- due to the increase risk of bleeding. (Image 2 and Image 3). The female

newborn weighed 1890 gram (10% in the 34th week-1973g) and was healthy (Apgars 8/9).

Four days following the caesarean the patient underwent a CT scan of the abdomen due to worsening of her condition. The CT showed free fluid in the abdomen and bilateral plural effusions, but no signs of a hematoma or abscess. An increase in the size difference of the patient's legs as well as pain led to a doppler ultrasound to rule out a deep vein thrombosis. This as well as a spiral CT to rule out a pulmonary embolism were both negative. Due to an acute abdomen and fear of a uterine torsion due to the large remaining fibroid the patient was re-operated with the diagnosis of chronic appendicitis and a fibroid removal was performed during the same operation (Image 4).

Overnight the patient lost a considerable amount of blood vaginally which was unable to be stopped conservatively and was taken to the operating room again. An abdominal hysterectomy (Image 5) was necessary due to diffuse bleeding in the placenta insertion areas, which was unable to be stopped following one hour of conservative methods. The patient received 8 packs of Red Blood Cells and 8 Units of Fresh Frozen Plasma, and was stabilised at a Haemoglobin of 8,9 g/dl at the time of discharge (almost 4 weeks after her initial caesarean).



Image 1: Ultrasound depiction of large fibroid

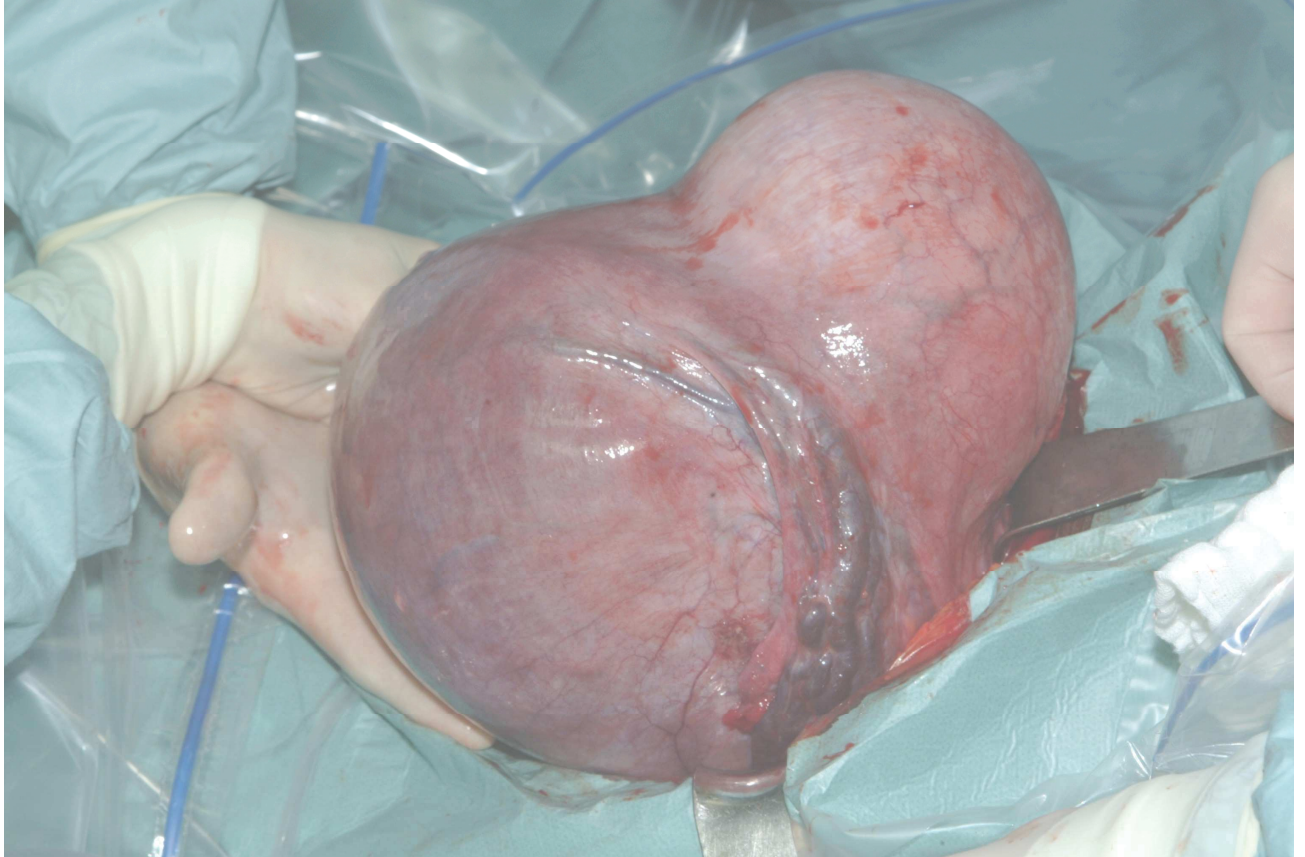


Image 2: Twisting of the pregnant uterus due to large fibroid

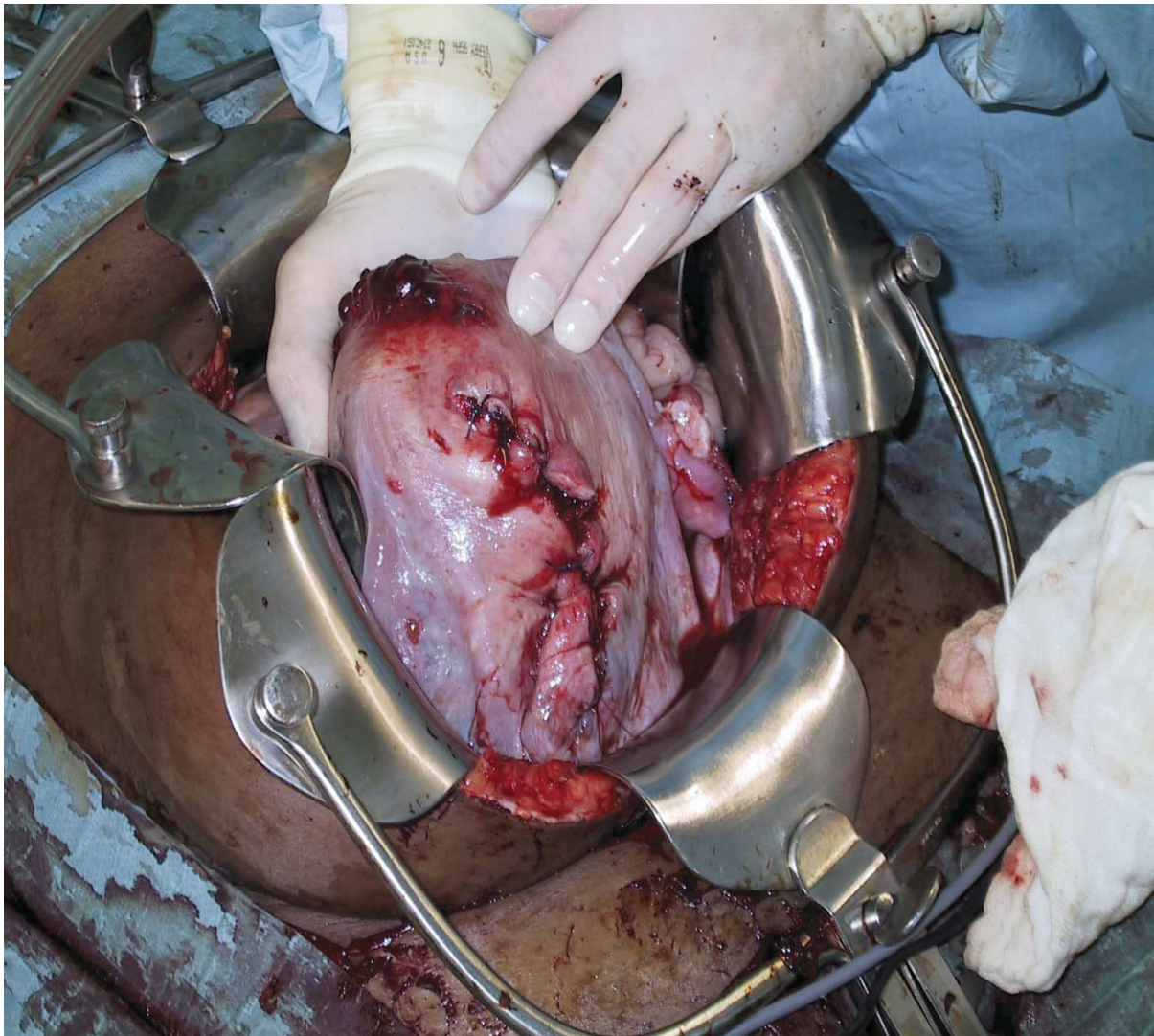


Image 3: Re-laparotomy and removal of fibroid

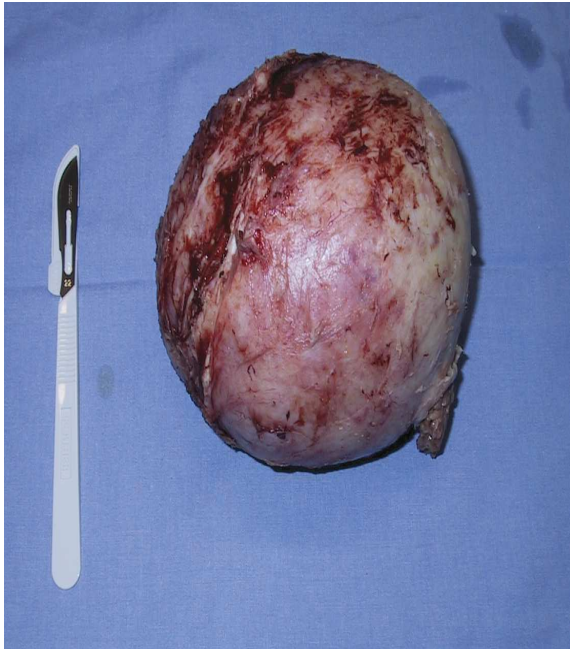


Image 4: Fibroid removed 4 days following Cesarean due to acute abdomen

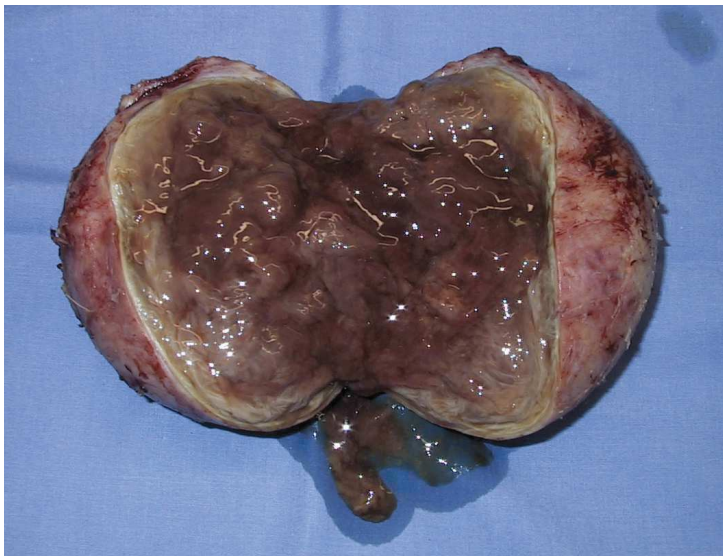


Image 5: Necrotic fibroid

Patient 4

29 year old G1P0 having undergone a myomectomy one year prior where a posterior wall fibroid measuring 5cm was removed via laparotomy. The patient was admitted with abdominal pain in the 15th pregnancy week and was found to have multiple fibroids, the largest of which was a cervical fibroid measuring 15cm x 13cm. The patient was admitted for a total of three weeks and conservatively managed, and following discharge continued to be followed as an outpatient. The fibroid showed minimal growth, throughout the remainder of the pregnancy, however an MRI in the 26th week of pregnancy showed the uterine wall at the fundus as being less than 1cm thick, (Image 6) with a left sided lateral placenta. In the 28th week the patient was found to have polyhydramnion although TORCH and OGTT (oral glucose tolerance test) results were all normal. The patient was admitted again in the 31st week due to premature contractions and remained under close observation until delivery in the 32+6 week of pregnancy via primary caesarean, due to an extreme fibroid uterus. At the time of caesarean a hysterectomy was also performed, due to the inability to re-approximate the uterus as a result of its hypertrophy. The 2120 gram male infant with Apgars of 8/8, required CPAP (continuous positive airway pressure) over a few days, but was otherwise healthy. The uterus according to the pathology report weighed 3560 grams and was 30cm x 20cm x 20cm large.



Image 6: MRI 26+0 weeks of pregnancy - myometrium at fundus less than 1cm in Patient 4

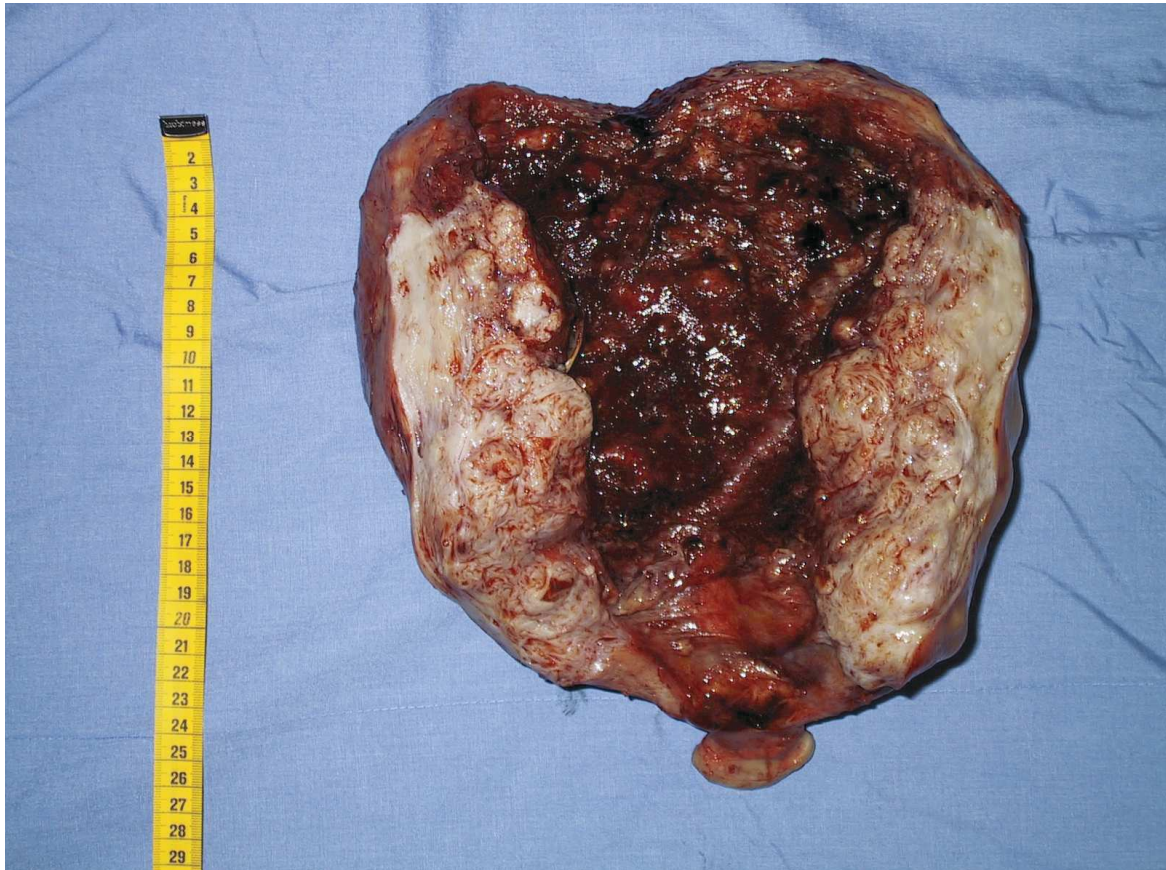


Image 7: Uterus showing necrotic edges unable to be re-approximated in Patient 4

Patient 5

38 year old G2P1 with a prior caesarean delivery 2 years prior and a laparoscopic fibroid enucleation of a 4cm posterior wall fibroid two years before that, with documented opening of the uterine wall. The patient was seen in the 22nd week of pregnancy due to vaginal bleeding and abdominal pain. An MRI in the 22nd week showed a left lateral intramural 13,8cm x 7cm fibroid, as well as multiple intramural fibroids and one 4,2cm submucosal fibroid on which the fetus was lying. The patient was observed as an outpatient and was delivered via primary caesarean in the 39th week of a 3580g healthy, male infant. At the time of caesarean no mention of a submucosal fibroid was made.

Two weeks following the delivery the patient had increased infection parameters (CRP-C-Reactive Protein max. 20,6mg/dl-normal under 0,5mg/dl)

and an abdominal CT showed possible fibroid necrosis. The patient was treated conservatively with analgesics and antibiotics and was discharged.

Patient 6

29 year old G2P0 with dichorionic–diamniotic twins following ICSI, and a known fibroid uterus. Prior to the pregnancy, a diagnostic laparoscopy for infertility had been performed. The patient was admitted in the 9th week due to vaginal bleeding-but was discharged within 4 days, and was readmitted in the 11th week due to abdominal pain. In the first admission a 9cm subserosal Fundus fibroid was discovered, and two weeks later diffuse fibroids were seen from portio to fundus measuring 15cm x 10cm. The patient was observed as an outpatient and was readmitted in the 25+2 gestational week with premature contractions. The patient was treated with antibiotics (Augmentan®, SmithKline Beecham Pharma, Munich, Germany) and tocolysis (magnesium sulfate and Partusisten , Boering) as well as 2 injections of Betamethason (Celestan®, Essex Pharma, Munich, Germany) for RDS (Respiratory Distress Syndrome) prophylaxis. However increasing infection parameters (CRP 6,3mg/dl) and premature rupture of membranes, with green coloured amniotic fluid and cervical dilation to 2cm with prolapse of a foot in the cervical canal, led to a clinical diagnosis of amniotic infection syndrome, and the patient was delivered via secondary caesarean (longitudinal) in the 25+4 week of gestation. The 750 gram female and 770gram male infant (both with APGARS 8/8) were intubated, but otherwise discharged after 8 weeks in the neonatal intensive care unit, healthy and without long term problems.

Four fibroids were removed at the time of the caesarean section, one of which interfered with uterine incision closure.

Patient 7

38 year old G3P2 with a laparoscopic myomectomy 6 years prior, followed by 2 spontaneous term deliveries who presented for delivery registration, asymptomatic, during the current pregnancy in spite of a documented 12cm x 10cm uterine fibroid located in the cervical region. The patient was delivered via primary caesarean in the 39th week of gestation delivering a 2730g infant with APGAR (9/10). The assessment of the uterus intra-operatively deemed a very difficult repair with an intraligamentary cervical fibroid and due to completed family planning, a hysterectomy was performed after obtaining patient consent (Image 12).

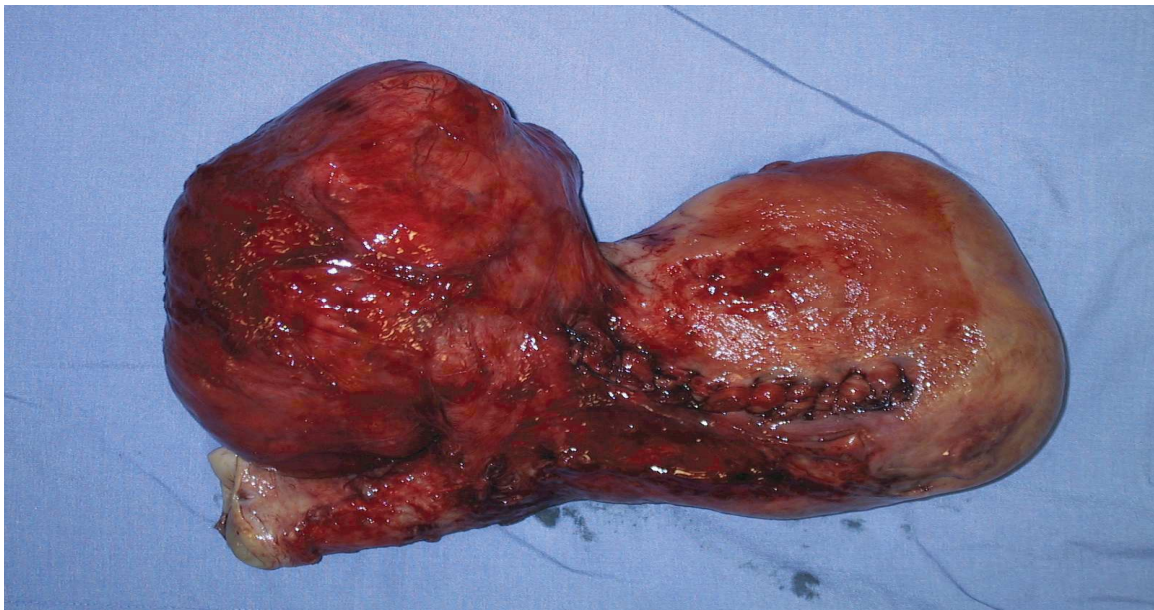


Image 8: Intraligamentary cervical fibroid and Uterus - Cesarean hysterectomy in Patient 7

Patient 8

33 year old G2P0 (one missed abortion in the 8th week) presented at 17 weeks of pregnancy with a subserosal 14cm x 11cm x 10,7 cm fundal uterine fibroid and a few posterior wall fibroids, who was admitted in the 19th week due to

abdominal pain and feeling of abdominal fullness. The fundal fibroid reached almost to the patient's sternum, and was confirmed via MRI as being almost 15cm and showing degenerative changes. The patient was aware of her fibroids but had not been recommended to have her fibroids removed prior to getting pregnant. The patient underwent at first conservative therapy but due to the rapid growth in size of the fibroid (the referring physician documented a 6cm growth within 4 weeks) and the risk of a potential sarcoma, the patient underwent a myomectomy in the 19th week of pregnancy. A subserosal fundal myoma (14.5cm x 14.5cm x 13.0cm; 1570g) was removed, under general anesthesia. The uterine cavity was opened, exposing the dorsal plane of the fundal placenta but without rupture of the amniotic membranes. Other additional fibroids on the posterior wall were left intact to avoid a second transmural defect. Perioperative normovolemic hemodilution and intraoperative blood salvage reduced blood loss during the operation and prevented the need of postoperative transfusion. The histopathological examination of the fibroid showed 6 mitosis per high power field, minimal cell atypia, focal regressive changes and necrosis, all of which classified the fibroid as a neoplasia of uncertain malignant potential. As a result of this diagnosis, the remaining fibroids were examined via ultrasound and MRI every 4 weeks, without further growth being observed for the remainder of the pregnancy. The patient underwent an MRI of the thorax which showed no pulmonary metastasis

The patient had an uncomplicated further pregnancy and was delivered at 36 weeks of gestation via caesarean, to avoid the onset of spontaneous labour due to increased uterine rupture risk following myomectomy. The baby was a 2495gram healthy female infant with (APGAR 8/8/9). At the delivery it was noted for the first time that the newborn was missing the right hand up to the wrist. The family history was empty for limb defects.

At the time of cesarean, biopsies were taken from the prior site of the fibroid. No signs of increased mitosis was found.

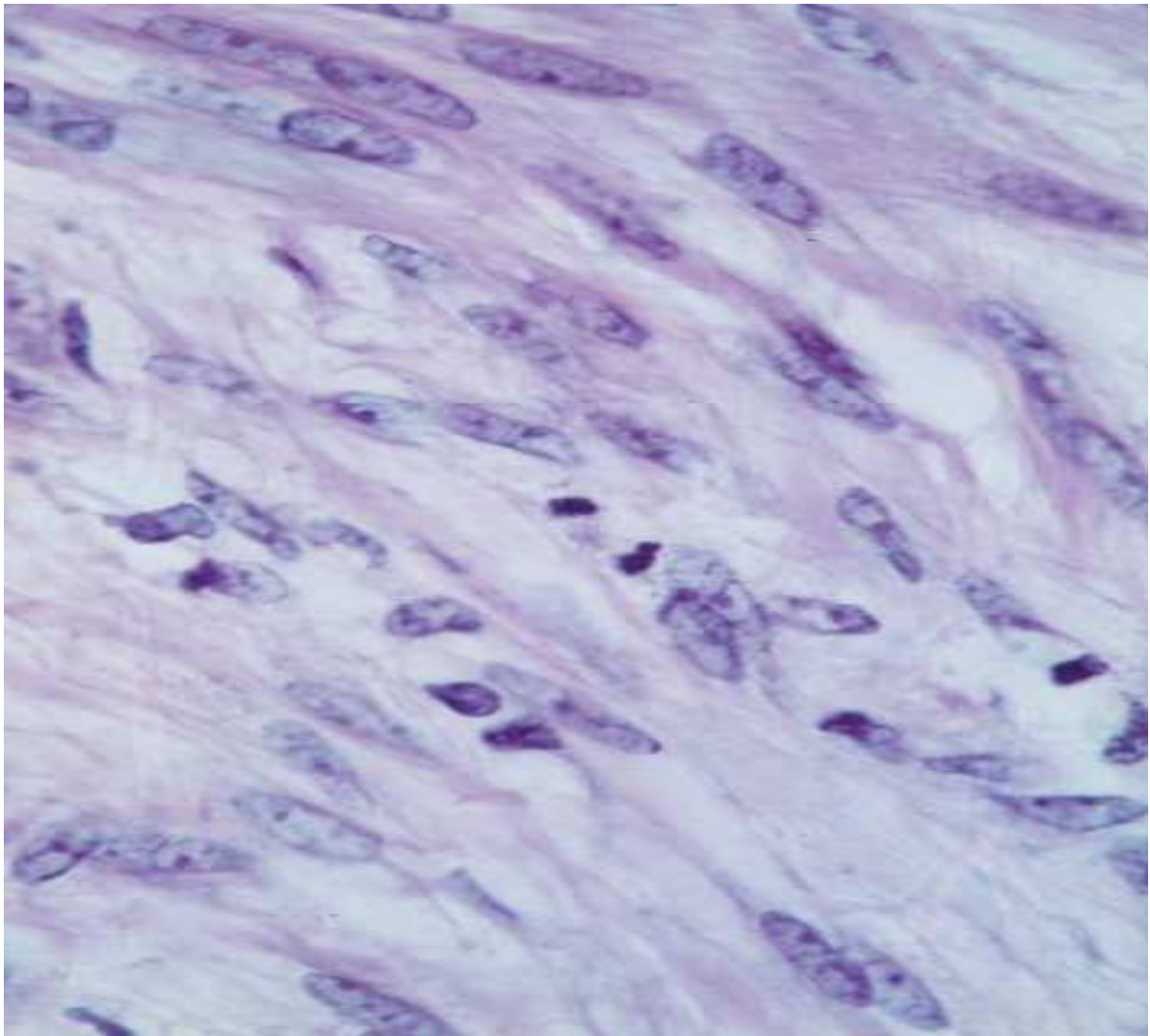


Image 9: Focally increased cellularity, mitotic activity and minimal cellular atypia in the smooth muscle tumor. H+E object magnification 64x in Patient 8

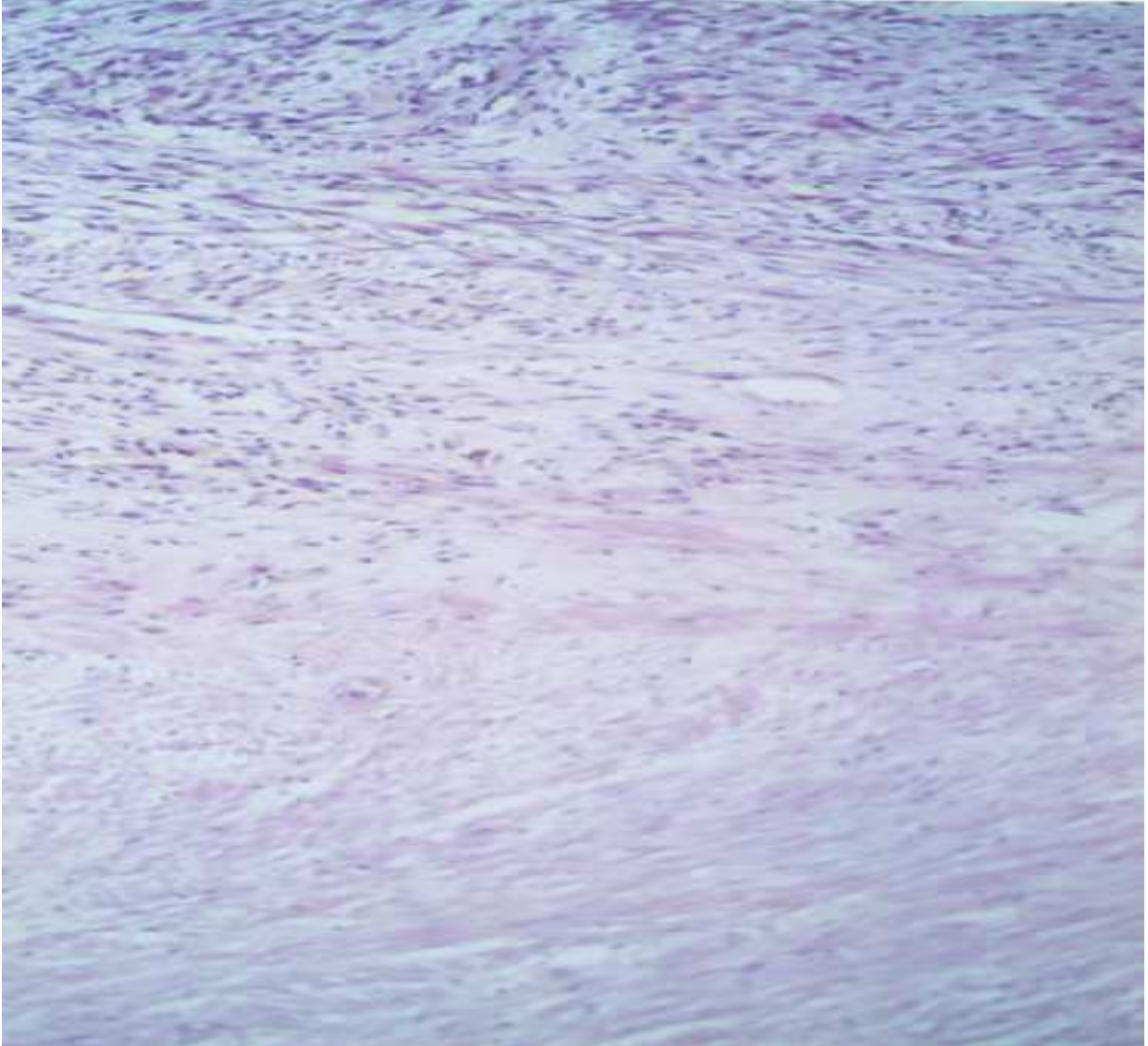


Image 10: Focal regressive changes with necrosis. H+E, object magnification 10x in Patient 8

Mitoses/10 HPF	Atypia	Cellularity	Diagnosis
0 – 4	-	Normocellular	(Typical) leiomyoma
0 – 4	-	Hypercellular	Cellular leiomyoma
0 – 4	+	Variable	Atypical leiomyoma
5 – 15	-	Normocellular	Mitotically active leiomyoma
> 5	Minimal	Hypercellular	Leiomyomatous neoplasia of uncertain malignant potential
> 5	+	Hypercellular	Leiomyosarcoma

Table 1: Histologic criteria for the diagnosis of uterine smooth muscle tumors (HPF = High power field; mod. from Zaloudek and Norris, 1994)

Patient 9

The patient was admitted in the 19th week of pregnancy due to abdominal pain. The patient was found to have a 14cm fibroid, which was removed due to persisting symptoms in the 19th week and weighed in at 1420gram. The patient was delivered in the 37th week via primary caesarean and had an uneventful postpartum.

Patient 10

42 year old G2P1 with prior caesarean due to preeclampsia in the 38th week, presented in the 18th week of pregnancy with right hydronephrosis and abdominal pain. The patient had a known fibroid uterus, which had been followed the prior 3 years and had been treated with ultrasound waves, with minimal reduction in size of the fibroids (fibroid 7,3cm x 5,4 cm one year prior to pregnancy). At her admission an ultrasound showed a normally developed fetus in the 18th week, with a large inhomogeneous fibroid 14cm x 12cm on the right side of the uterus, adjacent to the cervix and the placenta, with central

necrosis. A placenta previa was also seen, and the patient had some bleeding in the early pregnancy.

The patient was observed and conservatively treated over the next 3 weeks until the decision to undergo a myomectomy during the pregnancy was met, because of the continued signs of necrosis seen sonographically as well as via MRI and the worsening hydronephrosis which was anticipated would cause future problems in the remaining months of pregnancy. A myomectomy of the 12cm necrotic Cervix fibroid as well as of a 4cm pedunculated posterior wall fibroid was performed in the 21st week of pregnancy, using monopolar electric current and closing the bed with single vicryl stitches. The fetus and patient tolerated the operation well, and the patient was seen as an outpatient in the 27th week, with reduced hydronephrosis and an appropriately growing fetus. In the 28th gestational week the patient was admitted to her neighbourhood hospital due to a partial placenta previa and placenta accreta. Further ultrasounds disputed a placenta previa but due to increased vascularisation in the lower uterine segment a primary caesarean was performed in the 36th week. The female infant weighed 2570g and had Apgars of 9/10. During the caesarean the placenta was removed uneventfully, however a hysterectomy was performed, due to uncontrollable bleeding in the lower uterine segment. The patient received a blood transfusion of 2 units Red Blood Cells.

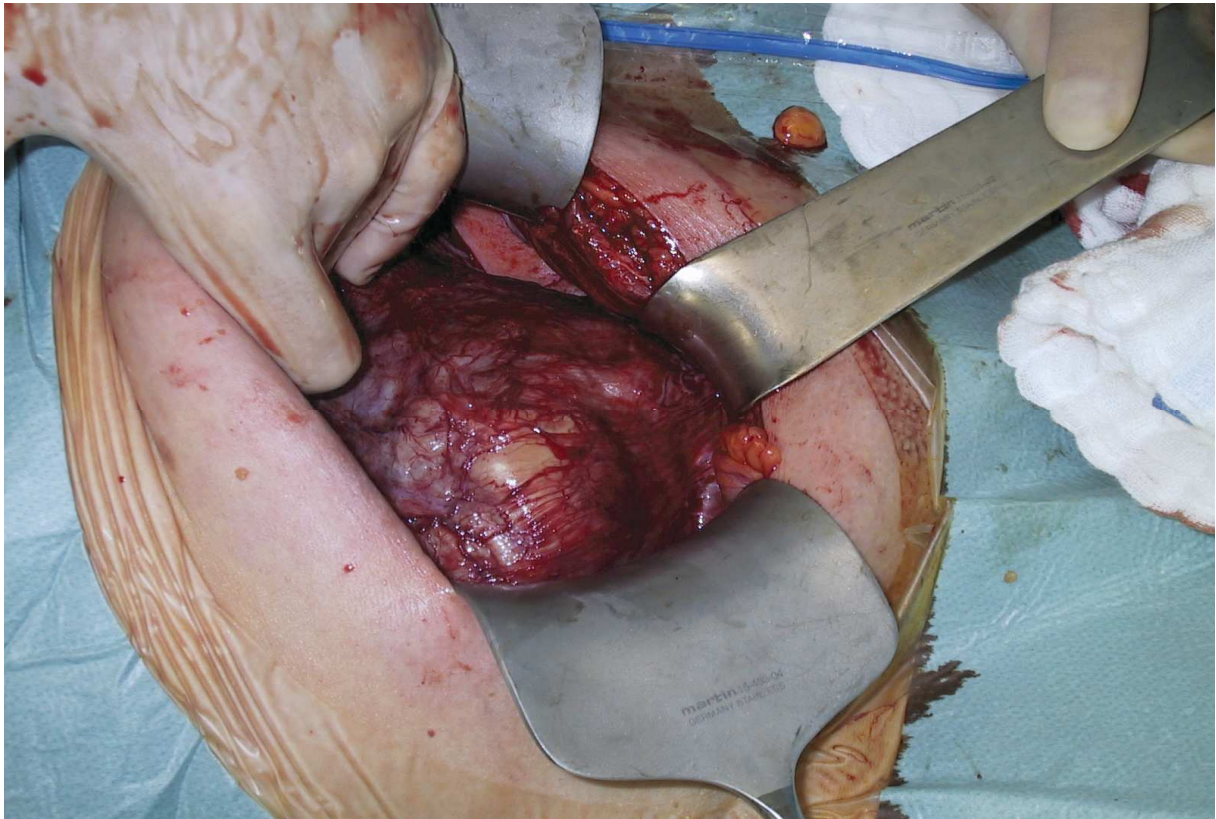


Image 11: Large Uterine Fibroid at intrapartum myomectomy in Patient 8

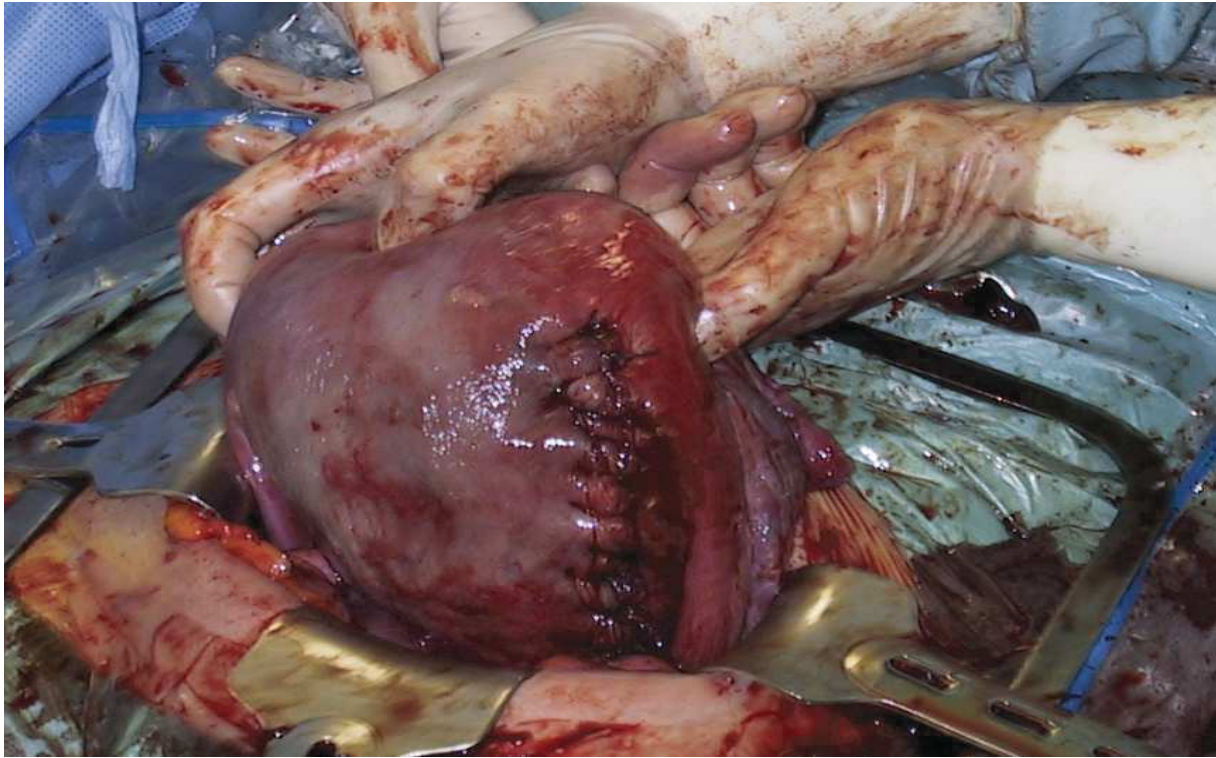


Image 12: Pregnant Uterus following intrapartum myomectomy in Patient 8

Patient 11

33 year old G1P1 who was followed as an outpatient throughout the pregnancy. The patient was first seen in the 11th week with a 11,4cm x 8,7cm x 11,7cm fundal uterine fibroid. The patient was closely followed as an outpatient, with ultrasounds every 2-4 weeks, without any documentation of fibroid growth, and no signs of central necrosis. The patient remained asymptomatic throughout her pregnancy. The patient was last seen in the clinic in the 37th week with normal fetal measurements and was then delivered via vacuum in the 38th week of gestation due to a protraction of the second phase of labour and green amniotic fluid. The healthy 2610g male infant had APGAR 10/10. The fundal uterine fibroid measured 10cm x 10cm (smaller than initially) and was left in place. The patient was discharged without any postpartum complications.

Patient 12

30 year old G2P0 seen in the clinic once during her 33rd week of pregnancy with a 8,0cm x 8,0cm fibroid, which according to the patient had grown during the pregnancy. The patient was admitted due to abdominal pain and premature labour with a 1cm long cervix. In spite of tocolysis and RDS prophylaxis the patient delivered in the 33rd week of pregnancy spontaneously a 2110 gram healthy, female infant APGAR 9/9. The placenta showed no signs of chorioamnionitis.

The patient was contacted a few years after delivery and mentioned that one year following delivery, the fibroid had gotten smaller (5cm), but because of abdominal discomfort it was eventually removed via laparoscopy.

Patient 13

26 year old G1P0 with a known fibroid prior to pregnancy measuring 5cm. The patient was first seen in the clinic in the 16th week of gestation where the fibroid measured 8,5cm x 8,6cm x 9,5cm, and was found to be lying near the placenta bed according to the ultrasound examination with central fluid necrosis. The patient was asymptomatic. A MRT showed an 8,6cm x 8,2cm x 7,5cm intramural fibroid with central necrosis and fluid, but without any relation to the posterior placenta. Follow up outpatient control showed an increase in the fibroid growth, measuring 9,7cm x 9,0cm x 7,7cm with central echoes in the 20th gestations week, with normal biometric measurements of the fetus.

The patient remained asymptomatic and was followed as an outpatient. She delivered spontaneously in the 42nd week of pregnancy a 3500g infant with APGAR 10/10. The 10cm fibroid was left in place and caused no complications postpartum.

The patient was contacted a few years following her delivery and she reported having had a second uncomplicated spontaneous delivery two years after the first. The fibroid is still present and not causing any symptoms.

Patient 14

35 year old Pt. G1p1 was admitted in the 10th week of pregnancy with a large fibroid uterus, abdominal pain, and increased infection parameters. The patient was treated conservatively with intravenous antibiotics, and pain medication. The diagnosis was one of presumed central necrosis of the 11cm x 8cm uterine fibroid. In addition, a 7,3cm x 7,0cm fibroid was also seen. The patient was released asymptomatic a week later with normal blood levels and no further fibroid growth. The patient was followed on an outpatient basis with a normal documented fetal growth and normal doppler parameters.

In the 39th week of pregnancy due to contractions and deceleration on CTG, it was decided to deliver via caesarean. A 3330g, female fetus with APGARS 10/10 was born. On further inspection of the uterus a 12cm x 8cm fibroid with a three cm. base, consistent with the growing myom in the pregnancy was found but left in place.

Patient 15

42 year old G2P1 (one spontaneous delivery 7 years prior at which point no fibroids were known), had a spontaneous pregnancy following years of infertility and numerous inseminations. Prior to the pregnancy, the patient was known to have a fibroid uterus with at least three fibroids the largest of which was 5cm. The patient was seen in the ultrasound ambulance in the 8th week at which time her fibroid measured 8,6cm x 6,5cm x 5,0cm. The patient continued to remain asymptomatic throughout an uneventful pregnancy, without complications through the fibroid.

She delivered in the 41st week via secondary caesarean due to vaginal bleeding of which the cause was thought to be either uterine rupture (with a sonographically measured uterine thickness of less than 0,5cm) or placental abruption. At the time of caesarean no uterine rupture was found, but sinus

bleeding due to a partial placenta separation (anterior placenta), as well as a 8cm intramural fibroid in the right isthmic area. A 3260g normally developed female infant APGAR 10/10 was delivered. The fibroid was left intact and the patient had an uneventful postpartum.

The patient was contacted a few years following delivery, and reported that the fibroid had decrease to 4cm following delivery. It managed however to grow slowly again over the 8 years following delivery to a maximum of 10cm at which time it was surgically removed.

Patient 16

37 year old G3P3 with two prior spontaneous deliveries and known uterine fibroids and gestational diabetes in the current pregnancy. The patient remained asymptomatic and was followed as an outpatient throughout the pregnancy. The multiple fibroids (5 all together) of which the largest measured 8,9cm x 8,4cm x 7,2cm transmural right in the 28th week did not show any increase in growth throughout the pregnancy (followed every two weeks sonographically till 37th week). A 1,8cm submucosal anterior wall fibroid was also documented. The placenta was posterior and without contact to fibroids.

The patient delivered vaginally in the 38th week a 3420g healthy male infant, APGAR 9/9 and had an uncomplicated postpartum.

Patient 17

39 year old G3P2 who was first seen asymptomatic in the 12th week of gestation, with a 9cm x 8cm x 8cm right wall fibroid. The same fibroid seemed unchanged in the 20th week fetal organ scan. The placenta was anterior. The pregnancy continued uneventfully and the patient remained asymptomatic from her fibroid.

The patient underwent induction of labour due to uncontrollable hypertension, (the patient was hypertensive also prior to the pregnancy and had Pregnancy induced hypertension with the first two pregnancies) and was delivered spontaneously in the 35th week of a healthy 2539g male infant. APGARS 9/10.

The patient was contacted a few years following delivery, and she reported still having a currently 9cm asymptomatic fibroid.

Patient 18

33 year old G1P0 first seen in the 10th gestational week with two large intramural fibroids measuring 6,8cm x 6,2cm x 6,0cm and 8,8cm x 8,0cm x 8,5cm respectively. The patient remained asymptomatic and a follow up measurement of her fibroid in the 19th week showed growth to 11cm x 9cm inhomogeneous with central necrosis and adjacent to the placental edge (placenta posterior). The fibroid continued to grow, measuring 14cm x 7,3cm x 7,9cm in the 26th week of gestation.

The patient was followed as an outpatient, and was delivered per primary caesarean in the 39th week due to cephalopelvic disproportion. The healthy male infant weighed 3690g and had APGAR 10/10. The double fist large cauliflower fibroid appeared partially necrotic and had a 3cm base and was intra-operatively removed because of risk of causing problems postpartum due to its necrosis. The fibroid was removed without entering the uterine cavity and

a future spontaneous delivery was not threatened. The postpartum time was uncomplicated.

This same patient went on to become pregnant again within two years of her initial caesarean. In the 39th week the patient was delivered via repeat caesarean because of the fear of uterine dehiscence. Truly, the area of the prior uterine incision was paper thin, and a 6cm defect only covered via serosa could be seen at the prior fundal myomectomy site. This 6cm defect extended all the way up to the tubal origin and could not be re approximated and was left unchanged. The patient was instructed to not get pregnant before the fundal dehiscence area was operatively corrected.

The patient neglected the warnings and became pregnant again 3 years later without prior operative repair of the dehiscence. In the 15th week of pregnancy an MRI showed the dehiscence in the fundus and it was decided that a continuance of the pregnancy without intervention was too risky. The patient underwent a laparotomy, and the dehiscence area was covered with an ethicon ultrapro monocryl prolene patch. The patient was admitted to the hospital after the operation due to premature contractions which were stopped with tocolytics. The fetus was monitored via ultrasound every two weeks and showed normal growth. The contractions returned in the 32nd week and could no longer be stopped with tocolysis.

The patient was delivered via repeat caesarean, revealing an adherent Peritoneum to the patch. A hysterectomy was performed by completed family planning and the patient had an uneventful postpartum.

Patient 19

41 year old G2P1 was first seen in the 21st week of pregnancy with premature contractions, and lightly increased infection parameters. The patient received intravenous antibiotics and analgesics (ibuprofen, paracetamol) and via

ultrasound a placenta previa as well as a large uterine fibroid measuring 8,2cm x 6,7cm were found. The fibroid was known before pregnancy to be 3,5cm. Due to a new rise in the infection parameters (elevated CRP) an MRI was performed which showed a necrotic 8,5cm x 6,4cm fibroid between the rectum and the bladder, as well as a second 4,9cm x 4,2cm intramural fibroid. Renewed antibiotic therapy reduced the pain as well as the infection parameters. In addition the patient received ibuprofen, and paracetamol. The pregnancy continued uneventfully and the patient was delivered in the 37th week via longitudinal caesarean of a 2720g male newborn, with APGARS 10/10. During the caesarean the large posterior fibroid near the rectum, showing degenerative changes was removed, leaving the other smaller fibroid behind. The histology showed no increased mitotic activity and no atypical cells, ruling out a sarcom.

4. Results

4.1 Distribution of Patients

We conducted a retrospective observational study of **19** pregnant patients, with a median age of **35** years, all with large uterine fibroids ranging from **8-25 cm** in size, referred to the university clinic of Großhadern in Munich, Germany, between 1996 and 2007 either due to symptoms or due to routine registration for delivery.

As depicted in **Table 2 - Study Design**, **7 (37%)** of these Patients were followed as asymptomatic ambulatory patients, **12(63%)** patients were admitted to the hospital with complaints varying from vaginal bleeding, abdominal pain, increased infection parameter, and premature contractions. From the **12** admitted patients, **9(75%)** received conservative medical therapy and **3(25%)** underwent myomectomy between the 19th and 21st week of their pregnancy. The decision to treat surgically was based on the characteristics of the fibroids and their symptoms, and non-response to initial conservative therapy. **5(26%)** Women delivered spontaneously. **14 (74%)** patients were delivered via caesarean section following the threshold of viability: **11(79%)** via primary caesarean and **3(21%)** via secondary caesarean. **4(29%)** of the patients undergoing caesarean required hysterectomy, and only **1(25%)** of the hysterectomy patients had undergone myomectomy during the pregnancy.

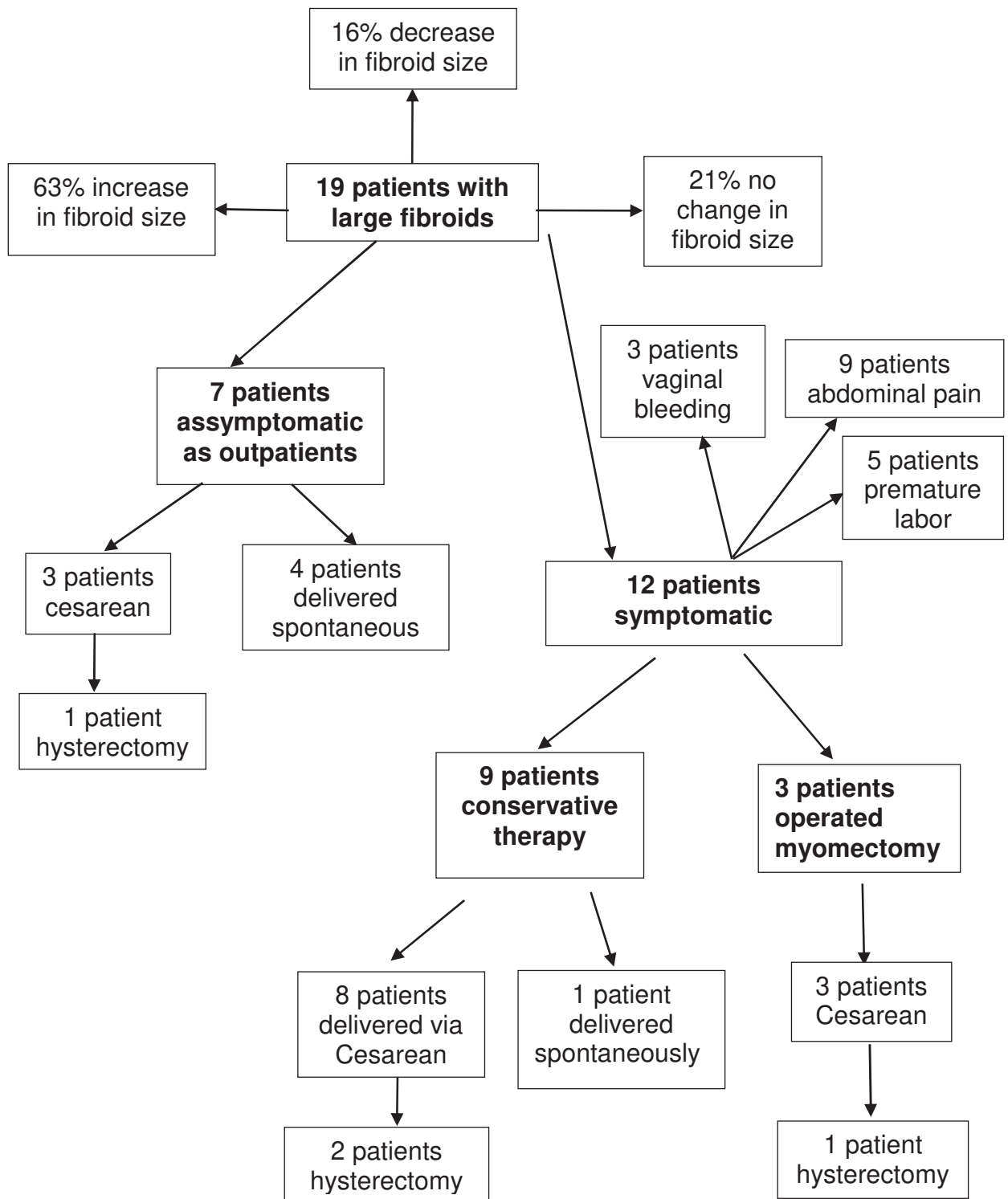


Table 2: The Study Design

4.2 Age at Presentation

All patients presented at differing gestational ages ranging between the 7th and 37th weeks of gestation. Patient ages ranged from 26-42 years of age, with the mean age being 35. (Table 3) All pregnancies with the exception of one, via assisted reproductive therapy (ICSI-Pt. 6), were spontaneous and in three patients subsequent to prior first trimester spontaneous abortions (Patients 8, 12, 19).

	Patient initials	Patient age	Delivery date
Patient 1)	KE	39	5/2002
Patient 2)	SY	37	2/2002
Patient 3)	SK	33	4/2002
Patient 4)	HMD	29	5/2002
Patient 5)	RH	38	7/2002
Patient 6)	HGE	29	4/2002
Patient 7)	ZG	38	7/2002
Patient 8)	GS	33	12/1996
Patient 9)			
Patient 10)	SS	42	10/2007
Patient 11)	HS	33	1/2002
Patient 12)	RD	30	1/2004
Patient 13)	SA	26	1/2003
Patient 14)	RA	36	11/2002
Patient 15)	NG	42	10/2003
Patient 16)	DB	37	5/2001
Patient 17)	SMP	39	9/2003
Patient 18)	FS	33	12/2004
Patient 19)	SB	41	10/2006

Table 3: Study Patients

4.3 Symptoms at Presentation

With the exception of seven asymptomatic patients, all other patients presented with pain, contractions, or vaginal bleeding as their primary complaint and reason for hospital admission. Twelve patients were admitted to the hospital between 18 and 33 weeks of gestation for a length of one to thirteen weeks prior to delivery.

Increased infection Parameters	Premature Contractions	Abdominal pain (11-33w)	Vaginal bleeding (13-17w)
3, 6, 10,14, 19 (42% of symptomatic patients)	4, 6, 12, 19 (33% of symptomatic patients)	2, 3, 4, 5,6, 8, 9, 10, 12, 14 (83% of symptomatic patients)	1, 5,6 (25% of symptomatic patients)
Asymptomatic Pts. 7, 11, 13, 15, 16, 17, 18 (37% of all patients)			

Table 4: Chief complaints leading to admission of pregnant patients with fibroids

4.4 Prior Myomectomy

Three patients (Patients 4, 5, 7) had a myomectomy prior to their current pregnancy (two via laparoscopy (Patients 5, 7), one via laparotomy (Patient 4)).

	Myomectomy during Pregnancy	Cesarean Delivery	Hysterectomy With Delivery	Spontaneous Delivery
Prior myomectomy 3 Patients (4,5,7)	0	3 Patients (4, 5, 7)	2 Patients (4, 7)	0
No prior myomectomy 16 Patients	3 Patients (8, 9, 10)	11 Patients (1, 2, 3, 6, 8, 9, 10, 14, 15, 18, 19)	2 Patients (3, 10)	5 Patients (11, 12, 13, 16, 17)

Table 5: Mode of Delivery with vs. without Prior Myomectomy

4.5 Diagnosis and Dynamic of the fibroids during Pregnancy

Ultrasound confirmation of the fibroids was based on criteria described by [Muram et al. 1980]: 1) spherical mass greater than 3cm in diameter, 2) distortion of the myometrial contour by the mass, and 3) differentiation of the mass from the myometrium by different acoustic structure as seen on ultrasound. The myoma was characterized as retroplacental in location when an intramural or submucous mass was present deep to the placenta, as described by Lev-Toaff et al.1987 The location of the fibroids were classified as by Benson et al as submucosal if part of the fibroid bordered on or protruded into the endometrium, intramural if the fibroid was within the wall of the uterus surrounded by myometrium, and subserosal if the fibroid extended to the serosal surface of the uterus.

In eight Patients (Patients 1, 3, 4, 5, 8, 10, 13, 19) an MRI was done in addition. (Table 7.) An MRI was usually done by patients with prior myomectomy or caesarean to assess the uterine wall thickness, and to decide delivery modus. According to Rozenberg [Rozenberg et al. 1996] a trial of labour could be proposed when the thickness of the lower uterine segment is >3,5mm. In patient 7 no MRI was performed because the patient had two spontaneous deliveries two and three years following her laparoscopic myomectomy and was also first seen as she came to register for her delivery in our clinic in the 37th gestational week. She had been asymptomatic throughout her whole pregnancy.

The majority of patients, 79%, had multiple fibroids. Only 21% had a single large fibroid. The types of fibroids and structure of fibroids as well as their relationship to the placenta are listed in table 7.

Interestingly enough as depicted in Table 6: 16 % of the fibroids decreased in size during gestation, 63% increased in size and 21% showed no change. From the fibroids which showed increase in size during the pregnancy four

(33%) showed signs of contact to the placental bed, and 7 (58%) showed signs of necrosis. From the fibroids which showed no change in size during the pregnancy 2 of the four (50%) interestingly enough showed signs of necrosis, as opposed to none in the group of fibroids which showed a decrease in size during pregnancy.

	Patients	%
Single Fibroid	11, 12, 13, 17	21
Multiple Fibroids	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 15, 16, 18, 19	79
No change in Fibroid size	15, 16, 17, 19	21
Decrease in Fibroid size	2, 5, 11	16
Increase in Fibroid size	1, 3, 4, 6, 7, 8, 9, 10, 12, 13, 14, 18	63
Placenta adjacent to fibroid	1, 3, 7, 8, 10, 18	32

Table 6: Change in size of Fibroid during pregnancy

Pt. #	GW	Fibroid Position	Fibroid Type	Fibroid size in mm	Fibroid structure	Placenta	MRI	Symptoms
1	7	Cervix	intramural	17x18x12	inhomogen. with subacute bleed	Fundal-contact with 2 fibroids	yes	vag. bleeding
2	14	Posterior right	transmural	120x120x120	homogeneous structure	Anterior	no	abd. pain,
3	21	side wall right	intramural	150x120	barely vascularised	side wall right low lying	yes	pain,crp
4	15	Cervix	subserosal	150x130	inhomogen.	posterior	yes	abd. pain,
5	22	side wall left	intramural	138x70	Myxoid-degenerative changes	side wall left	yes	abd. pain, vag. bleeding
6	9	Fundal	subserosal	90	inhomogen, central necrosis	di di Gemini	no	vag. bleeding
7	37	anterior	intra-ligament	120x100	homogeneous	Anterior	no	none
8	18	Fundal	subserosal	145x145x130	6cm growth within 4 weeks myxoid deg.	fundal-contact with fibroid	yes	abd. pain,
9	19			140				abd. pain,
10	18	Cervix	transmural	144x121x112	central necrosis	adj. to placenta, previa totalis	yes	abd. pain, Hydronephrosis
11	11	Anterior	intramural	114x87x117	homogeneous	posterior	no	none
12	33	Fundal	intramural	80x80x80	homogeneous	posterior	no	premat Cxs
13	16	Anterior	transmural	97x90x77	inhomogen, central necrosis	posterior adjacent to fibroid	yes	none
14	10	Side wall right	transmural	118x82x82	central necrosis	anterior	no	abd. Pain, CRP
15	8	Side wall right	subserosal	86x65x50	homogeneous	anterior	no	none
16	28	Side wall right	transmural	89x84x72	homogenous	fundal	no	none
17	12	Side wall right	transmural	110x90	inhomogen, central necrosis	side wall left-contact w: fibroid	no	none
18	10	Fundal	intramural	140x80x80	inhomogeneous central necrotising area	posterior adjacent to fibroid	no	none
19	21	between rektum/bladder	intramural	85x64	central necrosis	previa totalis	yes	none

Table 7: Fibroid numbers, types and relation to Placenta

4.6 Mode of Delivery

Fourteen of the nineteen patients were delivered through caesarean between the 26th and 41st week. Eleven of these fourteen caesareans were primary (main reason being the existence of a large fibroid, one transverse fetal position, one due to desire to avoid vaginal birth, one presumed placenta previa and one due to premature rupture of membranes and amnion infection syndrome in the twin gestation with ICSI in the 26th week.) Three caesareans were secondary (one due to arrest of labour, one due to fetal distress signs on cardiotocograph and one due to vaginal bleeding and a feared partial placental abruption).

	Myomectomy during Pregnancy	Cesarean Delivery	Hysterectomy with Delivery	Spontaneous Delivery
Prior myomectomy 3 Patients (4,5,7)	0	3 Patients (4, 5, 7)	2 Patients (4, 7)	0
No prior myomectomy 16 Patients	3 Patients (8, 9, 10)	11 Patients (1, 2, 3, 6, 8, 9, 10, 14, 15, 18, 19)	2 Patients (3, 10)	5 Patients (11, 12, 13, 16, 17)

Table 8: Mode of Delivery with vs. without Prior Myomectomy

Pt. #	GA Adm	Dur. Adm	Prior OP	Therapy	GA Deliv	Mode Deliv.	Fibr@ Deliv	Fibr remov	Compli-cations	GP
1	13	5	no	conserv.	39+0	prim. Cesa	20cm	no	none	G1P1
2	12	2	no	conserv.	40+2	sek. Cesa	8x8cm	no	none	G1P1
3	21	13	no	conserv.	33+2	prim. Cesa	25cm	yes HE	reop/HE	G1P1
4	15	3	LapM	conserv.	32+6	prim. Cesa	15,6x11	yes HE	HE	G1P1
5			LSK M-Ut op/Cesar	outpatient	39+0	prim. Cesa	12x6cm	no	postp fever	G2P2
6	9	2	LSK diagn.	conserv.	25+4	prim. Cesa Di.Di.Twins	4x9cm	yes	none	G1p2
7			LSKM.	outpatient	38+1	prim. Cesa	12x12 Zervix	yes HE	HE	G3p3
8	18	2	no	op19w	35+4	prim. Cesa	1575g 19w	yes 18w	lack of right hand	G2P1
9	19			op 19w	37+0	prim. Cesa	14cm 19w	Yes 19w	none	
10	18	24	yes Cesar ean	op 21w	35+2	prim. Cesa	HE	Yes 21w	bleeding/ HE	G2P2
11			no	outpatient	38+0	spont. Vacuum	10x10	no	none	G4P1
12	33	1	no	conserv.	32+5	spont.	8x8cm	no	none	G2P1
13	0	0	no	outpatient	41+5	spont.	10cm	no	none	G1P1
14	10	1	no	conserv.	39+0	sek.Cesa	12x8cm	no	none	G1P1
15			no	outpatient	ET+4	sek.Cesa	8cm	no	Placental Abruption	G2P2
16			no	outpatient	37+0	spont.	8,9cm	no	none	G3p3
17			no	outpatient	35+2	spont.	9cm	no	none	G3p3
18			LSK diagn. 94	outpatient	38+5	prim. Cesa	15cm	yes	none	G1P1
19	21	17	no	conserv.	37+0	prim. Cesa	85cm	yes	none	G2P1

Table 9: Mode of Delivery

4.7 Hysterectomy at time of Delivery

Four patients according to Table 9 underwent caesarean deliveries with subsequent hysterectomies. The first of these patients was delivered in the 34th week because of persistent contractions and an MRI showing a uterine wall thickness in an area of prior myomectomy of less than one centimeter, and the associated risk of uterine rupture. During the caesarean, a

hysterectomy needed to be performed due to uterine atony and uncontrollable bleeding from the uterine incision.

The second patient underwent a hysterectomy five days following caesarean delivery, at which time a large 25cm anterior wall fibroid was left behind with the plan of future removal following postpartum involution. During the following four days the patient developed fever and complained of right sided abdominal pain. Due to an acute abdomen the patient underwent a second exploratory laparotomy at which time the 25cm fibroid was removed and an appendectomy for a chronically inflamed appearing appendix (most likely in association with the prior caesarean), was performed. Due to uncontrollable vaginal bleeding following closure of the abdomen, the patient was operated within 12 hours of the second laparotomy again and received a hysterectomy as well as a blood transfusion. Mother and child were discharged 3 weeks later in good condition.

The third of these patients, the patient with the fetus in transverse position and a 12cm cervical/intraligamentary fibroid following an uncomplicated caesarean underwent a hysterectomy due to completed childbearing and risk of worsening of the existing rotation of the uterus and risk of postpartum degeneration of the large fibroid.

The last patient undergoing hysterectomy at the time of caesarean delivery underwent uterine removal due to uncontrollable lower uterine segment bleeding. She was the only one from all hysterectomy patients who had undergone a myomectomy during the pregnancy.

4.8 Myomectomy during Pregnancy

The three patients who underwent myomectomies during their pregnancies all presented with abdominal pain resistant to medical therapy.

In one of the three patients the fibroid in addition to causing pain also showed a rapid growth of 6cm within a 4 week period. This was an additional factor for

surgical removal, due to the potential concern of malignancy and as the final pathology report showed, the fibroid had an increased mitotic activity and was classified as a leiomyoma neoplasia of uncertain malignancy. This patients remaining fibroids were subsequently followed with monthly ultrasound and MRI and remained quiescent during the pregnancy. The second patient had a right hydronephrosis which was being caused from her 14cm right sided fibroid. Due to worsening hydronephrosis und due to persistent signs of necrosis which was feared to cause further problems during the remaining 20 weeks of pregnancy, the decision was made to remove the necrotic fibroid in the 21st week.

4.9 Infant Outcome

All 20 infants were live born without malformations, with the exception of one infant born with a limb defect, to a mother who had undergone myomectomy during her pregnancy (Patient 8).

All infants as depicted in Table 10, with the exception of one (1890g. in the 34th week) were born with a weight appropriate for their gestational age. This SGA newborn (10% in the 34th week-1973g) , born to the mother with the 25cm fibroid, requiring two laparotomies and a hysterectomy postpartum, had APGARS of 5/7/8/9, was stable on room air, and was discharged four weeks later without complications with his mother. Three other newborns had initial low APGARS, among them the premature dichorionic-diamniotic twins both born with APGARS of 4/5/8/8, requiring immediate intubation, and the infant born in the 33rd week with 7/8/8/8 initially requiring CPAP. The remaining 4 infants all had initial APGARS over 9.

Pt.#	GA Deliv	Delivery Mode	Birth weight in g	Apgars 5 and 10min	Size Fibr@Deliv	Fibr remov	Complication
1	39+0	prim. Cesa	2820	9,10	20cm	no	none
2	40+2	sek. Cesa	3100	9,10	8x8cm	no	none
3	33+2	prim. Cesa	1890	8,9	25cm	yes/HE	reop/HE
4	32+6	prim. Cesa	2120	8,8	15,6x11cm	yes HE	HE
5	38+4	prim. Cesa	3580	10,10	12x6cm	no	postp fever
6	25+4	prim. Cesa Di.Di Twins	770,750	8,8	4x9cm	yes	none
7	38+1	prim. Cesa	2730	9,10	12x12cm cervix	yes HE	HE
8	35+4	prim. Cesa	2495	8,9	1575g 19w	yes 18w	lack of right hand
9	37+0	prim. Cesa			14cm 19w	Yes 19w	none
10	35+2	prim. Cesa	2570	9,10	HE	Yes 21w	bleeding/HE
11	37+5	spontVacuum	2610	10,10	10x10cm	no	none
12	32+6	spontaneous	2110	9,9	8x8cm	no	none
13	41+5	spontaneous	3820	10,10	10cm	no	none
14	39+0	sek.Cesa	3330	10,10	12x8cm	no	none
15	40+4	sek.Cesa	3260	10,10	8cm	no	Placental Abruption
16	37+0	spontaneous	3420	9,9	8,9cm	no	none
17	35+2	spontaneous	2530	9,10	9cm	no	none
18	38+5	prim. Cesa	3690	10,10	15cm	yes	none
19	37+0	prim. Cesa	2720	10,10	85cm	yes	none

Table 10: Neonatal Outcome

5. Discussion

Fibroids are the most common solid pelvic tumours in women, occurring in 20-25% of women in their reproductive years and with an incidence between 0,3% and 2,6% in pregnant women [Zaloudek et al. 1987, Muram et al. 1980]. Uterine fibroids are observed more frequently in pregnancy nowadays, due to woman's delayed childbearing into their thirties, the age where fibroids are most likely to grow. Women with leiomyomas were more likely to be over the age of 35 at delivery, nulliparous or black [Coronado et al. 2000].

Although most fibroids remain asymptomatic, they may complicate the course of pregnancy, labor and delivery. Complications that may arise in 10-40% of pregnant women with uterine fibroids [Exacoustos et al. 1993, Mollica et al. 1996], include increased frequency of spontaneous abortion, placental abruption, premature rupture of membranes, premature labor, fetal malpresentation, postpartum hemorrhage postpartum sepsis and postpartum hysterectomy [Mollica et al. 1996]. According to Coronado et al., complications in pregnancy, labour and delivery were nearly twice as frequent among women with diagnosed uterine fibroids than among those without them. Such complications are dependent on the size, location and relation of the fibroid to the placenta, and they may arise during pregnancy, at delivery or postnatally [Coronado et al. 2000].

Spontaneous abortion
Preterm labor
Premature rupture of membranes
IUGR-Intrauterine Growth Retardation
Malpresentation
Caesarean birth
First trimester bleeding
Placental abruption
Oligohydramnion
Placenta previa
Fetal malformations
Pain (compression or fibroid degeneration)
Fever
Uterine compression (Hydronephrosis)
Birth obstruction
Postpartum involution disorder and atonic bleeding

Table 11: Possible Complications of Fibroids in Pregnancy

The actual mechanism through which the uterine fibroids cause the above pregnancy, and labour complications is unclear. Whether the restriction in space, fetal growth and movement or interference with the effectiveness of labour contractions or obstruction of labour through lower uterine segment fibroids, the exact mechanism behind the complications arising from large fibroids is unclear [Coronado et al. 2000]. Interestingly enough, the Coronado study showed that women with uterine fibroids were at a higher risk for poor birth outcomes, defined as newborns with APGAR scores less than 7, with low-birth weight <2500g or with malformations. Whereas Coronado in her

large population-based study observed that uterine fibroids were strongly related to caesarean delivery and low birth weight, Exacoustos [Exacoustos et al. 1993] as well as Muram [Muram et al. 1980] found that mode of delivery and fetal growth were not affected by the presence of fibroids. Rice [Rice et al. 1988] found no significant incidence of intrauterine growth retardation (IUGR) or low APGAR scores in his population of pregnant women with uterine fibroids. In our small collective there was one small for gestational age infant born in the 34th week of gestation to a mother with a large 25cm fibroid, which most likely caused a structural restriction of intrauterine fetal growth. In our study this newborn as well as the two premature 27th week twins had APGAR scores less than 7. Otherwise all other infants, including both infants born to the two patients that underwent myomectomy during pregnancy had APGAR scores of 9 or better, and weights appropriate for their gestational age. In our study there was no miscarriage and no perinatal death. One of our newborns in the study however did have a malformation in the form of a missing right hand.

In a study by Exacoustos [Exacoustos et al. 1993], an increased risk of abruption was associated with submucosal, retroplacental fibroids, with volume greater than 200 cm. This association between fibroids and placental abruption is shown in Coronado's study [Coronado et al. 2000] to be even stronger as previously reported, with a nearly fourfold increase of placental abruption among women with uterine fibroids. Muram [Muram et al. 1980] in his study concluded that the relationship between the location of the fibroids and the placental site emerged as a significant prognostic clue to the outcome of the pregnancy. In our patient group although three patients had retroplacental fibroids, one of which underwent myomectomy, there was no occurrence of placental abruption.

The standard rule for fibroids in pregnancy is conservative management. In a study of 64 pregnant patients with uterine fibroids Döring [Döring et al. 1987], confirmed that under conservative management 2/3 of the pregnancies remained uncomplicated, 9/10 reached the 38th week and that spontaneous

births were two times higher than caesarean. We suggest that medical therapy including analgesics, fluids, antibiotics and prostaglandin inhibitors may be of use in patients who do not fit the high risk group. High risk groups are those with symptoms resistant to medical therapy, with complaints since the early pregnancy, patients with an increased rate of fibroid growth and fibroid degeneration, patients with retroplacental fibroids and patients who have undergone prior myomectomies. According to Dubuisson [Dubuisson et al. 2000] patients having undergone a laparoscopic myomectomy have a 1% uterine rupture risk. This risk can be associated with the use of unipolar electrocautery during the laparoscopic myomectomy, as shown in the case report by Hasbargen et al. 2002, stemming from the same institution as our study. Patients in whom there is a close proximity between fibroid and placental site seem to be at greater risk and should be followed more carefully. Muram and Rice [Muram et al. 1980, Rice et al. 1988] found that leiomyomas that were located retroplacental were associated with a higher incidence of adverse outcome such as premature rupture of membranes, antepartum bleeding and postpartum hemorrhage. Conversely, Lev-Toaff [Lev-Toaff et al. 1987] believed that leiomyoma location with respect to the placenta did not increase these complication rates. In such patients an MRI can reveal the relationship of placenta to fibroid as well as assess the thickness of myometrium at prior myomectomy sites. Interestingly enough, the one patient with a thin uterine wall at the fundus area was patient 4 who had undergone a myomectomy via laparotomy, whereas the two patients with prior laparoscopic myomectomies (Patient 5 and Patient 7) had no signs of increased risk for uterine dehiscence. According to Muram [Muram et al. 1980] in this high risk subgroup of patients a timely, well planned myomectomy should be an option offered to the patient, avoiding the morbidity and mortality associated with emergency procedures. According to Burton [Burton et al. 1989] if symptoms persist following 72 hours of medical therapy, surgical intervention must be considered.

In regards to the three patients that were operated, when one looks at the literature with regard to myomectomy during pregnancy, there is much

controversy. Although Phelan [Phelan 1995] believes that myomatous degeneration resistant to medical therapy is an indication for surgical intervention, he limits myomectomy to pedunculated fibroids with stalks no larger than 5 cm, and avoids dissection of fibroids from the uterine wall due to risk of bleeding and resulting hysterectomy. Phelan also recommends postpartum removal of fibroids having caused pregnancy complications prior to the next pregnancy allowing first a potential decrease in size through postpartum uterine involution. Most authors caution against elective myomectomy at time of caesarean because of increased morbidity especially haemorrhage. Burton [Burton et al. 1989] showed that elective myomectomy at caesarean may be safe in carefully selected patients. From a series of 13 patients with incidental myomectomy during caesarean only one was complicated by intraoperative haemorrhage. In our study, 3 patients underwent a myomectomy during caesarean. The main reasons for the myomectomies were the interference of the fibroids with uterine closure or due to existing signs of degeneration/necrosis which would increase the risk of postpartum symptoms-possibly requiring additional medical or surgical therapy.

The risk of surgery associated spontaneous abortion has also been raised, but refuted by Mollica [Mollica et al. 1996] who found a 13.6% spontaneous abortion rate in conservatively treated pregnant patients with fibroids, and a rate of zero in the surgically treated group. The conservatively treated group also had higher premature membrane rupture and preterm labour rates, and 4.5% of them required post-caesarean hysterectomies. In our study there was no spontaneous abortion in the myomectomy during pregnancy group and no fetal loss in both operated and conservatively managed groups. According to Mollica [Mollica et al. 1996] the lowest incidence of abortion is reported after myomectomies performed electively, while the highest incidence occurs after emergency operations for acute complications. His study showed that elective surgery does not increase the incidence of spontaneous abortion in pregnancy with fibroids, and it moreover improves fetal and neonatal outcome [Mollica et al. 1996]. The only neonatal death occurred in Mollica's study, in the patient

who refused surgery. Mollica's data regarding elective conservative management of fibroids in pregnancy have shown better results compared with those regarding untreated patients. However, conservatively treated patients had a higher incidence of premature labor, premature rupture of membranes and preterm labor compared to the nontreated or to the surgically treated group. Mollica concludes patients with a myoma that may compromise the outcome of pregnancy should be operated on, whereas all the others should be treated conservatively [Mollica et al. 1996]. Our three patients were electively operated under controlled circumstances, and their fetal outcome was good. Another study from Lolis [Lolis et al. 2003] confirms this view by stating that there are two basic complications of myomectomy during pregnancy: abortion and haemorrhage.

Exacoustos [Exacoustos et al. 1993] study data suggest that myomectomy during pregnancy has a high preterm delivery rate with a good perinatal outcome when performed in patients selected on the basis of clinical and ultrasound criteria, and that the decision to perform myomectomy during caesarean delivery must be made with caution because of the risk of haemorrhage. According to Exacoustos [Exacoustos et al. 1993] the use of ultrasound in detecting myoma position, size, location, relation to placenta and echogenic structure can aid in identifying women at risk for fibroid-related complications in pregnancy. According to Muram [Muram et al. 1980], clinical detection of the fibroids depended on their size and location. Only two of 16 fibroids between 3 and 5 cm. were found by physical examination, whereas there was a pickup rate of 80% when the fibroid was larger than 10cm. All the fundal, corneal, and isthmic fibroids were detected clinically. Fibroids that were situated on the corpus uteri often escaped detection. The overall rate of clinical diagnosis was 42%. The location of the fibroid especially its relationship to the placental site is more significant than its actual size in predicting pregnancy outcome. According to Rice [Rice et al. 1988], patients with fibroids >3cm had a significant increased rate of premature labour, placental abruption, pelvic pain and caesarean section, whereas fibroids <3cm were not clinically significant. The rate of placental abruption in patients with

submucosal location of the myoma was 31% according to Exacoustos [Exacoustos et al. 1993].

Fibroids increase in size during pregnancy under the influence of estrogen and a better blood supply. According to Rosati [Rosati et al. 1992] myoma growth occurs in the first trimester, particularly prior to 10 weeks of gestation and he advises sonographic monitoring in pregnancy, particularly during the first weeks of gestation. In our study however, the 63% of fibroids that increased during gestation all showed growth after the 10th week of gestation. These results differ with those of Phelan [Phelan 1995] showing that 80% of uterine fibroids during pregnancy remained the same or decreased in size. In our one patient (Patient 8) the concern for a possible malignancy had been considered with regards to the rapidity with which the patient's fibroid had grown over the 4 weeks prior to surgery, even though according to Parker [Parker et al. 1994], the association between rapid growth of leiomyoma and sarcoma is not substantiated. In Muram's [Muram et al. 1980] study in 38 out of 41 patients there was no demonstrable change in fibroid size, whereas in two patients an increase of up to 25% was noted and one patient's fibroid diminished in size by 20%. This is in agreement with Phelan's [Phelan 1995] thumb rule of 20% of fibroids increase during the course of pregnancy and 80% remained the same or decreased in size. In our study, aside from the one patient with rapid myomal growth and histologic borderline lesion, in the majority of patients (63%) the fibroids increased in size. In 21% the fibroids did not change in size and in 16% even grew smaller. The risk of acute red degeneration of a myoma is a problem which occurs between the 14th and 20th weeks when the growth of the uterus is most active. In Hasan's study it occurred in 10% of pregnant patients and they were all treated conservatively with bed rest and analgesics and the symptoms usually subside within 10 days [Hasan et al. 1990]. According to Exacoustos, the necrotic areas are a perfect medium for anaerobic infection, which may be resistant to therapy. Myoma degeneration with pelvic pain resistant to medical therapy should be an indication for myomectomy during pregnancy. However in Exacoustos's study, only myomas that were subserous or pedunculated and caused severe pain resistant to

therapy were considered for removal before 26 weeks of gestation [Exacoustos et al. 1993].

A final point of interest meriting discussion is the unexpected limb defect found at birth in one of our patients having undergone a myomectomy during pregnancy. There have been a few cases in the literature, of fibroid associated fetal limb defects, thought to stem from the spatial restriction caused by large fibroids [Danzer et al. 2001, Graham et al. 1980, Romero et al. 1981]. Danzer et al. report the only case associating a fetal limb defect and hydrocephalus in one twin, in a dichorionic diamniotic twin pregnancy, with a perioperative retroplacental haemorrhage possibly resulting from a myomectomy performed at 10 weeks of gestation [Danzer et al. 2001]. In Grahams case, a 10cm cervical fibroid was found in conjunction with a hypoplastic right lower leg and foot in a female infant [Graham et al 1980], and in Romeros case an infant with a head deformation and congenital torticollis [Romero et al. 1981], both of which did not undergo a myomectomy during pregnancy.

In our patient, the surgery itself is unlikely to have caused the limb defect, since it was performed at 19 weeks gestation and the fetal membranes were never violated. In addition, during retrospective review of the imaging studies prior to the patient's myomectomy, the fetal limb defect could be visualised, and it was most likely not diagnosed prenatally due to human error. Thus, pregnant patients with large myomas, should have thorough fetal anatomical scans due to the possible restrictive effect of the fibroids, which may lead to a higher risk for fetal limb abnormalities.

A multitude of factors must be considered before arriving at the best course of management in any given pregnant woman with fibroids. A thorough understanding of the pathogenesis of uterine myomas, clinical presentation, and the available diagnostic tools are the keys to selecting which course to follow in treating any given patient with fibroids. Our data show that patients with large, retroplacental, rapid growing fibroids in pregnancy, whose

symptoms are resistant to medical therapy are candidates for myomectomy during pregnancy, for the purpose of improving pregnancy outcome.

6. Summary

Objectives: To present the indications for conservative medical therapy vs. myomectomy during pregnancy, as treatment of symptomatic large uterine fibroids and to discuss possible complications arising with either mode of therapy.

Methods: A retrospective observational study of **19** pregnant patients, with a median age of **35** years, all with large uterine fibroids ranging from **8-25 cm** in size, referred to the university clinic of Grosshadern in Munich, Germany, between 1996 and 2007 either due to symptoms or due to routine registration for delivery was conducted.

Results: **7 (37%)** patients were followed as asymptomatic ambulatory patients, and **12 (63%)** patients were admitted to the hospital with complaints varying from vaginal bleeding, abdominal pain, increased infection parameters, and premature contractions. From the **12** admitted patients, **9 (75%)** received conservative medical therapy and **3 (25%)** underwent myomectomy between the 19th and 21st week of their pregnancy. The decision to treat surgically was based on the characteristics of the fibroids and their symptoms, and non-response to initial conservative therapy. **5 (26%)** Women delivered spontaneously. **14 (74%)** patients were delivered via caesarean section following the threshold of viability: **11 (79%)** via primary caesarean and **3 (21%)** via secondary caesarean. **4 (29%)** of the patients undergoing caesarean required hysterectomy, and only **1 (25%)** of the hysterectomy patients had undergone myomectomy during the pregnancy.

All infants were live born without malformations, with the exception of one infant born with a missing limb, to a mother who had undergone myomectomy during her pregnancy.

Conclusions: Certain known risk factors in pregnant women with fibroids such as size, continuous growth, texture and position of the fibroid in relation to the placenta, leading to symptoms not treatable via conservative methods, can predispose to complications during pregnancy. Women with such risk factors or women who have failed medical therapy, should be offered the option of undergoing myomectomy during pregnancy, in the hope of improving pregnancy outcome.

7. Zusammenfassung

Zielsetzung: Es sollen die Indikationen für konservative medizinische Therapie vs. Myomektomie während der Schwangerschaft als Therapie symptomatischer großer Myome gezeigt werden und eine Diskussion über die bei der jeweiligen Therapieart auftretenden Komplikationen erfolgen.

Methoden: Es wurde eine retrospektive Beobachtungsstudie von 19 schwangeren Patientinnen mit einem mittleren Alter von 35 Jahren durchgeführt, wobei alle Patientinnen große uterine Myome im Größenbereich von 8 bis 25 cm aufwiesen und zwischen 1996 und 2007 entweder wegen Beschwerden oder aufgrund einer routinemäßigen Geburtsanmeldung an die Universitätsklinik Großhadern in München, Deutschland, überwiesen wurden.

Ergebnisse: 7 (37%) Patientinnen wurden als asymptomatische Patientinnen ambulant überwacht und 12 (63%) Patientinnen wurden aufgrund von Beschwerden, welche von vaginaler Blutung, abdominalem Schmerz, erhöhten Infektionsparametern bis zur vorzeitigen Wehen reichten, stationär aufgenommen. Von den 12 aufgenommenen Patientinnen erhielten 9 (75%) konservative medizinische Therapie und 3 (25%) erhielten eine Myomentfernung zwischen der 19ten und 21ten Woche ihrer Schwangerschaft. Die Entscheidung einer chirurgischen Behandlung erfolgte auf Grundlage der Myomeigenschaften und deren Symptome sowie das Nichtansprechen auf anfängliche konservative Therapie. 5 (26%) Frauen entbanden spontan. 14 (74%) Patientinnen wurden mittels Kaiserschnitts nach Erreichen der Lebensfähigkeitsgrenze entbunden: 11 (79%) mittels Primärsectio und 3 (21%) mittels Sekundärsectio. 4 (29%) der durch Kaiserschnitt entbundenen Patientinnen benötigten eine Hysterektomie und nur bei 1 (25%) der Hysterektomie-Patientinnen war eine Myomentfernung während der Schwangerschaft durchgeführt worden.

Alle Neugeborenen waren Lebendgeburten ohne Missbildungen mit Ausnahme eines Neugeborenen mit einer fehlenden Extremität einer Mutter, bei der eine Myomektomie während ihrer Schwangerschaft durchgeführt worden war.

Schlussfolgerungen: Gewisse bekannte Risikofaktoren bei schwangeren Frauen mit Myomen, wie etwa Größe, fortgesetztes Wachstum, Oberflächenstruktur und Position des Myoms in Bezug auf die Plazenta, welche zu nicht mittels konservativen Verfahren behandelbaren Symptomen führen, können zu einer Prädisposition bezüglich Komplikationen während der Schwangerschaft führen. Frauen mit derartigen Risikofaktoren oder Frauen, bei denen medizinische Therapie nicht erfolgreich war, sollte die Option einer Myomektomie während der Schwangerschaft in der Hoffnung der Verbesserung des Schwangerschaftsergebnisses angeboten werden.

8. Annex

Pt.#	GP	GW	Position of Fibroid	Type of Fibroid	Symptoms On Admission	GA Adm	Len Adm	Prior OP	Therapy
1	G1P1	7	Cervix	intramural	vag. Bleeding	13	5w	no	conserv.
2	G1P1	14	Posterior right	transmural	abd. Pain,	12	2w	no	conserv.
3	G1P1	21	side wall right	intramural	pain,crp,	21	13w	no	conserv.
4	G1P1	15	Cervix	subserosal	abd. Pain, prem Ctxs	15	3w	LapM	conserv.
5	G2P2	22	side wall left	intramural	abd. Pain, vag. Bleeding			LSK M prim.Cesa.	outpatient
6	G1p2	9	Fundal	subserosal	vag. Bleeding, abd. Pain,CRP	9	2w	LSK diagn.	conserv.
7	G3p3	37	anterior	inraligamen	none			LSKM.	outpatient
8	G2P1	18	fundal	subserosal	abd. Pain,	18+0	2w	no	op19w
9		19			abd. Pain,	19			op 19w
10	G2P2	18	Cervix	transmural	abd. Pain,hydron CRP	17+4	24w	yes Cesarean	op 21w
11	G4P1	11	Anterior	intramural	none			no	outpatient
12	G2P1	33	fundal	intramural	prem Cxs abd. Pain	32+5	1w	no	conserv.
13	G1P1	16	Anterior	transmural	none	0	0	no	outpatient
14	G1P1	10	Side wall right	transmural	abd. Pain, CRP	10	1w	no	conserv.
15	G2P2	8	Side wall right	subserosal	none			no	outpatient
16	G3p3	28	Side wall right	transmural	none			no	outpatient
17	G3p3	12	Side wall right	transmural	none			no	outpatient
18	G1P1	10	fundal	intramural	none			LSK diagn. 94	outpatient
19	G2P1	21	Posterior between Rektum/Blader	intramural	fever, Pain CRP	20+4	17w	no	Conserv.

Table 12: Additional Information on Study Patients

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Ich erkläre hiermit an Eides statt,

dass ich die vorliegende Dissertation mit dem Thema
**Conservative Medical vs. Surgical Therapy Management of High Risk Pregnancies,
Complicated by Large Uterine Fibroids, A Single German University Center
Experience at the University Clinic Großhadern from 1996-2007**

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