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FERTILITY FOLLOWING MYOMECTOMY

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SUMMARY – The aim of the present study was to analyze the effect of abdominal myomectomy on subsequent fertility. Medical records of 78 women having undergone myomectomy between 1980 and 2000 were retrospectively analyzed. A questionnaire was e-mailed to all women. The overall pregnancy rate in 66 patients that attempted pregnancy following myomectomy was 59.1%. The pre-myomectomy abortion rate of 35.4% fell to 22% after myomectomy. The incidence of cesarean section before and after myomectomy was 7.3 and 15.6%, respectively. Age above 30 at the time of myomectomy significantly reduced the chance of conception ($P<0.0001$). Subsequent fertility was significantly reduced by greater number and deeper localization of myomas ($P<0.005$ to $P<0.001$). The coexistence of pelvic infection and adhesiolysis significantly reduced the pregnancy rate ($P<0.0001$). Recurrence of uterine leiomyomas was recorded in 12.8% of study patients. More than half of the women with uterine leiomyomas were able to conceive and nearly half (48.5%) of them were able to bear children following myomectomy. Patient age at the time of myomectomy, the number and localization of leiomyomas, and coexistence of pelvic adhesions significantly reduced subsequent fertility. In spite of the emergence of new treatment options, it is evident that conventional abdominal myomectomy still has a major role in the treatment of women with fibroids.

Key words: *Uterine neoplasms – surgery; Fertility – prevention and control; Leiomyoma – surgery; Infertility, female – etiology*

Introduction

Uterine myomas or fibroids occur in 20%-50% of reproductive age women and can be identified by ultrasound in approximately 80% of African-American women and in almost 70% of white American women by the time they reach menopause[1]. Although estrogen may stimulate myoma development, it may also grow when circulating estrogen levels are low, possibly because ovarian and adrenal androgens may be converted to estrogens by aromatase activity within myoma cells. The growth of myomas is also regulated by progesterone and a number of local growth factors, and the genetic basis of myoma growth may be primarily related to these factors and their receptors[2].

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Uterine leiomyomas have been associated with a higher abortion rate, at an incidence of up to 41%, particularly if implantation occurs in relation to submucosal fibroid[3]. However, only 2%-3% of infertility cases may be attributed to the effects of myomas when all other causes are excluded[4]. The role of fibroids as a causative factor in infertility remains controversial. It has been speculated that fibroids interfere with sperm transport, impinge on the tubal lumina, distort the course of the fallopian tube, and compress the cervical canal, thereby interfering with sperm capture. In addition, disruption or distortion of the endometrial cavity and implantation due to venous ectasia over a submucosal myoma, endometrial inflammation or secretion of vasoactive substances, abnormalities of blood supply to the endometrium, atrophy and ulceration may occur, thereby preventing implantation[5-7].

More than 100 years have elapsed since the introduction of conventional abdominal myomectomy in gynecologic surgery. Earlier studies report on myomec-

tomy with the menstrual and reproductive functions preserved as the treatment of choice to be associated with the overall pregnancy rate of 25% to 50%[8,9]. Some later studies report on myomectomy as the treatment of infertility with pregnancy rates ranging between 50% and 65%[5,10,11]. Recently, it has been concluded that conventional myomectomy still has a major role because there are no limitations in the size and number of fibroids, as in some newer treatment options[12].Clinical studies found the rate of recurrence to range from 5% to 30%[13].

In the current retrospective and prospective study, the effect of abdominal myomectomy on uterine fibroids was assessed in patients with menometrorrhagia and infertility, associated with uterine enlargement.

Patients and Methods

From January 1, 1980 till December 31, 2000, 236 myomectomies were performed. The clinical data accumulated during the 20-year period were analyzed and presented in detail for 78 (33.1%) subjects available to follow up. Data on maternal age, reproductive histories, presenting symptoms, clinical findings, intraoperative findings, possible concomitant surgical procedures performed and postoperative complications were collected from case records. In patients with very low hemoglobin and a history of prolonged periods of irregular and profuse bleeding on preoperative preparation, blood loss was corrected by repeat transfusions until normalization. Blood was usually available during and after the operation. The Pfannenstiel abdominal incision was used in the presence of fibroid uterus of up to 8- to 12-week gestation in size. In the presence of larger fibroids, median incision was performed. The uterus was exposed and if possible delivered through the incision to allow exploration of the entire pelvic situation. As midline uterine incisions are generally less vascular, the incision was so placed as to enable removal of as many tumors as possible through a single incision, thus avoiding uterotubal junction. Familiar techniques of blunt and sharp dissection with conventional instruments were employed on myoma removal. Vigorous traction on the tumors was avoided, particularly when they were located close to the endometrial cavity. Our choice of suture material for the myometrial reconstruction was catgut and Dexon. Questionnaires were sent to all 236 women to analyze subsequent reproductive and therapeutic outcome.

Statistical analysis was performed using χ^2-test and statistical significance was set at $P<0.05$.

Results

The response rate to the questionnaires was 33.1% (n=78). The time of patient follow up after myomectomy ranged from 10 to 30 years. Twelve patients were not interested in subsequent pregnancy and they did not conceive. Of 66 women that attempted pregnancy, 39 (59.1%) achieved a total of 41 pregnancies. Nine (22%) of these ended in spontaneous abortions, six of them in first and three in second trimester. Thirty-two (78%) pregnancies resulted in term viable infants, five (15.6%) of them delivered by cesarean section. The indication for cesarean section was previous myomectomy in three and cephalopelvic disproportion in two cases. The remaining 27 (84.4%) patients had vaginal and uneventful delivery. The overall rate of pregnancy irrespective of planning to conceive was 52.6%. Twenty-two (56.4%) women conceived within four years of myomectomy, ten (25.6%) in the next four years, five(12.8%) four years later, and the last two patients became preg-

Table 1. Effect of age at myomectomy on pregnancy planning and later fertility

Patient age (yrs)	Study patients	No pregnancy wanted	Pregnancy wanted	Later pregnancy	
	(N = 78)	(n = 12)	(n = 66)	No (n = 27)	Yes (n = 39)
<30	21	2	19	–	19*
30-35	27	4	23	7	16
>35	30	6	24	20	4

*P<0.0001

Table 2. Premyomectomy reproduction and its effect on pregnancy planning and later fertility in study patients

Previous pregnancies	Study patients	No pregnancy wanted	Pregnancy wanted	Later pregnancies	
	(N = 78)	(n = 12)	(n = 66)	No (n = 27)	Yes (n = 39)
Delivery	41	24*	17*	3	14
Miscarriage	23	–	23*	8	15
Ectopic pregnancy	1	1	–	–	–
Induced abortion	66	66	–	–	–
Total	131	91	40	11	29

*P<0.0001

nant after a period of 13 and 18 years, respectively. The mean operation-to-conception interval was 4.7 years. Of the last five pregnancies, male subfertility was implicated in two cases and another partner in three cases.

The mean age of 78 patients undergoing myomectomy was 34.1 (range 21-45) years. In all study patients, the highest incidence of uterine leiomyomas occurred between 30 and 39 years of age. The group of 39 women that conceived after the operation was predominated by younger subjects, under age 30 in particular, as compared with the group of 27 patients that remained infertile, predominated by subjects aged >35 (P<0.0001) (Table 1).

In Table 2, previous reproductive history according to desire for pregnancy and later fertility are compared. Of 78 patients, there were 29 (37.2%) women with deliveries (12 with undesired pregnancy and 17 with desired pregnancy), 23 (29.5%) women with spontaneous abortions, and 26 (33.3%) women with primary infertility and no pregnancy in their history. In the group of 12 women with undesired pregnancy there were 66 induced abortions. In the group of 29 women with 41 deliveries there were 40 living infants and one neonatal death. Three (7.3%) deliveries were performed by cesarean section, including one case of tubal gestation. Twenty-three (35.4%) of 65 wanted pregnancies terminated by spontaneous abortion (18 in first trimester and 5 by 27 weeks of gestation), 41 (63.1%) by deliveries and one (1.5%) as tubal gestation. In the group of 66 patients that wanted later pregnancy there were significantly more spontaneous abortions and less deliveries in comparison with 12 women with no interest in pregnancy (P<0.0001).

Table 3. Effect of other operative procedures on fertility following myomectomy with regard to pregnancy planning

Operations	Study patients	No pregnancy wanted	Pregnancy wanted	Later pregnancies	
	(N = 78)	(n = 12)	(n = 66)	No (n = 27)	Yes (n = 39)
Concomitant	15	–	15	13*	2*
– adhesiolysis	15	–	15	13	2
– ovarian resection	14	–	14	11	3
– cystectomy	1	–	1	1	–
– appendectomy	1	–	1	1	–
Previous	8	5*	3*	2	1
– cesarean section	3	2	1	–	–
– appendectomy	2	1	1	–	1
– cystectomy	2	1	1	1	–
– salpingectomy	1	1	–	1	–

*P<0.001

Table 3 relates other operations to desire for pregnancy and later reproduction. Concomitant operations had significant impact on later fertility. Among 15 concomitant operations, 13 (48.1%) were performed in 27 infertile women and 2 (5.1%) in 39 pregnant patients. The difference was statistically highly significant ($P<0.001$). Similarly, out of 8 previous operations, 5 (41.7%) were performed in 12 women without desire for pregnancy and 3 (4.5%) in 66 women with attempted pregnancy ($P<0.001$). Fifteen (19.2%) of 78 patients with primary infertility had macroscopic evidence for pelvic inflammatory disease at operation, and a single adhesiolysis was performed as a concomitant procedure. The highest incidence of pelvic infection (46.2%) was found in 12 of 26 women complaining of primary infertility.

Out of 78 women, uterine size equivalent to less than and over 12-week gestation was recorded in 68 (87.2%) and ten (12.8%) patients, respectively. Less fibroids were removed in the group of patients with attempted pregnancy than in those without it ($P<0.001$). In the group of patients that conceived, the fibroids were also less numerous ($P<0.001$) and superficially localized ($P<0.005$) as compared with the group of women that remained infertile. The incidence rate of entry in the endometrial cavity was 23.1%, of which 50% in the group of patients without desire for pregnancy and 15.4% in the women that conceived postoperatively (Table 4).

Recurrence of leiomyomata was recorded in ten (12.8%) women. Seven (8.9%) patients underwent hysterectomy between 7 and 11 years following myomectomy for recurrent leiomyomas. Eight of ten patients with recurrent leiomyomas were not interested in subsequent reproduction and two women conceived, however, both ending in abortion.

There were few complications following myomectomy. The most common was pyrexia of over 37.5 °C within the first 2 or 3 days, which was found in 18 (23.1%) cases. Abdominal wound infection developed in eight and urinary tract infection in three patients. Ten patients (12.8%) received whole blood transfusion during or within 24 hours of the operation. The blood loss was about 1 liter in seven subjects, whereas heavier bleeding of 1.5 liter occurred in three patients. There was no case of postoperative death.

There were 158 (66.9%) non-responders, thus being unavailable for follow up. They did not differ from responders according to background factors.

Discussion

Although a major drawback of this study was the high percentage of women (66.9%) lost to follow up, a total of 78 patients observed was consistent with other reports[3,5]. The observed period of 20 years differed from other shorter and longer studies[9,14-16]. Another drawback of our study was the long follow up time (between 10 and 30 years). This long period enabled us to obtain more follow up data and may explain the low questionnaire response rate. Our results pointed to the importance of premyomectomy reproductive performance for desire for later pregnancy. The abortion rate was considerably higher and the birth rate lower in women interested in pregnancy in comparison with women that did not want subsequent pregnancy (Table 2). Our results confirmed numerous series that investigated the use of myomectomy as a treatment for infertility.

All patients were advised to try to conceive several months after myomectomy. The overall pregnancy rate of 59.1% in those patients that attempted pregnancy

Table 4. Number, localization and size of fibroids removed at myomectomy

Fibroids	Study patients	No pregnancy wanted	Pregnancy wanted	Later pregnancies	
	(N = 78)	(n = 12)	(n = 66)	No (n = 27)	Yes (n = 39)
1 to 2	66	6*	60*	21*	39*
>3	12	6	6	6	–
Subserous	37	6	31	7**	24**
Intramural	41	6	35	20	15
Open uterine cavity	18	3	15	9	6
1-2 cm	58	7	51	19	32
>3 cm	20	5	15	8	7

*P<0.001; *P<0.005

compared favorably with the crude pregnancy rates of 38%-65% reported elsewhere[5,10,11,14,17]. The majority of pregnancies were recorded in the first four years (56.4%) of the procedure, a feature common to most reports. The late occurrence of pregnancies in our study could be explained by the implicated change of partners and male subfertility, which contributed to prolonged infertility. Importantly, nearly half (48.5%) of the women undergoing myomectomy were able to successfully bear children. It is important to recognize that our retrospective and prospective study, like many other reports on myomectomy, was descriptive in nature and subject to the potential biases found in uncontrolled studies.

There are many factors that may contribute to the state of infertility and myomas are rarely implicated as the sole cause[10,14,15,18]. Our results suggested the age below 30 at the time of myomectomy to significantly improve the chances for successful pregnancy outcome. Similarly, Berkely *et al*.[10] report on fertility reduction after myomectomy over age 30. Babaknia *et al*.[5] report on no pregnancy success over age 35. However, Smith and Uhlir[14] report that half of the patients having conceived were aged 35 or older. Our intraoperative findings would seem to agree with other reports, which suggest the association between leiomyomas *per se* and infertility to be lower than generally presumed[4,6,14,15]. Nearly 47% of our patients that complained of primary infertility had macroscopic evidence of pelvic infection. It seems likely that the incidence of pelvic infection in women may even be higher, implying that it would be possible to obtain histologic information on the state of the fallopian tube mucosa. However, adhesion formation is a well-recognized complication of myomectomy, but there is little objective data on its incidence. Berkely *et al*.[10] conclude that myomectomy itself may decrease fertility, probably as a result of adhesion formation. Lev-Toaff *et al*.[18] report that hysterosalpingography following myomectomy was associated with complications such as synechiae and diverticula, which may affect subsequent fertility. Gehlbach *et al*.[17] found adhesions in 68% of those women that underwent subsequent surgery. In our series, adhesions were found in 50% of 12 women that subsequently underwent cesarean section or hysterectomy. The majority of adhesions developed *de novo* and involved the uterus. The development of new adjuvants may provide another avenue for reducing or preventing adhesion formation following myomectomy.

The characteristics of leiomyomas themselves may affect pregnancy rate following myomectomy. Fibroids have also been associated with a higher rate of miscarriage, particularly if implantation occurs in relation to a submucosal fibroid. In their review of myomectomies with known preoperative miscarriage rates, Buttram and Reiter[3] found the preoperative and postoperative rate of miscarriage to be 41% and 19%, respectively. They also observed association with preterm delivery, abnormal presentation, outlet obstruction, postpartum hemorrhage and puerperal sepsis. Egwuatu[15] found the abortion rate to be considerably higher and fetal salvage lower in women with leiomyomas as compared with control group. Similarly, the results of this study on a 35.4% miscarriage rate preoperatively and 22% postoperatively also support the widely held impression that uterine leiomyomas markedly influence pregnancy outcome. In our series, the number and deeper localization of myomas and entering endometrial cavity significantly reduced postoperative fertility. Contrary to these reports, several other studies noted that neither the number nor the size or localization of myomas and entering endometrial cavity had any effect on the final pregnancy rate[14,17]. However, recently published data suggest that fertility outcomes are decreased in women with submucosal fibroids that distort the uterine cavity, and removal seems to confer benefit. There was no conclusive evidence that intramural or subserosal fibroids adversely affected fertility. It seems that larger intramural fibroids decrease fertility, but therapeutic results are ambiguous[6,19,20]. We had no objective data to clarify whether the success of the procedure was altered by entry in the endometrial cavity and intrauterine adhesion formation because hysteroscopy was not available. In the event of delivery, cesarean section need not be necessary. It was formerly held that entering endometrial cavity during myomectomy was an absolute indication for delivery by cesarean section on subsequent pregnancy.

Cesarean section rates between 9% and 79% have been recorded[8-10,15,16]. Although it is generally recommended that women undergoing abdominal myomectomy should deliver by cesarean section, at least one study observed no uterine ruptures in 83% of vaginal deliveries after myomectomy. Our cesarean section rate of 15.6% exceeded the preoperative rate of 7.3% and may be explained by our belief that vaginal delivery may be anticipated unless uterine scars are known to have been weakened by postoperative infection. Laceration of a significant portion of the myometrium and invasion of the endometrial cavity were of secondary importance on assessing the need of cesarean section. In our series,

the rates of febrility and blood transfusions associated with abdominal myomectomy were quite low and consistent with literature reports[14,15,21] .

The significance of myoma regrowth after myomectomy remains a controversial issue. Some authors consider it as a persistent disease, i.e. as the result of unintentionally incomplete operation that has left an undetected myomatous formation *in situ* in the myometrium. Recurrence may be a measure of the surgeon's thoroughness in his search for and removal of seeding tumors during the first operation[5]. On the other hand, an individual genetic predisposition has been hypothesized, which would absolve the gynecologist; despite complete operative removal of all fibroids, some uteri may have scattered cells that can later develop into myomas. In such cases, it is correct to talk of recurrence[13]. Literature reports show marked differences in the probability of recurrence after myomectomy. Early studies generally report rates of 5% to 10%[9]. In later studies, recurrence rates of 25% to 47% were observed[16,17]. However, recently published 5-year cumulative rates of leiomyoma recurrence diagnosed by transvaginal ultrasonography were up to 62%[22]. In our series, an overall recurrence rate of 12.8% could be partly explained by the criteria for the diagnosis of recurrence and deficiencies in long-term follow up.

Fortunately, the past decade has witnessed the emergence of highly sophisticated therapeutic technologies for fibroids including medical treatment, laparoscopic myomectomy, uterine artery embolization, magnetic-resonance-guided focused ultrasound surgery, hysteroscopic resection, myolysis by heat, cold coagulation, and laser[23]. Although the newer treatment modalities are promising they have significant limitations and their safety and effectiveness in women with myomas seeking to maintain or improve their fertility have yet to be established[6]. Therefore, it is evident that conventional abdominal myomectomy still has a major role because there are no limitations in the size and number of fibroids, and there also are data showing improvement in outcomes of assisted reproduction treatment following myomectomy. However, there is a need to continue to refine and innovate this treatment option, especially in terms of reducing blood loss during surgery and the risk of adhesions and recurrence, along with uterus reconstruction to approximate anatomical normality and physiological integrity, so it can carry pregnancy without complications such as scar rupture[12].

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Sažetak

PLODNOST NAKON MIOMEKTOMIJE

M. Kasum

Cilj studije bio je analizirati utjecaj abdominalne miomektomije na kasniju plodnost. Od 1980. do 2000. godine miomi su enukleirani u 236 žena. Na upitnik je odgovorilo 78 (33,1%) žena, a od 66 žena koje su željele zatrudnjeti zanijelo ih je 39 (59,1%). Pojavnost spontanih pobačaja od 35,4% prije miomektomije smanjila se na 22% nakon operacije, a dovršenje trudnoće carskim rezom povisilo se sa 7,3% na 15,6%. Dob bolesnica iznad 30 godina u vrijeme operacije znakovito smanjuje izglede za začeće ($P<0,0001$). Veći broj mioma i njihova dublja lokalizacija znakovito smanjuju kasniju plodnost ($P<0,005$ do $P<0,001$). Istodobna prisutnost zdjelične upalne bolesti i operacijskog zahvata radi rješavanja priraslica znakovito smanjuju kasniju stopu začeća ($P<0,0001$). Ponovno javljanje mioma nakon operacije zabilježeno je u 12,8% žena. Više od polovice žena s miomima zainteresiranih za trudnoću je zanijelo, a gotovo polovica (48,5%) ih je rodila nakon miomektomije. Životna dob bolesnice u vrijeme enukleacije mioma, broj i njihova lokalizacija te istodobna prisutnost priraslica u zdjelici znakovito smanjuju kasniju plodnost. Unatoč pojavljivanja novih terapijskih mogućnosti konvencionalna abdominalna miomektomija još uvijek igra glavnu ulogu u liječenju bolesnica s miomima.

Ključne riječi: *Novotvorine maternice – kirurgija; Plodnost – prevencija i kontrola; Leiomiom – kirurgija; Neplodnost, ženska – etiologija*