

## TREATMENT OF INTRAMURAL FIBROIDS BEFORE IVF- THE NEW DILEMMA

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Myomectomy or art: which comes first?: Fibroids of the uterus are among the most common benign pelvic tumors reaching an incidence of 25-40% in women during their reproductive years. The rate is higher with advancing age. The prevalence of fibroids without any obvious cause of infertility is estimated to be between 1 and 2.4% (1, 2). However, modern sophisticated ultrasound equipment provides the means for more frequent diagnosis of fibroids of all shapes, sizes and in different locations, whether symptomatic, or asymptomatic. This fact adds to the basic dilemma of whether to excise an existing fibroid in an infertile patient despite the potential complications, or whether surgery should be avoided despite possible lower "take home baby rates".

The relationship between uterine fibroids and infertility remains a controversial issue. The precise mechanism by which fibroids may cause infertility is unknown and includes: occlusion of fallopian tubes, alterations of tubal function and motility, alteration of cervical and vaginal pool of semen, dyspareunia, and thin, poorly vascularized endometrium (1). Only the latter can directly affect implantation and IVF results. Our knowledge of the effect of fibroids is based on several lines of evidence, none of which is well controlled. Many studies, some from the 70's and 80's and others more recent, collectively indicated that after myomectomy in infertile women a success rate of approximately 50% may be expected (3). However, some of these studies are outdated and include fibroids of various sizes, numbers and different locations. All these studies were uncontrolled or non-randomized, hence the results varied from <10% to >70% (4). As a consequence of all these studies, it is generally accepted (even if not scientifically proven), that regardless of the means by which myomectomy is performed (hysteroscopy, laparoscopy or laparotomy), excision of submucous myoma can improve the chances to conceive, whereas myomectomy of large intramural fibroids can improve the overall outcome of pregnancy.

Other evidence was obtained from IVF treatments. The current trend to delay childbearing to the 4<sup>th</sup> or 5<sup>th</sup> decade of life, when fibroids and infertility are more prevalent, increases the risk of this association and induces renewed interest in the effect of fibroids on IVF outcome.

It is obvious that depending on the number, size and location, some fibroids may cause infertility or pregnancy failure, together with other symptoms, such as pain, pressure and bleeding. However, these symptoms are not pathognomonic, nor are they consistent in indicating a causal relationship. There is no simple way to decide if an existing fibroid may affect fertility directly, indirectly, fully or marginally. Moreover, case reports of large fibroids, encountered during delivery or caesarean section (CS), including intracavitary fibroids, are well known and are an indication that not all fibroids are symptomatic. An additional difficulty stems from the fact that fibroids are more common during advanced maternal age which *per se* is correlated with lower-quality oocytes and infertility. Hence, it is difficult to know with certainty whether infertility is due to an existing fibroid, or to other factors.

Despite numerous publications relating to fibroids and infertility, it is still difficult to formulate precise rules and guidelines regarding treatment in each case, mainly because of the small sample size and lack of randomized control trials. We were the first to draw the line and suggest that in an IVF setting, fibroids that distort the uterine cavity can affect implantation (5), this finding being later confirmed by other non-randomized studies (6,7). However, these studies reported that intramural fibroids may also have a deleterious effect on IVF results, and consequently excision should be considered. This conclusion remained controversial and was not confirmed by others (8). Despite the lack of first-degree evidence, an interim summary of the literature permits the conclusion that fibroids that distort the uterine cavity may lower implantation rates, and thus should be performed prior to IVF. Conversely, the effect of intramural fibroids that do not distort the uterine cavity warrants further investigation.

Treatment of intramural fibroids before ivf - the new dilemma: The current dilemma mainly resides in the possible deleterious effect that small intramural fibroids may have on implantation. Donnez and Jadul (4) performed a meta-analysis of six studies (5-10) and found a pregnancy rate of 9% in women with fibroids that distorted the cavity, compared to pregnancy rates of 33.5 and 40% in women with fibroids that did not distort the cavity, and the control groups, respectively. These authors concluded that the large differences observed among the various series raised the question of proper evaluation of the cases and the lack of clear definition of the fibroid location, thus casting doubts on the true value of the studies. Check et al. (11) found no difference in implantation and pregnancy rates in patients with or

without intramural fibroids smaller than 5 cm, but they did find a distinct trend for lower delivery and higher miscarriage rates. They concluded that only a large prospective, matched, control study with sufficient strength would be able to assist in solving the issue of fibroid removal before treatment. Oliviera et al (12) found that intramural fibroids smaller than 4 cm that do not distort the uterine cavity did not affect pregnancy potential, or cause more miscarriages over one cycle only, a fact that also represents the limitation of the study.

Khalaf et al. (13) studied the effect of small intramural fibroids not encroaching on the cavity on implantation, ongoing pregnancy, and live births over three treatment cycles. Overall, 606 cycles were studied. Pregnancy, ongoing pregnancy and live birth rates in the study group were 23.6%, 18.8%, and 14.8%, respectively, compared with 32.9%, 28.5% and 24 % in the control group, respectively ( $P < 0.05$ ). Regression analysis showed about 40% reduction in success rates during each cycle, thus they concluded that small fibroids (<5cm) do significantly affect IVF outcome.

Taken together, these studies indicated that large intramural fibroids or fibroids that distort the uterine cavity can negatively affect the results of IVF and hence should be surgically removed prior to IVF treatment. However, the dilemma lies in the intramural fibroids that are smaller than 7 cm, and even smaller than 5 cm. In the various studies there is no consensus regarding the effect of such fibroids on IVF outcome. The differences are probably related more to the inability to properly evaluate the exact location of the fibroid and its imprint on the cavity. Admittedly it is difficult to comprehend how a 5-cm fibroid on the uterine wall does not bear any relationship with the cavity. More precise evaluation of the fibroids, possibly with the help of modern 3D devices is certainly warranted.

In summary: The role of uterine fibroids as a cause of infertility remains controversial. The lack of randomized control trials does not provide the means of establishing definitive causal relationships. The sharp decline in pregnancy rates in cases of submucous myomas appears to be quite convincing; however, the less significant effect of intramural fibroids on the outcome is probably

one of the reasons for the diverse results reported in different studies. New randomized studies that evaluate the size and location by 3-D ultrasound or MRI, should be able to define more precisely which fibroids should be excised and when we can proceed with IVF, despite the fibroids.

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