Uterine myomas are present in approximately one third of women of reproductive age [1]. Although 5% to 10% of cases of infertility are associated with myomas, they are estimated to be the sole factor for infertility in only 1% to 3% of cases [2,3].

The mechanisms by which myomas may affect reproductive outcome are as follows [4–6]:

Interference with sperm transport or access by: (1) anatomic distortion of the cervix; (2) enlarging or deforming the endometrial cavity; (3) altering the uterine contractility; and (4) obstructing tubal ostia.

Implantation failure by: (1) physically changing the shape of the endometrium; (2) preventing discharge of intrauterine blood or clots; and (3) altering the normal endometrial development.

The goal of this review of the literature is to answer two consecutive questions: Do the location and size of myomas reduce the success of assisted reproduction? If the answer of this question is yes, do different treatment modalities for myomas improve the reproductive outcome?
Myomas and assisted reproduction

Check and colleagues [7] investigated the effect of intramural myomas (≤5 cm in diameter and not compressing the uterine cavity) on in vitro fertilization–embryo transfer (IVF-ET) cycle outcome. The additional requirements were that the myomas did not have a submucosal component, the patient had not undergone previous uterine surgery for leiomyomata or other reasons, and no other uterine cavity abnormalities existed (eg, uterine septum or polyps). Sixty-one women who had myomas in their first IVF cycle were matched prospectively by age with 61 women who did not have leiomyomata. The maximum number of myomas in a given patient was seven. The outcome measurements were positive pregnancy test, clinical pregnancy, spontaneous abortion and live birth rates. Although the comparison of all results showed no significant difference between the study and control groups, the investigators indicated that a multicenter study is essential because the trend for increased miscarriage and decreased term delivery rates may become significant.

A letter to the editor by Nawroth and Foth [8] in response to the study by Check and colleagues [7] brought forth a discussion about the nomenclature of myomas. They stated that myomas that compress the uterine cavity with an intramural portion of more than 50% should be classified as submucous myoma type II. Therefore, intramural myomata per se do not compress the uterine cavity [9].

Hart and colleagues [10] investigated the outcome of assisted reproduction in women who had intramural myomas that were up to 5 cm in diameter, and reached totally different results than did Check and colleagues [7]. In this study, instead of case-matching, 112 women who had myomas were compared with 322 women who did not have any uterine pathology. Pregnancy, implantation, and ongoing pregnancy rates were reduced significantly and were 23.3%, 11.9%, and 15.1%, respectively, compared with 34.1%, 20.2%, and 28.3% in the control group. When the results of logistic regression were adjusted for the number of embryos transferred and the women’s age, the odds ratio (OR) of an ongoing pregnancy in the presence of an intramural fibroid that was up to 5 cm in diameter was halved (OR, 0.46; CI, 0.24–0.88), especially among women who were at least 40 years of age.

Ramzy and colleagues [11] aimed to study the success of IVF/intracytoplasmic sperm injection (ICSI) in patients who had subserous or intramural myomas that did not encroach upon the endometrial cavity. Among a total of 406 patients, 51 (12.6%) had myomas. Twelve of these were excluded from the study and were advised to have myomectomy—for submucous or intramural myomas that were deforming the endometrial cavity—before assisted reproduction. Because it was a mixed group and consisted mainly of patients who had subserous, rather than intramural, myomas (32 versus 12, respectively), the results are not definitive for the group that had intramural myomas. The mean diameters for both groups were 3 to 4 cm. No significant difference was found between the two groups for total pregnancies, clinical pregnancies, implantation
rate, abortions, preterm labor, or deliveries. The only significant finding was the increased incidence of myoma with increasing age, especially after 35 years. The investigators concluded that subserous or intramural myomas that do not encroach the endometrial cavity and are less than 7 cm in diameter do not affect the IVF/ICSI outcome.

An older case-matched study by Stovall and colleagues [12], which was performed between 1993 and 1995 and included 182 patients, also questioned the difference in pregnancy rates after assisted reproduction in nonmyomatous patients and in patients who had myomas [33]. Although the pregnancy rate for the former group was higher (52.7% versus 38.3%), several confounding factors may have altered the results. First, the mean age of the control group was younger, 35.9 years versus 36.8 years. Second, male factor infertility was lower in the control group (23.1% versus 31.1%). Finally, the mean number of embryos that was transferred in the control group was higher than in the study group (3.6 versus 3.2). Despite these differences in the two groups that were undergoing assisted reproduction, the investigators found a significant Mantel-Haenszel estimate of relative risk (RR) for the presence of myomas for lower pregnancy and delivery rates (RR, 0.71; CI, 0.51–0.98 and RR, 0.68; CI, 0.47–0.98, respectively).

In a retrospective case-controlled analysis, Surrey and colleagues [13] investigated the impact of intramural myomas on assisted reproduction. Three hundred and ninety-nine consecutive fresh IVF-ET cycles were grouped into four major groups and a subgroup. Groups that did and did not have myomas were divided according to age (<40 years and ≥40 years). A group that did not have myomas and was between the ages of 35 and 39 was used as another control subgroup. All patients had undergone hysteroscopy during the midfollicular phase within 6 months of the cycle, and all had normal endometrial cavities. In addition, a baseline precycle transvaginal ultrasound examination was performed in each case. For patients who were younger than age 40, the implantation rate was significantly lower in the group that had myomas compared with the group that did not have myomas or with the subgroup (21.4%, 57.5%, and 57.0%, respectively). For the patients who were at least 40 years of age, the presence or absence of myomas did not create a significant difference (11.6% versus 17.5%, respectively).

Eldar-Geva and colleagues [14] compared pregnancy and implantation rates in women who had myomas in different locations with women who did not have myomas. Women who had submucous myomas had the lowest pregnancy and implantation rates (10.0% and 4.3%, respectively). The group that had intramural myomas also had significantly reduced pregnancy and implantation rates compared with the groups that had subserous myomas or no myomas (16.4% and 6.4%, 34.1% and 15.1%, 30.1% and 15.7%, respectively). This is one of the rare studies in which cases of submucous myomas were included. The investigators made it clear that all submucous myomas caused cavity distortion, and that the intramural myomas were completely within the myometrium or had subserosal parts only.
Unless a myoma is purely subserous, surgery before assisted reproduction should be considered as an option. Most investigators suggest surgery for submucous and intramural myomas that depress the endometrial cavity [15]. There is no consensus for intramural myomas that do not encroach upon the cavity; however, most surgeons would agree to remove them if they are larger than 7 cm or are associated with multiple failed IVF cycles.

Treatment of myomas and the reproductive outcome

Hysteroscopic myomectomy

Although endoscopic visualization of the endometrial cavity has been performed for more than a century, the first hysteroscopic myomectomy was performed in 1957 by Norment [16,17]. Repeat procedures for incomplete resections, uterine perforation during surgery, and uterine rupture in a subsequent pregnancy are rare risks about which patients should be informed [18,19].

Emanuel and colleagues [20] showed a 46% conception rate after hysteroscopic myomectomy. Vercellini and colleagues [21] subgrouped submucous myomas, and reported conception rates after hysteroscopic surgery—over a 3-year period—of 49% for pedunculated myomas and 33% for myomas with intramural components. The benefit and efficacy of hysteroscopic myomectomy in cases of pedunculated myomas and myomas with more than 50% in the uterine cavity is generally accepted.

Abdominal myomectomy

A review by Vercellini and colleagues [22] in 1998 confirmed the fertility-improving effect of abdominal myomectomy. The 23 studies that were included in the review were highly heterogenous by all means (eg, type of study, location of myomas, causes of infertility, years of infertility). Cases in all studies, except 4, were followed for up to at least 12 months. Among the included studies, 564 infertile women underwent myomectomy, and 269 pregnancies (47.7%) occurred during the follow-up period. The pregnancy rate for the 9 prospective studies was 57% (CI, 48–65%). The overall conception rate among 7 prospective studies, in which only unexplained cases of infertility were included, was 61% (CI, 51–70%). The conception rates after myomectomy were 58%, 64%, and 70% in the three studies of women who had only intramural or subserous myomas [23].

Li and colleagues [24,25] performed myomectomy using microsurgical techniques on 51 women who had intramural or subserosal myomas, and no other significant infertility factors, and who wished to conceive. No myomas caused any deformity of the endometrial cavity. Before surgery there were 40 pregnancies among these 51 women and 24 pregnancies were lost among 19 women. Following myomectomy, there were 33 spontaneous pregnancies.
among 29 women. The rate of pregnancy loss after myomectomy was significantly lower than before surgery (24% versus 60%).

In a retrospective analysis Marchionni and colleagues [24] evaluated the results of abdominal myomectomy for intramural and subserosal myomas that might influence the reproductive outcome. Seventy-two women were included in the study. There were 26 pregnancies before myomectomy and 68 pregnancies after myomectomy in 51 of these 72 women. The pregnancy loss rate was significantly lower (25%) after myomectomy compared with that before the operation (69%). The live birth rate also improved significantly after surgery (31% versus 75%).

Frederick and colleagues [26] performed a prospective cohort study of reproductive outcome after a second myomectomy for recurring myomas. Nine (15.5%) of 58 women became pregnant after the second surgery; however, only 5 (56%) had live births. The investigators constructed a model depending on the likelihood ratios of different parameters. The number of myomas present, was the third significant factor for a successful pregnancy outcome, where age and the presence of tubal adhesions were first and second, respectively.

Laparoscopic myomectomy

Laparoscopic myomectomy has been the subject of several studies since the late 1980s; however, data on reproductive outcome after this procedure have become of concern in the last decade [27–29]. Because it is a difficult procedure that requires advanced surgical skills, especially in endoscopic suturing, the use of this technique is limited.

In a study of the comparison of reproductive outcome after abdominal and laparoscopic myomectomy, Seracchioli and colleagues [30] treated 65 patients by abdominal technique and 66 patients by laparoscopic technique. Pregnancy rates were comparable (55.9% and 53.6%, respectively). Miscarriage rates were 12.1% and 20.0%, respectively, but this difference was not significant.

Fauconnier and colleagues [31] performed laparoscopic myomectomy on 91 infertile patients who had at least one subserous or intramural myoma that was larger than 2 cm. Eighty-one of these patients were followed-up for 2 years and 43 (53.1%) of them became pregnant. The spontaneous pregnancy rate was 44% (CI, 32–56%) for the same time period. In the multiple regression of prognostic factors for fertility after myomectomy, intramural myomas were significant in reducing the pregnancy rate (RR, 0.4; CI, 0.2–0.8), whereas, subserosal myomas did not affect the reproductive outcome.

Seinera and colleagues [32] reported 202 cases of laparoscopic myomectomy and 65 subsequent pregnancies in 54 patients. Twenty-one of these were after IVF, and 51 (78.5%) pregnancies were completed uneventfully.

Ribeiro and colleagues [33] performed laparoscopic myomectomy on 28 infertile patients, each of whom had at least one myoma that was larger than 5 cm in diameter. Two patients also underwent simultaneous hysteroscopic myomectomy. Eighteen (64.3%) of these patients, including one who also underwent
hysteroscopic myomectomy, became pregnant after the procedure and 14 delivered viable term babies.

Other techniques

Hutchins and colleagues [34] described selective uterine artery embolization for symptomatic uterine myomas with a high treatment effect. Goldberg and colleagues [35] investigated the reproductive outcomes after coagulation of uterine vessels (CUV) and laparoscopic myomectomy. A significantly increased risk for preterm delivery and malpresentation, as well as an increased risk for spontaneous abortion were found for CUV. Chen and colleagues [2] treated 142 women who had myomas by CUV; the myoma sizes were reduced significantly after the procedure. When a subgroup of 36 sexually active women that was not using contraception was followed after CUV, 15 (41.6%) became pregnant (17 total pregnancies); however, a high rate of miscarriages (7/17, 41.2%) occurred in this group. Therefore, the investigators advised that the procedure be reserved for women with no desire for pregnancy.

Laparoscopic coagulation of uterine myomas, namely myolysis and MRI-guided focused ultrasound surgery, are recent alternatives for the treatment of uterine myomas [36,37]. The accumulation of data about these procedures is scarce, and the safety of the procedures needs to be evaluated before the reproductive outcomes can be discussed [38–42].

Summary

The effect of myomas on reproductive outcome has been the subject of many studies; however, a definitive answer is still missing. Therefore, the authors have tried to outline some guidelines for the management of women who have uterine myomas and desire to conceive.

The location and size of the myomas are the two parameters that influence the success of a future pregnancy. Subserosal myomas seem to have little, if any, effect on reproductive outcome, especially if they are up to 5 to 7 cm in diameter. Intramural myomas that do not encroach upon the endometrium also can be considered to be relatively harmless to reproduction, if they are smaller than 4 to 5 cm in diameter. This is the ambiguous gray zone of the subject, and where research should be focused before a consensus can be established. Myomas that compress the uterine cavity with an intramural portion (submucous myoma type II) and submucous myomas significantly reduce pregnancy rates, and should be removed before assisted reproductive techniques are used.

Hysteroscopic myomectomy is the gold standard for the treatment of submucous myomas. For other myomas, abdominal myomectomy, or laparoscopic myomectomy—when the experience of the surgeon and the facilities are sufficient—are the best alternatives. In most of the literature, the pregnancy rates
were increased and the miscarriage rates were decreased after surgery with these two techniques. Other alternative treatment modalities, such as CUV, laparoscopic myolysis, or MRI-guided focused ultrasound, are to be monitored and evaluated thoroughly before they are applied as routine procedures.

References