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Laparoscopic Versus Open Myomectomy and Fertility – A Meta-Analysis

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Abstract

***Background:** Fibroids (leiomyomata or myomas) are themost common benign tumours of the female genital tract and may have a negative effect on fertility. In women with symptomatic fibroids wishing to conserve fertility thefibroids can be surgically removed with preservation of the uterus (myomectomy). This operation is achieved by laparotomy, laparoscopically or hysteroscopically depending onthesite, size and type of myoma. However, myomectomy is a procedure that is not without risk and may, on occasion, result in serious complications. Therefore, it is essential to detect whether this procedure can improve fertility and, if so, to determine the ideal surgical approach.*

Laparoscopicmyomectomy, in subfertile patients, is a common surgical procedure. Despite the observation that the laparoscopicapproach to myomectomy has many advantages, its role ininfertility treatment remains controversial.

***Aim:** To undertake a systematic review to examine the effect of laparoscopic myomectomy on fertility outcomes compared with abdominal myomectomy.*

***Methods:** The following databases were used in this review: PubMed Central, Medline, BioMed Central, CINAHL with Full Text (EBSCO), , ScienceDirect – Full text only, Cochrane library ,Google search in general and Google scholarly. Studies which met the inclusion criteria were selected and analysed.*

***Results:** The evidence from two randomised control trials suggests that there is no significant difference between laparoscopic and open myomectomy for large myomas with respect to fecundity for women in the reproductive age group. This evidence requires cautious interpretation because of the small number of studies available. Thus more studies are required to add power to the findings. Many surgeons prefer the laparoscopic approach, if it is practicable because of the proven benefits including less post operative pain, less fever, reduced blood loss, enhanced recovery and shorter length of hospital stay. There is paucity of data regarding the effect on fertility and our meta-analysis attempts to clarify this gap in the literature.*

Keywords: *preterm, rupture, membranes, neonatal, outcome*

Back Ground

Fibroids (also known as leiomyomata or myomas) are benign tumours that arise from uterine smooth muscle cells. They are the most common benign tumour of the female genital tract. They are found in 20-50% of women.[1]Leiomyomata are associated with many symptoms including heavy menstrual bleeding and sub- fertility. Fibroids are estimated as the sole cause of infertility in 3% of cases with different mechanisms depending on the fibroid type.[2]

Anatomical changes are one of the mechanisms which may affect the uterus, cervix and fallopian tubes. Other mechanisms are an inflammatory reaction of the endometrium which leads to impaired receptivity of the endometrium to implantation, impaired sperm transport and myometrial contractility.[3]

Fertility may be affected differently according to the type of fibroid. The different types of fibroid include: submucous, intramural or subserous and the effect on fertility has been reviewed in several studies.[4]

Evidence from a recent review confirms the effect of submucous fibroids on fertility. However, there is little evidence of subserous fibroids adversely affecting fertility. On the other hand the evidence regarding intramural fibroids is less conclusive and there is no clear agreement regarding the effect of these fibroids on pregnancy outcomes.[5]

Surgical removal of fibroids with preservation of the uterus is called myomectomy. This operation is performed open, laparoscopically or hysteroscopically depending on the size, site and type of fibroid.[4]

Most of the evidence which suggests an improvement in pregnancy rates after surgical removal of fibroids (myomectomy) is derived from observational studies rather than randomised controlled trials.[2]Some authors predict that an RCT would not be easy to recruit tofor the procedure of myomectomy given thenumerous factors that might affect the fertility outcome.[5] Moreover, myomectomy may be associated with risks that mayaffect the chances of pregnancysuch as intrauterine or intraperitoneal adhesions.If there is a whole thickness breach of the uterine wall during the myomenctomy, there is a significant risk of scarrupture in a future pregnancy. In view of the controversy about the effect of some types of fibroid on fertility outcomes, in particular the intramural type, it is fundamental for clinicians to have robust evidence on whether surgical interventions to remove fibroids are associated with advantages rather than harm where fertility is concerned. A systematic review is the most robust method to support evidence-based practice:

Hence the importance of a systematic review of randomised controlled trials.

Pathogenesisand Description of the Condition

Fibroids (Leiomyomata or myomas) by definition are benign monoclonal tumours of smooth muscle which reveal different cytogenetic abnormalities. These tumours have a characteristic pearly white appearance with bundles of smooth muscle fibres creating a whorled appearance in cross-section. Leiomyomatahave oestrogen and progesterone receptors and are therefore hormone responsive. That is a plausible explanation for the higher incidence among women in the reproductive age group.[6]

The pathogenesis of fibroids is not fully understood. There are many factors that may be involved. Some of them are ovarian steroid hormones, genetic predisposition (for example the genes MED12 [7] and HMGIC [8]), growth factors (like transforming growth factor[9] and vascular endothelial growth factor-A VEGF-A [10]), in addition to up-regulation of type I and III collagen and interleukin 8(IL-8)[11].

Epidemiology

Uterine fibroids are the most common tumour found in the female reproductive system. They are found clinically in 20- 25% of women and are estimated in 40% of menstruating women with age more than 50 years.It can occur at any time between menarche and menopause but are most common in women 35-49 years of age. They typically resolve after menopause.[12]

The prevalence may be higher becausea high proportion of individuals with fibroids are asymptomatic and found incidentally in hysterectomy specimens approximately 77% of the time .[13,14] Fibroid prevalence rates vary according to racial group. The lifetime risk is 3 times more in black women than in Asian or white women. [15]

Classifications of the Fibroids

Fibroids can be classified according to location as follows: Figure1,2

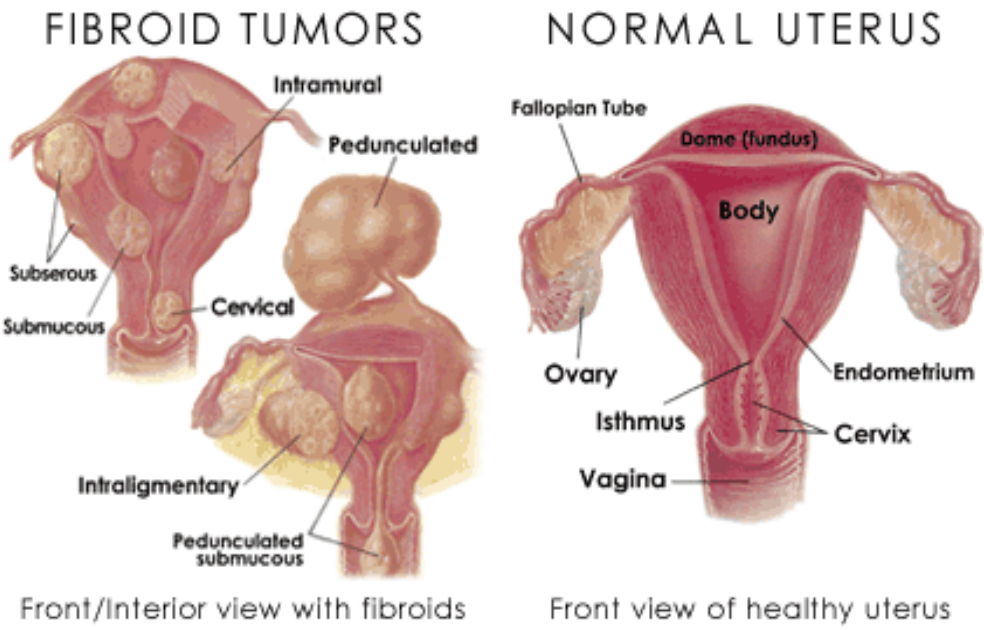


Fig1

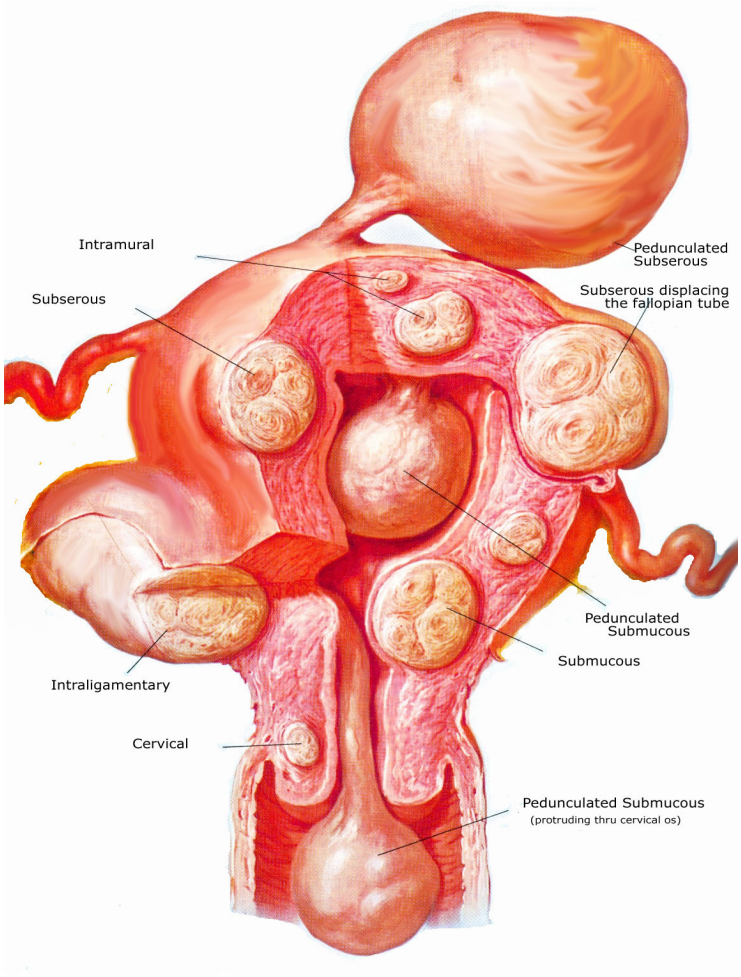


Fig2. Fibroids Type

- Submucosal Leiomyomata :it is in the submucosal layer of the uterus encroaching on the endometrial cavity. Sub mucous fibroids may be pedunculated, attached to the endometrial cavity by a stalk, and may be prolapsed through the cervix. The latter is the least common type of fibroid. Symptoms associated with Submucosal fibroid are prolonged and heavy menstrual periods and an increased miscarriage rate. Sometimes the fibroid tumour increases in the uterus size and blocks the fallopian tube and causes the infertility. On the other hand, some such fibroids cause no symptoms at all. [16] Classification of submucous fibroids is a useful tool when considering therapeutic options particularly the surgical approach.[17] The most widely used system was by Wamstekerand and adapted by European Society of Gynecological Endoscopy (ESGE). This system has categorised the myomasinto three subtypes depending on the percentage of the myoma that is within the myometrium(Table 1), which is detected by hysteroscopy or saline infusion sonography (SIS). The FIGO (International Federation of Gynecology and Obstetrics) system for classification adds a number of other categories, which include type 3 lesions that adjoin the endometrium without distortion the cavity of the endometrium. [17]

Table1. *ESGE: Classification of submucousmyomas*

Type 0 Entirely within endometrial cavity No myometrial extension (pedunculated)
Type I < 50% myometrial extension (sessile) < 90-degree angle of myoma surface to uterine wall
Type II ≥50% myometrial extension (sessile) ≥90-degree angle of myoma surface to uterine wall
Modified from Wamsteker et al. Obstet Gynecol. 1993

There are another classification system designed taking 4 criteria into consideration: the penetration of the fibroids into the myometrium (it is same as ESGE/ FIGO system for submucousmyomas), the diameter of the leiomyomata, the percentage of the endometrial surface area occupied by the base of the fibroid, and lastly, the topography of the fibroid, which is clarified as its location in the upper, middle, or lower third of the corpus and its orientation–transverse orientation (anterior-posterior or lateral); (Table 2).[17]

Table2. *Presurgical classification of SM myomas*

Points	Penetration of myometrium	Largest myo-madiameter	Extension of myoma base to endometrial cavity surface	Location along uter-ine wall (third)	Lateral wall (11)
0	0	≤2	≤1/3	Lower	
1	≤50%	>2–5	>1/3 to 2/3	Middle	
2	>50%	>5	>2/3	Upper	
Total score					
Modified from Lasmar et al. J Minim Invasive Gynecol. 2005					

The classification system for submucousmyomas is useful for clinical and surgical view, because it is highly correlated with completeness of myomectomy, the length of surgery and fluid deficit. The score calculated is determined the management protocol as seen in table 3.[17]

Table3. *Management protocol*

score	Group	indication
0 to 4	I	Low complexity hysteroscopic myomectomy
5 to 6	II	High complexity hysteroscopic myomectomy. GnRH? Two step hysteroscopic myomectomy.
7 to 9	III	hysteroscopic myomectomy is not indicated

- Intramural fibroids typically develop within the uterine wall and expand from there. Their growth may be associated with mass-related symptoms such as abdominal distention due to making the uterus larger than normal or urinary frequency due to bladder compression or pelvic pain due to pressure or fibroid on surrounding organ. These fibroids may also cause prolonged menstrual cycle with passage of clots. They may affect the fertility of the women [16,18].
- Subserosal fibroids typically develop in the outer portion of the uterine wall; they may be pedunculated, can potentially grow into the abdomen or in the ligaments of the uterus, and this put additional pressure on the surrounding organs; this may cause symptoms like bladder compression or abdominal distention. Symptoms of subserosal fibroids do not, in general, include excessive or prolonged menstrual bleeding or interfere with menstrual flow. This type of fibroid instead may cause pelvic pain and pressure which depend on the size and the location of fibroid. [16,18]

Clinical Presentation

Some patients are asymptomatic; the fibroids are discovered incidentally during routine gynecologic examination. While other patients have symptoms, which vary in severity. Most common symptoms are[18, 19]:

- Abnormal uterine bleeding
- Pelvic pain; the possible causes of pelvic pain include uterine contractions, torsion of a the stalk of the pedunculated fibroid, or intramural degeneration
- Distention of the abdomen
- Pelvic pressure
- Infertility and reproductive dysfunction
- Genitourinary dysfunction, which may present as increased urinary frequency due to bladder compression or flank pain due to ureteral compression and hydronephrosis
- In rare cases fibroids may present with lower extremity edema, venous thrombosis, intestinal obstruction or constipation

These symptoms may have a significant negative impact on quality of life and work productivity. [19]

The Mechanisms by which Fibroids can Lead to Infertility

A number of hypotheses exist to explain the mechanisms by which fibroids can affect on fertility, these are:

- Submucous and intramural Leiomyomata can lead to enlargement of the endometrial cavity and possible anatomical changes affecting the uterus, cervix, tubes and ovaries, or affect implantation.[20,21] Failure of implantation may also be explained by focal endometrial vascular disturbances, secretion of vasoactive substances and endometrial inflammation.[22,23]
- Fibroids may interfere with transport of ovum and sperm. They may cause dysfunctional uterine contractility. In addition, the tubal ostia may be obstructed by intramural Leiomyomata s.[22,24,25]
- The location of the Leiomyomata may play an important role in infertility. Submucosal fibroids may have detrimental effects on fertility. Removal of submucous fibroids appears to reveal fertility benefit. On theother hand, there is no observed effect of subserosal fibroids on fertility outcomes, and removal does not display any benefit on fertility. While Intramural fibroids appear to decrease fertility, but the therapy results are obscure.[25]
- The size of the Leiomyomata may be another important factor associated with infertility.[22,27] Large intramural type are thought to interfere with conception and decrease the assisted reproductive techniques effectiveness.[28] Fibroids with diameter of 5 cm are generally accepted as the minimal size for myomectomy. In some uncontrolled surgical trials improvement in fertility rates after myomectomy have been observed with subsequent pregnancy rates ranging from 44% to 62% .[29,30,31] The time to conception post-myomectomy is relatively short with about 80% of pregnancies recorded in the first year following surgery.

Some suggest that there is a relationship between the presence of menometrorragia and infertility associated with fibroids (50% for patients suffering from menometrorragia and infertility compared to 15% of those with menometrorragia and without infertility). The most likely interpretation could be

endometrial changes accompanied with fibroids, uterine cavity deformation, and changes in vascular plexus (ectasia of the submucosal venous plexus) associated with the presence of the myoma, which could play a role in infertility.[22]

Association between Fibroids and Infertility

Twenty to fifty per cent of women are estimated to have fibroids, and the incidence increases with age until the age of menopause.Fibroids are present in about 5-10% of the patients with infertility; however, they are estimated to be the sole cause of infertility in less than 3% of the patients.[32]

There is one study which gives an epidemiological estimation of fibroids impact on infertility, the review published by Buttram et al in 1981.[33] In 10 years of experience; the authors found that uterine fibroids could be the only cause of infertility in 2.4% of the cases. They concluded that fibroids alone are an infrequent cause of infertility.

Verkauf et al reported that only 1% of the 339 women with infertility required myomectomy between 1981 and 1990 for unexplained infertility.[34] It is important to note that these data are gathered from case series which are subject to observation bias and may not give the correct estimate of the prevalence of fibroids in the infertile population. Case series, in general, are not considered strong evidence. [35]

Some have suggested that to establish the association between fibroids and infertility, a case-control study may provide good quality evidence, where infertile women are cases and fertile women are controls.[35]

The influence of fibroids on fertility is poorly understood. Ezzati et al in 2009 carried out a systematic review and meta-analysis of studies to evaluate the association between fibroids and outcome of in vitro fertilization IVF. They have concluded that submucosal fibroids are associated with 70% reduction in delivery rate after IVF. While intramural fibroids have a lesser effect and reduce the delivery rate by approximately 30%. On the other hand, studies have demonstrated that there is no negative effect of subserosal fibroids on fertility.[36]

Donnez et al in 2002 undertook a literature review on studies which include both prospective and retrospective types. These studies are published between 1988 and 2001.[37] They concluded that in women with fibroids undergoing hysteroscopic and laparoscopic or abdominal myomectomy, the subsequent pregnancy rate in them were between 45 and 49%, respectively.[38-40] In general most epidemiological studies have not been able to provide clear evidence of the impact of fibroids on fertility.[40]

Description of the Intervention (Myomectomy)

Myomectomy is the name of the procedure by which fibroids are removed with preservation the uterus. Myomectomy has been reported in the literature as early as 1845. At that time, the *American Journal of Medical Sciences* described the removal of a subserous fibroid for a woman thought to have an ovarian cyst. Despite the fact that the procedure performed in the pre-anaesthetic era, it was successful. It was performed through a midline incision. However, hysterectomy has remained the operation of choice for symptomatic fibroids for many years, not least because myomectomy isoften associated with postoperative haemorrhage.

In the early twentieth century, abdominal myomectomy became popular following Victor Bonney's introduction of new surgical and haemostatic techniques.[41] Abdominal myomectomy is usually performed through a large (about 12 cm) transverse incision is the abdomen. The fibroid is excised, deep sutures are used to secure haemostasis and the abdominal layers are closed (usually a minimum of rectus sheath and skin layers).

More recently a number of minimal accesses surgical techniques have been developed as alternatives to abdominal myomectomy. These include hysteroscopic or laparoscopic myomectomy, laparoscopic myolysis (in situ destruction of the fibroid either with diathermy or laser) and laparoscopic-assisted mini-laparotomy (which is considered as an open myomectomy).[43] For the purpose of current review, laparoscopic and open myomectomy will be only included . Laparoscopic myomectomy is defined as the removal of fibroids via a diarthermy incision of the uterus, often assisted by morcellation, with small keyhole incisions in the abdominal wall through which instruments are deployed under telescopic control are passed. [44]

Hysteroscopic myomectomy is one of developmental sequelae of the urological resectoscope. In 1976, Neuwirth and Amin perormed the first hysteroscopicmyomectomy.[46] Hysteroscopic resection of fibroids (or myomectomy) is the preferred method when fibroids

are either submucosal or when the majority of an intramural fibroid protrudes into the uterine cavity. This technique involves removing the fibroids through the cervix and is generally limited to fibroids less than 4 cm in diameter in women seeking fertility.

How the myomectoy might work? Submucous fibroids have been suspected to cause a negative effect on fertility due to distortion of the anatomy of the uterine cavity, myomectomy may improve fertility by restoring the normal anatomy.[47]On the other hand, other types of myomas, such as intramural, their effect on fertility remains controversial. There is a possibility that myomectomy may improve some of the abnormalities associated with intramural type. An example may reduce the inflammatory reaction of the endometrium and abnormal contractility of the myometrium layer, which may lead to improvement in implantation.[48]

Laparoscopic Myomectomy in Infertility

In general, there are many management options for fibroids which may include observation (without intervention), medical therapy, or surgical resection like myomectomy or hysterectomy. Among ladies, who want to conceive, myomectomy is considered the treatment of choice (as mention above).

Since Semm and his colleague described laparoscopic myomectomy in late seventies this procedure is considered as one of the common surgical procedure. The laparoscopic approach has many advantages compared with laparotomy such as reduction in postoperative pain, necessity of analgesia, recovery time, febrile morbidity and blood loss.[49,50]

On the other hand, laparoscopic myomectomy carries a long learning curve, requires skilled instrumental handling by surgeon and may associate with more risks of pregnancy related to complications. These include uterine rupture during subsequent pregnancy or labour as a result of insufficient closure or healing defect at the site of the uterine incision site. The other complication may include adhesions, recurrence and pregnancy loss after myomectomy. [51]

Indications and Feasibility of Laparoscopic Myomectomy

Despite the laparoscopic myomectomy has well known benefits, it is still a debated operation. The indications for laparoscopic myomectomy, feasibility and risks are still matters of discussion. **Indications**: generally the indications include the existence of a submucous or intramural myoma that deform the uterine cavity, the presence of multiple fibroids and the fibroids size of greater than 3 cm. **Feasibility**: The feasibility of a laparoscopic approach has been examined with many studies. The size and location of uterine myomas are the most important factors for taking a decision about which surgical procedure is the most appropriate. The majority of opinion agreed that the maximum fibroid size should be 8-10 cm and the number of myomas in total must not be more than four.[52] There are some criteria for laparoscopic myomectomy suggested by surgeons such as a single intramural or subserosalmyomas less or equal 15 cm or there are three or fewer fibroids of less or equal 5 cm.[53] While , other surgeons believe that an individual option depend on pathological findings and surgical skill.[54]

It is judicious not to do laparoscopic procedures for myomectomies with large fibroids of more than five to seven in numbers. That is because in these situations the operation may take a long time and the surgeon can miss the smaller sized fibroids after the uterus has been incised and repaired in multiple sites.

Complication of Myomectomy

A study was undertaken in Italy in 2007 which was multicentre trial.This study is considered as one of the largest series focused on the complications of laparoscopic myomectomy. The authors reported that the risk of complications was significantly elevated with a highest fibroid number (more than three) and with the intramural type or the intraligamentous position of the fibroid, while, the size of myoma seems to influence the risk of major complications in particular way. [55] The possible complications include the following:

Uterine Rupture

Uterine rupture is considered as one of the major worries about myomectomy which may occur in pregnancy or labour. This complication risk exists with either a laparoscopic or an abdominal approach but may be higher with the laparoscopic approach. In one study of a retrospective type undertaken in the West Indies they found that the rate of uterine rupture observed at birth after open myomectomy was 5.3%.[56] On the other hand other there is debate if laparoscopic myomectomy has an increased risk of rupture. Regardless of the surgical approach, the

probability of uterine rupture leads to an increased rate of caesarean sections in pregnant patients post myomectomy. There appears to be agreement that caesarean section is advised if the percentage of disrupted myometrium is greater than 50% as this is postulated to confer uterine integrity.[57]

There are only nine cases of uterine rupture that have been recorded after laparoscopic myomectomy since 1991.[58-62] However, there is no mention of the incidence per number of performed procedures in these reports.[63] The authors reported many factors for this complication which could includelocal breach of endometrial cavity, excessive tissue coagulation, tissue approximation difficulties or unsuitable suture size are used with intramural hematomas, and uterine fistulas could occur. Laparotomic myomectomies permit the surgeon to do multilayered suturing by using suture materials of enough tensile strength. This manoeuvre allows closing the uterine defect optimally following enucleating. On the other hand, the surgeons in laparoscopical approach are trying to minimise the uterine rupture risk by changing the single-layer suturing techniques to multilayer one.[64] This principle is giving a good approximation without forming a hematoma which is essential for healing the wounds of myomectomy.[65] However, there are many studies which are suggested that uterine rupture is rare after laparoscopic myomectomy even when myometrium is closed in single-layer.

Adhesions

In 1998, Dubuisson et al reported the adhesions rate about 35.6% on second-look laparoscopy in patients underwent laparoscopic myomectomy.[68] and this result is confirmed by other studies did by Nezhat et al and Stringer et al.[69,70] The rates of adhesions after laparotomy ranged from 90% and more which are significantly high compared to those noted after laparoscopic myomectomy.[68] In other studies, they found that the incidence of adhesions is highest with posterior uterine incisions and the incidence is lower with fundal or anterior uterine incisions.[71] The fact that the possibility of conception after myomectomy was lower with posterior myoma and intramural myoma, which suggests the hypothesis in indirect way that adhesions have responsibility for decrease postoperative fertility chance. Reduced fertility is a result of adnexa involvement in adhesions accompanied with scarring due to posterior myomectomy.

Pregnancy Wastage After myomectomy

The risk of abortion does not seem to be raised in women who underwent myomectomy in either laparoscopic or laparotomy procedure. Several studies suggested that the rate of abortion is significantly lowered after myomectomy. Verkauf et al did a review for 1941 patients who have undergone myomectomy, he found that the spontaneous abortion rate decreased from 41% before surgery to 19% after myomectomy.[34] Also, many recent studies came with results confirming the strong of the surgery[72-75]

Recurrence

In a Korean multicenter study, they was estimated the recurrence rate of fibroids and found to be 11.7%, 36.1%, 52.9%, and 84.4%, respectively, after one, three, five, and eight years following laparoscopic myomectomy.[76] the study include 512 women who did laparoscopic myomectomy between 1995 and 2004. However, the possibility of re-operation is 6.7% after five years, and 16% after eight years. The causes for recurrence of the fibroids is that, laparoscopic myomectomy has a difficulty in diagnosing small myomasin deep of the myometrium, particularly in multiple fibroids cases, hence these may be missed. It has been recorded that the higher rate of recurrence is with laparoscopic myomectomy compared to laparotomy approach.[77]

Also, another factor for recurrence is the treatment with GnRHanalogs preoperatively. This treatment may raise the difficulties in identifying and dissecting the cleavage plane between the myoms and its pseudocapsule. That is due to shrinkage size of fibroids after therapy, which lead to a higher risk of recurrence in GnRHanalog-treated patients. [78]

Other Complications

There are number of complications which could occur intraoperative and postoperative in laparoscopic myomectomy. These complications include bladder, ureteral and bowel injury, hemorrhage which could happen intraoperatively and postoperatively that required transfusion, unintended conversion to hysterectomy, fistula, thrombosis, and embolism.[79] Fortunately, the rates of complication with laparoscopic myomectomy have been decreased over time. In a multicenter study [55] of 2050 patients who underwent laparoscopic myomectomy, they found that the most serious com-

plications were hemorrhage (0.68%), postoperative hematoma (0.48%), bowel injury (0.04%), and emergency hysterectomy (0.09%). These figures propose that laparoscopic myomectomy procedure is safer with skilled laparoscopic surgeons.

Laparoscopic Myomectomy Versus Total Abdominal Myomectomy Intraoperative and Postoperative Outcomes

There are four randomized controlled trials (RCTs) that compare laparoscopic myomectomy with abdominal approach, regarding intraoperativeand postoperative outcomes.[80-83]

These trials concluded that there was no significant difference in the duration of the operation, blood loss, or postoperative complications (fever) between two procedures.[80] Women underwent laparoscopic myomectomy recorded a less postoperative pain (unlabeled scale), need less analgesia, and required a shorter recovery time than women having laparotomic myomectomy. Moreover, after two days of surgery, there is only 15% of women need analgesia with laparoscopic myomectomy compared with 85% of women with abdominal myomectomy, and by day 15 more women had fully recovered after laparoscopic myomectomy (90%) with laparoscopic as against (5%) abdominal myomectomy.[81] In one of RCT. The authors found a significantly greater decreased in hemoglobin with abdominal myomectomy more than laparoscopic approach (1.33 g / dL with laparoscopic versus 2.17 g / dL with abdominal myomectomy; $p < 0.001$), a lesser incidence of postoperative fever (12%) with laparoscopic versus (26%) abdominal myomectomy, and a shorter hospital stay (75.6 hours with laparoscopic versus 142.8 hours with abdominal myomectomy).[82] The RCT comparing minilaparotomy with laparoscopic myomectomy found that laparoscopic approach significantly decreased the hemoglobin decline, duration of ileus, time to discharge patients from the hospital, intensity of the pain even six hours after surgery, and the proportion of patient required analgesics, as compared to minilaparotomy.[83]

Non Surgical Management of Myomas

Medical treatment used to improve symptoms and avoid surgery. Some of these medications are oral contraceptive pills and nonsteroidal anti-inflammatory drugs, but these drugs do not affect the fibroid size. The size of fibroid could be reduced from 30% to 65% through three months of treatment with gonadotrophin releasing hormone (GnRH) agonist. But, unfortunately the fibroid size is return rapidly to pretreatment size after cessation of hormone treatment. Also, GnRH agonist used as an adjuvant preoperatively. There are other agents like raloxifene, mifepriston ,GnRH antagonist, levonorgestrel IUD, gestrinone and aromatase inhibitors are under investigation. Other procedures like endometrial ablation, uterian artery embolization, cryomyolysis, or high intensity ultra sound are used to treat menometrorrhagia in selected patients, but have limited application in women desiring fertility in future.[84]

Why it is Important to do this Systematic Overview

Decisions about health care and conclusions for individual patients and for public policy should be planned using the best accessible research evidence. Health care providers, researchers and policy-makers need to make use of the latest research and information about best practice, and to make sure that decisions are made in this knowledge. However, this can be difficult due to the excessive quantity of information present in individual studies. Furthermore, these may be biased, methodologically flawed and context dependent, and could be interpreted incorrectly. Most will not have the time, skills and resources to appropriately consider this evidence and for it to benefit their healthcare decisions. Moreover, individual studies can obtain conflicting conclusions. These differences could occur due to differences or biases in the design or method of the study, how it was conducted, or it could be simple due to chance. In such situations, it can be unclear which results are the most reliable, or which should be used to inform practice and policy decisions.[85]

Cochrane reviews help address this challenge through appraising and integrating all this research-based evidence and displaying it in an accessible format named systematic review.[86]

A systematic review is defined by Khan as a research article that identifies relevant studies on a clearly formulated question, appraises the quality of these studies, extract and analyse data from them and finally summarizes their results using a scientific methodology.[87]

The aim of this dissertationis to determine the effectiveness of laparoscopic myomectomy compared with abdominal myomectomy on fertility through considering the existing literature. A systematic review examining all the relevant outcomes is needed to enable women and their surgeons to make informed choices about the route of surgery.

As mentioned before, most of the evidence which indicated an improvement in pregnancy rates after surgical removal of fibroids (myomectomy) is derived from observational studies and case series rather than from experimental randomised controlled trials.[2] Moreover, myomectomy may be associated with risks that may affect the chances of pregnancy such as adhesions in the peritoneum and the intrauterine, and the possibility of scar rupture in a future pregnancy. Also, due to the controversy about the effect of some fibroid types on fertility, in particular, the intramural type, we found it is fundamental for clinician to have clear evidence on whether surgical interventions to remove fibroids cause more benefit than harm where fertility is concerned. A systematic review is the most accurate method for evidence-based practice.

Hence, the important type of evidence to be considered is available from the randomised controlled trials rather than the cohort studies or case controlled.

Nowadays, laparoscopic surgery has become an approved and efficient type of minimal access surgery which has been adopted in most of the abdominal and pelvic surgeries. As a result of the appearance of minimal invasive surgery and the advantages accompanied with the laparoscopic technique, the surgical trend is for myomectomy to increasingly be performed using this technique of surgery. The current study will assess, based on various other clinical studies, whether laparoscopy can be used successfully compared with the abdominal approach and analyse whether the benefits of minimal invasive surgery can be translated to the treatment of infertile women.

Strength

The strength of this systematic review to summarise the findings from various other studies conducted across the world. The study has been restrictedto a review of literature and studies originally writtenin the English language to eliminate the possibility of any translation bias. The current study aims to bring together all the findings and highlight the feasibility of laparoscopic surgery used in myomectomy around the world. All studies which are accessible through the e-library of the university are included. The advantages of systematic review is to resolve the controversy between conflicting findings, reduces bias by using quality assessment and provides reliable basis for decision making by analyzing the study's results using meta-analyses.[86]

Drawback

There is the probability of bias in this study due to the methodological bias arising from the various studies selected; the trials included in this dissertation arethe ones with are accessible through the electronic library of Canterbury Christ church university. Therefore, some studies could be missed for example the ones which are not accessible through the University site and those which are not freely available. Therefore there may be a bias in the results due to the restricted access of various studies.

Other limitation may occur, if poor quality studies,such as ones with a small number of participants, may have an effect on the estimation ofthe intervention's effectiveness. Thus, assessing the quality of the study is often used to overcome this.[88]

The Effectiveness of Laparoscopic Myomectomy Compared to Abdominal Myomectomy on Fertility was Selected

Despite the fact that laparoscopic surgery has many benefits,such as increased clarity of vision through magnification, improved cosmetic benefits, less pain and swifter recovery times etc., it is considered to be expensive and theris a steep learning curve for the surgeons.[89]

Regarding the types of myomas, there is already agreement regarding the infertility effects for subserous and submucousmyomas, based on the results of several case controlled studies and meta-analyses. These studies showed that submucousmyomas have been found to be associated with a negative effect on fertility while subserousmyomas appear to have no significant impact.[90]Opinionsof intramural myomasarestill divided. Some studies haveproposed a negative impact on fertility [90,91]while other recent studies havesuggested that the evidence is of inadequate quality to make any conclusions.[92] In the midst of such controversy, surgeons are left with difficult decisions

in whether or not to intervene surgically, especially when this intervention may pose an infertility risk due to the possibility of post operative complications like intrauterine and pelvic adhesions. Unfortunately, the current evidence does not solve this dilemma.

During the research process for this dissertation, it was found that there is considerable published literaturerelated to laparoscopy, hysteroscopy and abdominal myomectomy regarding different kind of fibroids and different outcomes. Most of them are observational studies. However, there isa limited number of RCT. While the literature review and research strategy wasdeveloped for observational studies,it was found to be toolarge task andexcessively laborious to go into them all. Furthermore, a meta-analysis of the results of these different studies would culminate inan unmanageably long research paper. As such, the study on the role of laparoscopy in fibroid excision isbeyond the scope of this dissertation and the possibility of that the presentation would not support the topic for this procedure of thesis.

The introduction to this paper and review ofthe different outcomes of laparoscopy and hysteroscopy to remove the different kinds of fibroidwas done and submitted to the supervisor. Aftermultiple meeting and initially some progress in the dissertationdue to the vastness of the topic,followinga review by the academic and clinical supervisorit was decided to restrict the dissertation to the study of the role of laparoscopic myomectomyin restoring fertility rather than all theother outcomes. Furthermore, it was decided to include only randomised control trials in this meta-analysis and exclude the observational studies. Moreover, studies on hysteroscopy will not be included. The risk of bias in the included studies will be assessed usingthe Cochran risk of bias assessment tool as it isvery comprehensive and easy to use. The research proposalhas suggested using theJadad score instead. However, these decisions were discussed in the review meeting which was attended by the academic guide Dr. Susan Plummer, Professor. Douglas Macinnes and my colleagues from other speciality. Furthermore, after due deliberations, it was decided that this dissertation would be on the effectiveness of laparoscopic myomectomy compared to abdominal myomectomy on fertility as an outcome in the treatment of intramural type of fibroids. The above restrictionspave the way for an effective study on the efficiency and feasibility of the laparoscopy contained within the scope of the dissertation.

The Review Question / Objective

To assess the effectiveness of laparoscopic myomectomy compared to abdominal myomectomy on fertility.

The PICOS approach: The population or patients intervention comparison outcome study design (PICOS) isa framework used to facilitate the procedure of designing and focusing on the research question. It is important to develop a clear question to beable to extractthe information required to answer the research question and for it later to be converted into searchable terms. [92]

Population / Participants

The participants in this review are womenaged18 to 52; this specific range was chosen as it representsthe ages ofreproductive. Therefore ladies within this age range who suffer from both infertility and fibroids might seek this treatment after other infertility causes have been eliminated.

Intervention

Intervention defined as the change or process which is carried out in response to a condition under study. Theresultsof the intervention arethe subject of interest. Surgical intervention is the preferred choice in the treatment of fibroids.This surgery includes the resection of the fibroid which is named myomectomy. This treatment is done either by the open technique of surgery i.e. laparotomy and minilaparotomic access (as defined in description of intervention section above) or by minimal access surgery which include Laparoscopy.

Over the last 20 years gynaecological surgery has developed to include minimal invasive techniques. Furthermore, the advantages oflaparoscopy are well established. However,until now, laparoscopic myomectomy has not been adequately evaluated. Laparoscopic myomectomy even for a well experiencedendoscopist can be a hard and troublesome procedure, in particular for largemyomas.This review is intended to assess whether laparoscopic myomectomy is safe, feasible and offers the same results in restoring fertility as the other technique. In this review, laparoscopic myomectomy will be considered as the intervention to be compared with open myomectomy.

Outcomes

We will consider the obstetric outcomes within the one year follow up period which begins 6 months after the initial operation. These outcomes include:

- Live birth rate defined as the number of live births per woman
- Clinical pregnancy ratewhich includesthe abortion (or miscarriage) rate, the ongoing pregnancy rate(after 12 weeks of pregnancy) and the ectopic pregnancy rate
- Caesarean section rate
- Vaginal delivery rate
- Preterm delivery rate

In several studies, restoration of fertility after myomectomy has been reported with a pregnancy rate of between 44 -62 %. The time to conception after myomectomy is generally short with about 80% of pregnancies occurringwithin the first year of surgery. Therefore, myomectomy is considered as a valuable approach for treating patients with unexplained infertility.[89]

The Study Design

The study design for this dissertation is the randomized controlled trials (RCTs). These RCTs are comparingfertility outcomes of laparoscopic myomectomy and abdominal myomectomy. RCTs are considered as the gold standard for assessing the effectiveness of a treatment.

A systematic review is a scientific tool that can be used to assess, collate and present the results and implications of otherwise unmanageable quantities of research which is related to a specific research question. It brings together evidence and informationrelevant to the review questioni.e it brings together two or more studies on a particular topic and collates the results of these studies.[90]

Search Strategy

The aim of this search is to find the relevant literature onlaparoscopic myomectomy and abdominal myomectomy for intramuraluterinefibroid to determine the effect of these operations on fertility. This search will consider all the published literature fromwhen laparoscopic myomectomy was first used, in 1991, to the end of 2013. It will be based a list of keywords related to the topic used to search in major electronic databases. A comprehensive search has also been done to know the prevalence, incidence, pathology and epidemiology of the disease.

Databases Searched

The databases used in the search were the BioMed Central, CINAHL with Full Text (EBSCO), Medline, PubMed Central, ScienceDirect – Full text only, Google search in general, Google scholarly and finally Cochrane library.

The Search Terminology (Keyword) Used

The search terminology or keywords used in this dissertation were fibroid, fibroma, fibromyoma, leiomyomata, leiomyoma, myoma, myomectomy, laparoscopic myomectomy, laparoscopic surgery, laparoscopic-assisted minilaparotomy, abdominal myomectomy, laparotomy, fertility, subfertility, pregnancy, abortion or miscarriage.

Inclusion Criteria

Inclusion criteria are the attributes that the RCT studies must have if they are to be included in the systematic review. These criteria or attributes are decided upon before the start of a review and are used to determine whether a piece of literature can be included in the systematic review. Inclusion criteria include the characteristic criteria of participantslike age, type of disease being treated, previous treatment history, and other medical conditions. Also include the criteria for intervention group,control group and the outcome of the study. The inclusion criteria for the current review are present in Appendix 1.

The inclusion criteria for a studyto be considered as relevant for this thesis are :

- Studies published from January1991
- Studies underwent by laparoscopic intervention
- Studies done on ladies with intramural or subserosaluterin fibroid who were previously infertile for at least one year
- Studies involving either laparoscopic myomectomy or abdominal myomectomy as the intervention
- Only Randomised controlled trials
- Studies on uman

- Studies involving all women within the reproductive age i.e from 18 – 52 years old
- Studies published before December 2013
- Studies considered any population
- Studies available in English
- Studies accessible by the electronic library of Canterbury Church University
- Studies which are freely accessible

Exclusion Criteria

The criteria which are decided upon before a review which are used to determine whether an individual study should be excluded from a systematic review are known as exclusion criteria.

The following are the exclusion criteria a study to be excluded from this dissertation:

- Unpublished studies
- Literature published before the year 1991
- Literaturepublished after the December 2013
- Studies on animal
- Studieson Cadaver
- Studies not accessible from the electronic library of Canterbury Christ church university
- Studies published in a language other than English (with no English translation)
- Studies in protocol stage
- Studies based on trials
- Case reports, case series, abstracts, letters to the editor and articles without outcome measures
- Cohort and Case control studies (observational study)

The bibliographic references of the studies selected for the literature review are also scrutinized and studied. All the studies that met the inclusion and exclusion criteria were quality assessed using the Cochran risk of bias assessment tool (see Appendix II).[86] Among the various advantages of the Cochran risk of bias scale are its reliability, external validity, its ease of use and the fact that it contains many of the key elements that have been shown to correlate with bias.[86]

Phase 1 Literature Search

The search list of keywords are used in the BioMed Central, CINAHL with Full Text (EBSCO), Medline, PubMed Central, ScienceDirect – Full text only, Google search in general, Google scholarly and finally Cochrane library is accessed through the electronic library of Canterbury Christ Church University. These databases are selected as they are widely recognised to provide accurate and authenticate results. In the first phase, the search was done using the word fibroid and it resulted in a vast combined hit rate (search results) of 13387.

Resource Name	Hits
BioMed Central	125
CINAHL with Full Text (EBSCO)	266
ScienceDirect – Full text only	9751
MEDLINE	1767
PubMed Central	1478
Combined Results	13387

As shown above the maximum number of results was obtained from the PubMed Central, followed by ScienceDirect, Medline and CINHAL whereas the least results were from BioMed Central.

The search was refined by introducing the word laparoscopic myomectomy and the results drastically shrunk to 2152 combined hits.

Search for "Any word = (fibroid) And Any word= (laparoscopic myomectomy)

Resource Name	Hits
BioMed Central	14
CINAHL with Full Text (EBSCO)	21
ScienceDirect – Full text only	1496
MEDLINE	82
PubMed Central	539
Combined Results	2152

When the search was further refined by adding abdominal myomectomy as one of the keywords the search results significantly reduced to 1335 hits.

Search for "Any word= (fibroid) And Any word= (laparoscopic myomectomy) And Any word= (abdominal myomectomy)" found 1335results

Resource Name	Hits
BioMed Central	13
CINAHL with Full Text (EBSCO)	2
ScienceDirect – Full text only	1165
MEDLINE	22
PubMed Central	133
Combined Results	1335

When the search was further refined by adding fertility as one of the keywords the search results significantly reduced to 48 hits. This emphasises the fact that although laparoscopic myomectomy has gained popularity for a variety of procedures, laparoscopic myomectomy as a cure for infertility is still not widely used and the literature on it is relatively sparse.

Search for "Any word = (fibroid) And Any word= (laparoscopic myomectomy) And Any word= (abdominal myomectomy)" And Any word= (fertility)" found 48 results

Resource Name	Hits
BioMed Central	3
CINAHL with Full Text (EBSCO)	1
ScienceDirect – Full text only	2
MEDLINE	8
PubMed Central	16
Combined Results	30

Further the search was refined by adding "Randomized controlled trial" in the search and the number of results were narrowed to 5. There were 25 observational studies.

Search for "Any word= (fibroid) And Any word= (laparoscopic myomectomy) And Any word= (abdominal myomectomy")And Any word= (Randomized Control Trial)"

Resource Name	Hits
BioMed Central	3
CINAHL with Full Text (EBSCO)	0
ScienceDirect – Full text only	0
MEDLINE	0
PubMed Central	2
Combined Results	5

Phase 2

The five studies found as a result of the first phase of the search process were:

1. Seracchioli R, Rossi S, Govoni F, Rossi E, Venturoli S, Bulletti C, Flamigni C. Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal delivery. Human Reproduction 2000
2. Campo S, Campo V, Gambadauro P. Reproductive outcomebefore and after laparoscopic or abdominal myomectomy for subserous intramural myomas. European Journal of Obstetrics, Gynecology, and Reproductive Biology 2003;
3. Bulletti C, DE Ziegler D, Levi Setti P, Cicinelli E, Polli V,Stefanetti M. Myomas, pregnancy outcome, and in vitro fertilization. Annals of the New York Academy of Sciences 2004
4. Casini ML, Rossi F, Agostini R, Unfer V. Effects of the position of fibroids on fertility. Gynecological Endocrinology 2006.
5. Palomba S, Zupi E, Falbo A, Russo T, Marconi D, Tolino A, et al. A multicenter randomized, controlled study comparing laparoscopic versus minilaparotomic myomectomy: reproductive outcomes. Fertility and Sterility 2007

The phase 2 of the search strategy consisted of individually scrutinizing the 5 search results. Thedate of publication was checked and all 5 results were found to be published after the year 1991.As per the inclusion criteria 3 results are excluded from the current review.These studies were excluded due to either inadequate methodology or they compared laparoscopic approach with no intervention. After the thorough scrutiny of the search results two of them were selected.

The Cochrane Library was also searched. One study was found but the study was in protocol stage and had not been completed. It is:

Minimally invasive surgical techniques versus open myomectomy for uterine fibroids: Antonia Steed, Annefloor W Pouwer, Cindy Farquhar.

It is a systematic review of all randomised controlled trials comparing open myomectomy with laparoscopic or hysteroscopic myomectomy. The review examines all relevant outcomes like blood loss, recovery time,

postoperative pain, recurrence of fibroids and hospital stay. But it excluded fertility and pregnancy outcomes following the myomectomy.

Phase 3

The phase 3 of the search consisted of going through the 2 studies. Their bibliographies were also searched to find other relevant studies. Finally, after all the scrutiny, assessment against the inclusion and exclusion criteria and checking with the quality assessment framework,the following studies were selected to be included in the current systematic review for this dissertation.The search strategy was agreed by the academic guide and these two studies were agreed to be included in the dissertation.

The two studies are:

1. Seracchioli R, Rossi S, Govoni F, Rossi E, Venturoli S, Bulletti C, Flamigni C. Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal delivery. Human Reproduction 2000;15(12):2663–8.
2. Palomba S, Zupi E, Falbo A, Russo T, Marconi D, Tolino A,et al. A multicenter randomized, controlled study comparinglaparoscopic versus minilaparotomicmyomectomy: reproductive outcomes. Fertility and Sterility 2007;88(4):933-41.

Quality Assessment

The quality assessment isa critical appraisal of the included studies. It provides a measure of the degree of bias and error in study design, conduct and analysis.[93]

Quality assessments items can be found in a published guide as a checklist which is used as a basis of an in-depth appraisal of the literature.[93]

Certainly, a study's quality is important to identify its external and internal validity. External validity is a measure of whether the study is asking an appropriate research question. While internal validity is a measure how much of the result is free from bias.[94]

Bias can be defined as a systematic error that either exaggerates or underestimates the true effect of an intervention or exposure.[93]

The methodological quality of each study needs to be examined through this assessment of quality. This is because methodological flaws decrease the level of confidence that can be put in the findings. Poor quality studies have been shown to overestimate the effect of intervention. Thus quality assessment tools reduce the likelihood of poor quality studies being part of the review.

The biases that the quality assessments will seek to decrease are: [93]

- Selection bias (allocation bias)when there are systematic differences betweenthe fundamental characteristics of the comparison groups in prognosis or responsiveness to treatment;
- Performance biaswhen systematic differences among groups in the provided care, or exposed to items other than the intervention involved in the study;
- Measurement bias (detection bias, ascertainment bias) when there are systematic differences among groups in how outcomes are assessed.
- Attrition bias (exclusion bias) when there are systematicdifferencesamongthecomparedgroups in withdrawals or exclusions of participants from the study sample. This could include participants dropping out because ofsome side effects of the intervention.
- Reporting bias (incomplete outcome data)systematic differences among compared groups regarding reported and unreported finding. For example, in dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in the estimate of the intervention's effect.

In this review the quality assessment of the included RCTs is done via the Cochrane risk of bias assessment tool (Rev ManVersion 5.2). This specific tool is used for assessing the risk of bias in each included study. The results will be organisedin a ''Risk of bias'' table, where each entry addressesa specific feature of the study. The judgement for each entry involves assessing the risk of bias as 'low risk' (adequate), 'high risk' (inadequate), or 'unclear risk' (unclear). Each of these assessments it supported with the reasons for the decision. The Cochrane risk of bias assessment tool considers the following field:

- random sequence generation (selection bias)
- allocation concealment (selection bias)

- blinding of participants and personnel; blinding of outcome assessors (performing bias and detection bias)
- incomplete outcome data(attrition bias)
- selective reporting(reporting bias)
- other bias

The included studies have beenassessedbythe risk of bias tool in RevMan(version5.2) and the result as following:

1. Random sequence generation (selection bias)

The two studies were at low risk of selection bias related to random sequence generation. Palombaused randomisation via online software while Seracchioli used randomisation via number generation.

2. Allocation concealment;

Palomba is considered as lowrisk of selection bias related to allocationconcealment because there is adequate description of the process. In this study the random allocation sequence was concealed ina closed and dark-coloured envelope till before the patient enter the operating room. As for Seracchioli, there is no adequate mention of concealment making it at unclear risk of this bias.

3. Blinding of participants and personnel;

The absence of blinding could not be considered as performance bias because these trials are surgical ones and it would impossible to blind the participant and personnel.

4. **Incomplete outcome data**

Both studies reported and analysed all included patientsthus it is considered at low risk of attrition bias. Furthermore, ITT analysis are also mentioned.

5. Selective reporting

Both studies recorded all outcomes of interest, thus they areconsidered to be at low risk of reporting bias.

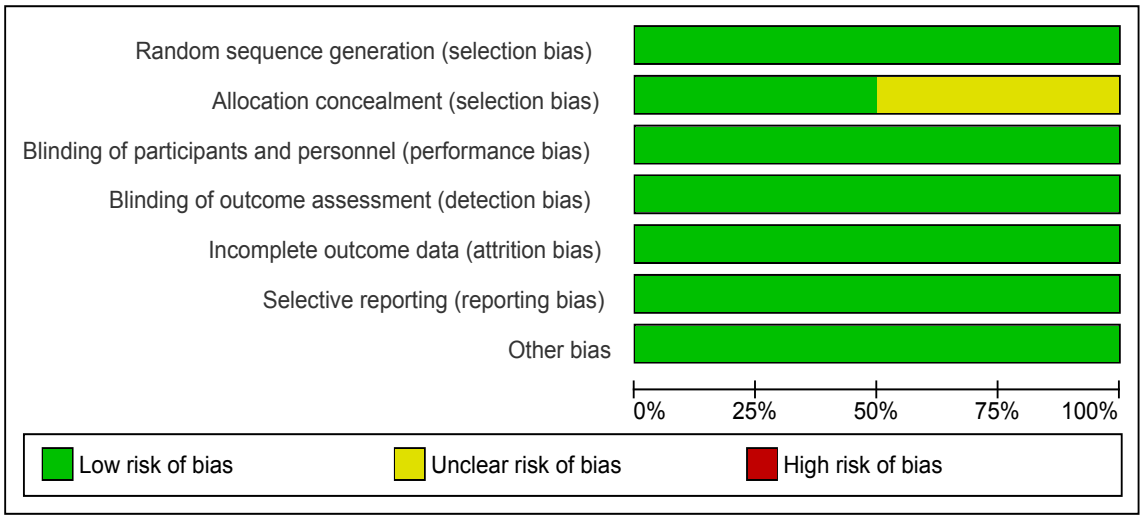
6. **Other potential sources of bias**

The includedstudies appears to be free of other source of bias.

It should also be noted that the trials weredone in adults with proper consent and no patient refused to take part in the trials. Furthermore, one of trials (Palomba) wasdone in multiple centres whereas the second onewasconducted in an individual centre. TheCriteria for judging risk of bias in the 'Risk of bias' assessment tool is present in the Appendix II.

Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Descriptive Analysis of Individual Trial

The content of theindividual trials will now be analysedthe assessed according to the quality assessment scale.

1) Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal delivery. [96] [Seracchioli R, Rossi S, Govoni F, Rossi E, Venturoli S, Bulletti C, Flamigni C.]

The aim of this study is to comparethe effectiveness of laparoscopic myomectomy versuslaparotomic myomectomy in restoring fertility in infertile women. This study is a randomised control trial (RCT) undertakenwithin the reproductive unit inOrsola hospital in Italy. It was published in 2000. This unit has been carrying out Laparoscopic myomectomy since 1991. Approximately 100 patients every year undergo myomectomy either by laparoscopy or the open procedure for infertility. It is the first RCT that compared the two surgical procedures inpost operative restoration of fertility. The study included131 patients who were suffering from infertility and fibroids.The myomectomies were carried out between January 1993 and 1998. There is no mention whether this sample size is representative or notof the study population. There is an adequate description of the fibroid diagnoses criteria and causes of infertility. All the women suffered from one or more fibroid,at least one of themof large size (5 cm or more). The diagnosis of the fibroid was done by abdominal and transvaginal ultrasonography. When there wasthe possibility of the involvement of endometrium layer of the uterus the surgeon did hysteroscopy 6 month before the operation. The presence of a large fibroid is considered one of the key indicators that they should be removed. This is because the size of the myomata is a significant prognostic factor for fecundity.[43]

The patients were within the reproductive age (21 – 42)and were suffering from either primary or secondary infertility(for 2 to 10 years). In order to estimate the existence of other infertility factors, women were assessed preoperatively through ovulation studies, the post coital test, hysterosalpingiogram and seminal analysis. There were no prescriptions of any hormone medication like Gonadotrophinreleasing hormone agonist before the surgery, but the reason for this is not mentioned.

Patients were rejected from the study if they metone of the following exclusion criteria: 1- pedunculatedmyomas (many studies suggest that pedunculated fibroid are not responsible for sterility)[44]; 2- the size of the uterus wasabove the umbilicus; 3- there weremore than three fibroids larger than 5 cm; 4-presence ofany other infertility causes like tubal or male factors; 5-uterine cavity abnormalities such as septum or subseptum.

There are,however, some missing confounders,for example: BMI, smoking, and previous surgery. These could have an effect on the post operativeresult.

The patients who participated in the study, after a

proper preoperative explanation of the procedure, signed a consent form. Ethical approval was not noted. There were 65 women underwent open myomectomy and 66 underwent laparoscopic intervention.

The patients were randomly distributedbetween the two groups via random number generation.This process was conducted without the knowledge of the surgeons. Therefore, the risk of random bias is low. The allocation concealment was not reported clearly. Consequently, there was insufficient information to allow judgment. Therefore, the selection bias is unclear.

In this study,it wasinapplicableto blind the participant or personnel as it is a surgical study. So it is not considered as having any blinding bias.

All surgical operations were underwent by the same investigators(R. Seracchioli, S. Venturoli).This is an important point to mention since this should minimise the post operative complications. This is because most complications occur when the procedure is performed by inexperienced laparoscopic surgeons.

There is an adequate description of surgicaloutcomes which include: 1-mean length of the operation 2- average haemoglobin dropspostoperatively 3- Incidence of postoperative fever 4- average postoperative stay in hospital. Fertility outcomes: 1- clinical pregnancy rate 2- misscareage rate 3- ongoing clinical pregnancy 4- preterm delivery rate 5- caesarean section rate 6. live birth rate.

Follow up information about obstetric outcomes were gained from hospital records, physicians and direct patients reports. Only the participants with 12 months follow up were included. The data about fertility outcome are only included in this review.

There is a clear explanation of the operations techniques:

Abdominal myomectomy was undergone by a transverse lower abdominal incision. Furthermore,a small incision was made on the prominent part of myomas. Most incisions were made on the anterior wall of uterus and as many leiomyomta as possible are removed from single incisions to decrease the possibility of adhesions. Even fibroids on posterior wall of uterus were removed through a fundal approach. The other steps of the operation are adequately presented.

Also the steps of laparoscopic myomectomy are adequately described and the surgeons used the manual laparoscopic morcellator to remove the myomas from abdominal cavity. The laparoscopic morcellator is a device used during minimally invasive surgeries. It is used to divide tissue like myomas or the uterus into small fragments to facilitate removalof thesepiecesfromthe small incision sites and it is often used during laparoscopic surgery.[98]

In 2014, the FDAdiscouraged the use of laparoscopic morcellation during hysterectomy or myomectomy because of the risk of spreading unsuspected cancerous tissue within the abdominal cavity.[98]However, this study wasconducted before this prohibition.

The statistical analysis was well described and usedrecognised methods. Although, there wasno mention of power calculation.

There is a clear explanation of the results with adequate interpretation. There is reporting of all the outcomes of all participants who started the study. Therefore, there is no attrition bias. Following a6 months recovery period (for uterin scar reparation) all the women were followed up for almost one year to evaluate their fertility. The pregnanacy rate was 33 out of 59(55.9%)for patients who underwent abdominal myomectomy (group 1) and 30 out of 56(53.6%)for patients who underwent laparoscopic myomectomy (group 2).

Caesarean section was done for 21 patients (77.8%) in group 1 and vaginal delivery occurred for 6 ladies (22.2%). While in group 2, Caesarean section was carried out on 13 patients (65%) and vaginal delivery occurred for 7 ladies (35 %).

The discussion part of the study is balanced and based on the resultobtained. The study demonstrates that there is no significant difference between the two groups with regard to pregnancy outcomes. It suggests that laparoscopic procedure may give the same result as abdominal myomectomy regarding restoration of fertility. But the laparoscopic approach has other significant advantages,for instance, short hospital stays and better post operative outcomes. In the authors' opinion, there is no longer any controversy over the effectiveness of laparoscopic myomectomy. It can be performedona larger number of patients even for ones with large myomas.

2) A multicenter randomized, controlled study comparing laparoscopic versus minilaparotomic myomectomy: reproductive outcomes [Palomba S,

Zupi E, Falbo A, Russo T, Marconi D, Tolino A, et al.] 2007

The aim of this study was to evaluatethe reproductive outcomes following laparoscopic myomectomy and minilaparotomic myomectomy in women desiring conception. The authors of this trial selected this topic as recent studies have suggested thatminilaparotomicisanalternative approachto laparotomy for myomectomy. Minilaparotomicprocedure are associated with the benefitsof laparotomy (such as easy to learn and perform) but also with those of minimal access surgery (such as less blood loss, short hospital stay, less pain postoperatively, enhanced recovery, faster return to daily activities like work)[99,100]

The study is a randomized controlled trial RCT. It isa multi-centredstudy which selected patients from three university departments of obstetrics and gynaecology (Catanzaro, Rome, and Florence) in Italy.

Between January 2002 and March 2003, 162 participants with fibroids and infertility were selected. The indications for surgery were fibroids related symptoms in addition to infertility, but only the infertility group were included in the current meta-analysis. There is no mention if this sample size is representative of the general population or not.

There is an adequate description of the data included in the diagnoses criteria for fibroids and infertility causes. Infertility was diagnosed after ruling out other endocrine abnormalities, tubal and male sterility causes with a whole hormonal assay. Every participant underwent hysterosalpingogram, and ovulation was verified by plasma P assay >10 ng/dLone weekbefore the expected menses. Also, these patients wereexamined by transvaginalsonography by three experienced operators (one in every centre) who evaluate the size, diameter, number, and location of uterine fibroids.

The exclusion criteria include the following conditions:

1- Women with major medical illness and endocrine diseases

2- basal FSH level more 10 IU/L

3- psychiatric disorders

4- present or previous history of acute or chronic physical illness

5- premenstrual syndrome

6- present or previous (within the last 6 months) use of hormonal treatment

7- effect of medication on cognition,mood or vigilance

8- lack of ability to complete the daily diary

9- history of alcohol abuse, tubal or male factor infertility

10- no desire to conceive

One limitation found in this study was that there is no clear definition of some of the criteria mentioned above, for instance, what major medical illness or endocrine diseases are included.

The characteristics of leiomyomata to be excluded from the trial are as follows:

1- patients suffering from three or moremyomas,

2- myomas with amain diameter less than 3 cm orlarger than 10 cm

3- hypoechoic or calcified myomas

4- existence of submucosalmyomas

5- distortion of the uterine cavity

6- otherabnormalities of uterus or adnexia found by sonography

7- hyperplasia or atypia of the endometrium

8- abnormality of the cervical smear.

Ethical approval for this study was noted and the procedures were undertaken according the Helsinki Declaration guidelines on human experimentation. Also, the study was confirmed by the Institutional Review Board (IRB) of the University ''Magna Graecia'' of Catanzaro, Italy. Moreover, the protocol was explained to the women, and informed consent was obtained.

The participantsare clearly describedspecifying their age, parity, body mass index (BMI), work andsocioeconomic condition, symptoms related to myomas, qualityof life (QoL), previous open abdominal surgery, and associated medical conditions. These factors were evaluatedforeach participant by the sameperson(clinician)in each centre.

There is a clear explanation of the randomization process for thedistribution of the patients into two groupsof 68 women (laparoscopic and minilaparotomic groups). This was done using online software

(www. randomization.it) which made a random allocation sequence. Therefore, selection bias is of low risk. The concealment of the random allocation sequence was well documented. It was done using sealed dark-coloured envelopeswhich were opened on the date of surgery prior to entering the operating theatre.

As with the former study, it wasinappropiate to blind the participant or personnel as it is a surgical study. Therefore,there isn't considered to be any blinding bias.

For both groups, there is a clear description of the operative steps, the duration of operation, amount of blood loss, post-operative analgesia, length of hospital stay, time to return to daily activity and quality of life. Additionally all patients wereexaminedgynecologically and sonography to assess the possibility ofmyomas recurrence at 1 and 3 months after operation.

Data was collected from patientsby telephone interview each month; the daily personal diary wasassessed every 3 months. Alsowhenmenses was absent, a serum b-hCGassay was done seven days after the expected date of menstrual bleeding.

All participants were followed-up for 12 months.The ladieswho became pregnant, were followedup for another 9 months to evaluate their reproductive events. Throughout the study,all reproductive outcomes were recordedfor each group.

There is an adequate description of surgical outcomes which include

1- Cumulative pregnancy ratedefined as the ratio between number of pregnant ladies and total number of womenstudied, 2-Cumulative live birth rate defined asthe ratio of live births to the number of pregnant women, 3- Miscarriage rate calculated as the ratio between the number of miscarriageswithin the first 12 weeks of gestation and total pregnancies, 4- caesarean section rate, 5-preterm delivery rate.

The procedure of statistical analysis was adequately described and well understood. In addition, it is appropriate to the research question. However, once again, there is no power calculation.

The outcomes are recorded for all patients who started the study. This made incomplete outcome data (attrition bias) of low risk.

There is a flow diagram inthistrial whichadequately describes the process by which a participant entered and categorised in the study. There were 162 eligible patients, 26 were excluded from the study (10 met the exclusion criteria, 9 refused to participate, 7 refused the randomisation). Thus, only 136 women entered the study. There were 68 women in each group. Only 30 women in laparoscopic myomectomy group and 32 women from minilaparotomic group were infertile. Consequently, these will be the patientsconcidered in this review. The rest of patients had fibroid related symptoms and will not be included in current meta-analysis.

All specified outcomes were recorded. Therefore, reporting bias is of low risk.

The discussion section is based on the result obtained and it is balanced. It demonstrates one limitation: that this study was underpowered to illustratea significant difference in cumulative pregnancy rate PR or live-birth rate.Including alarger sample of the population would have been essential to identify anysignificant-differences.

Finally, the authors conclude that laparoscopic andminilaparotomic myomectomy lead to the same reproductive outcomes in women with unexplained infertility, while symptomatic women with uterine myomas without sterility problems have better reproductive outcome from the laparoscopic approach.

This demonstrates the advantage of minimally invasive surgery(laparoscopy) over minilaparotomyin terms of reproductive outcomes in symptomatic patient with myomas. The explanation of these findings could be due to a lower pelvicadhesion rate with the laparoscopic intervention. That is because, myomectomyhas a higherrate of postoperativepelvic adhesions.[101] Unfortunately, there is no obvious data in the literature demonstrating the association between infertility and adhesions, and the exact efficacyof adhesiolysis intervention in patients with infertility. Moreover, second-look laparoscopy was not done in the currentstudy. Therefore, the de novo adhesion ratefollowingboth laparoscopic and minilaparotomic myomectomy cannot be estimated.

Results

Meta-Analysis

Meta-analysis is the procedure of joiningdifferent individual statistical methods so as to take out the best of the information from the systematic review to be used by exacerbate and enhancing the quality

of the analysis. By statistically joining the different results of studies which are similar it can enhance the preciseness of the judgmentin management ofspecific disease and the effects, and evaluate whether such treatment effects are same in similar situations. The resemblance of individual studies is very fundamental and the decision to select such studies is very applicable and necessary to the validity of the end result. [102]

There are twostudies which have been included in this meta-analysis. They arePalomba S andSeracchioliR whichare randomized control trialThe sample population for both studies posted for laparosopic surgery compared open (laparotomy or mini laparotomy) surgery to enucleated myomas (myomectomy). Dichotomous data for included studies will be used for analysis.

Study ⟶	Palomba S	SeracchioliR
Total patients. Included	136	131

The Palombastudyis amulticentrictrial and as mentionedbeforethe analysis of reproductive outcomes was categorised according to indication for myomectomy into symptomatic fibroids and unexplained infertility. Only the infertility group will include in this study.

Table to summarise the finding of Seracchioli R trial which is done in 2000

Intervention ⟶	laparoscopy	laparotomy
Number of patients	68	68
Number of patients with unexplained infertility (included in current met-analysis)	30	32
Clinical pregnancy rate.	8	8
Live birth	7	6
Miscarriage rate.	1	2
Caeserian section rate	5	4
Preterm delivery rate	1	1

The second trial is Seracchioli R, which was published in 2000. There are 131 patients included in this study with 66 patients underwent laparoscopic myomectomy (group 1) and 65 women did laparotomic myomectomy (group 2). But after follow up for one year to evaluate pregnancy outcome, seven women in group 1 and six in group 2 were lost from study. Moreover three cases from group 1 their laparoscopic operation converted to open one and they did not included in statistical analysis. The final number is 56 women in group 1 and 59 women in group 2 tried to get pregnancy. They did not take the intention to treat(ITT) in their analysis

Table to summarise the finding of Seracchioli R trial which is done in 2000

Intervention ⟶	laparoscopy	laparotomy
Number of patients	56	59
Clinical pregnancy rate.	30	33
Live birth	20	6
Miscarriage rate.	6	4
Caesarean section rate	13	21
Preterm delivery rate	1	2

To understandthe meta-analysisin best way, itcould be symbolisedin graphs, usually the graphsaredepicted as forest plots. The word "forest plot'' created from the concepts that these graphs have forest of lines. It started in the eighties of twentieth centurydespite the term forest plot was usedin1996. The latest design of plots finally produced in 1998. Each study is depicted by a line and a box is exist over each line which stand for the individual study, the mid-point of the box referred to thepoint effect estimate, this is represent

the mean effect appraise for every individual study. The area of the box portrays the weight granted to the study. The large area means more influencing of the study and the opposite is correct. This is formulatedto draw moreattention in the direction of the studies that are given more weight. The diamond shape in the graph represents the overall effect.The width of the line displays the confidence intervals of the effect estimate of individualstudies. The confidence interval for overall effect is revealed by the diamondwidth while the point estimate could be said to be thebest guess of the true effect in the specified population. The 95% confidence intervals indicate that in a given population there is a 95% chance that the true effect in the will fall within the range and it also indicate that there would be a chance of 95% for the point estimate to fall within the 95% confidence interval in case the trail is repeated again. These are found on the sample to be representative and the supposition that there are no systematic errors that could bias the results.

The graphs of the current meta-analysishave basically six columns and the results of individual study are shown in rows. The first column ('study') inscribes the IDs of individual study which are comprised in this meta-analysis whereas the studies are depicted by the first author and the publication year of the study.

The second and third columnsrepresent to the intervention used in the studies that is the laparoscopy, the second one the event or one of outcome wanted after the surgery. While the third column represents the total number of patients underwent the intervention in each of the study. While the fourth and fifth columns represent the comparison group which is abdominal or laparotomic myomectomy. The fourth column is the number of patients develop the wanted event and the fifth column is total number of patients did the compared procedure. The outcomes included are dichotomous type of data. While the horizontal lines symbolised the confidence intervals (CI) for each individual study, the longer the line it means the confidence interval is wider and when the confidence interval is wider that is mean the no effect of intervention. It can be obviously shown in the forest plot that confidence line representing the Seracchioli 2000 and Palomba 2007 studies extend beyond the midline thatis the line of 'no effect'

The diamond shape in the last row of the forest plot graph demonstrates the overall result of the meta-analysis. The middle of the diamond fits the value for the overall effect estimate (eg. OR or RR). In the current review, the RR will be used as an effect estimate.and the width of the diamond portrays the width of the overall CI. In addition, the total number of successful and unsuccessful events is presented in the same row.

When the diamond did not cross the 'line ofno effect', the calculated difference between the intervention and compared procedurescould be regarded asstatistically significant.

Another way to calculate the statistical significance of the overall result is using the probability value (p value) in the 'test for overall effect'. Usually, the result is considered as statistically significant if $p<0.05$. In present study, the p value is more than 0.05 which mean the result is statistically insignificant.

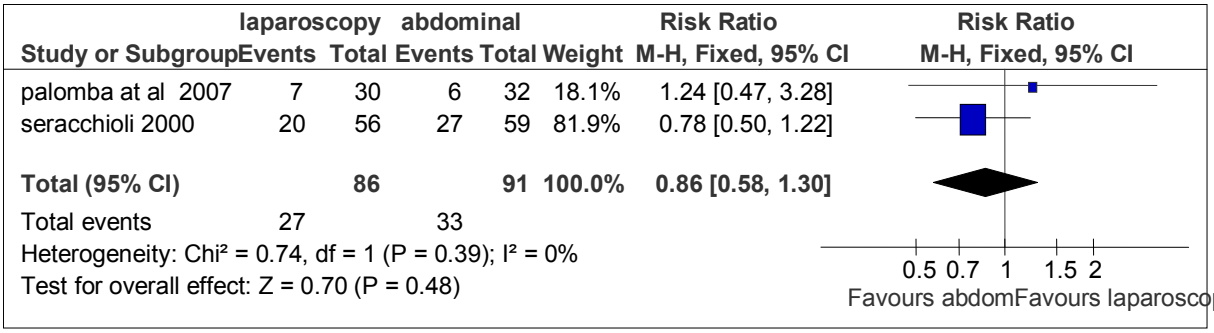
Furthermore, It is essential to check the details on the value axis at the bottom of the graph, because the orientation of the outcome values is not fixed. Some graphs exhibit the intervention to the left side of the 'line of no effect', some put it to the right side. In addition, the reader needs to be attentive if the meta-analysis deals with dichotomous or continuous variables. In case of dichotomous variables, the line of no effect is equal one, and the strength effects of a particular procedure is calculating as the distance more or less than one. In case of continuous variables, values can be negative or positive and the line of effect is zero.

As it mentioned previously there are five outcomes we looked after, all are related to reproductive outcomes. The statistical analysis for each outcome for each study is analysed by RevMan (version2.1) and the finding of comparison between laparoscopic myomectomy and abdominal myomectomy is as following:

Live Birth Rate

Live birthis defined as women with a baby alive over the total number of pregnant women.

Forest plot for comparison between laparoscopic and abdominal myomectomy. The outcomes is live birth

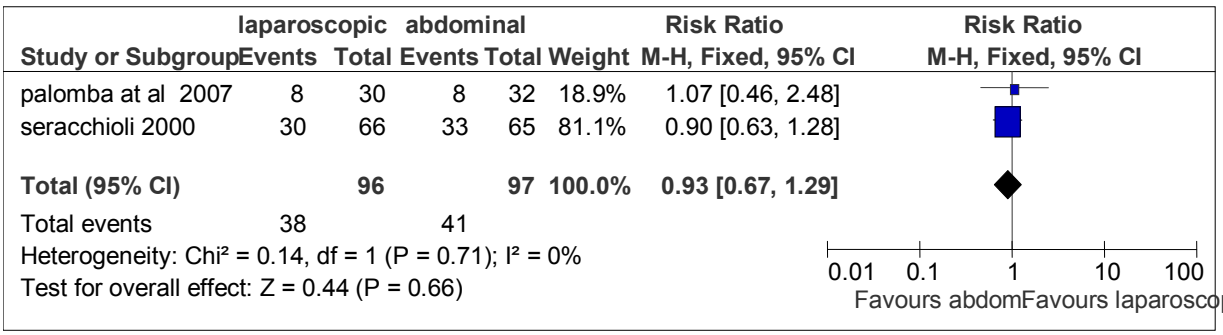


The forest plot is shown that there is no evidence of statistically difference in the effect of each surgical procedure on live birth outcome. As the statistical result (95%CI is 0.58 to 1.30, I^2=0, p=0.48) which means there is no significant different. Also the RR is 0.86 which means that there is decrease 14% of live birth in laparoscopic intervention when compared to abdominal myomectomy. This result means that more studies or more participants are needed to clear the relationship and to clear the effect of laparoscopic intervention.

Clinical Pregnancy Rate

It is calculatedas the ratio between number of pregnant ladies and total number of women studied

Forest plot for comparison between laparoscopic and abdominal myomectomy. The outcomes is pregnanacy rate

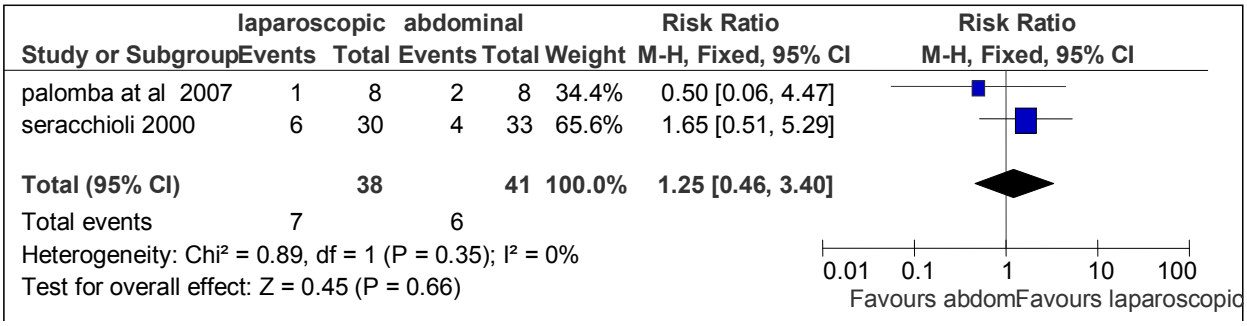


The forest plot is shown that there is no evidence of statisticallydifference in effect of each surgical procedure on pregnancy rate. As the statistical result (95%CI is 0.67 to 1.29, I^2=0, p=0.66) which means there is no significant different. Also the RR is 0.93 which means that there is decrease 7% of pregnancy rate in laparoscopic intervention when compared to abdominal myomectomy. This result means that more studies or more participants are needed to clear the relationship and to clear the effect of laparoscopic intervention

Miscarriage Rate

It is calculated as the ratio between number of abortions through the first 12 weeks of gestation and total pregnancies.

Forest plot for comparison between laparoscopic and abdominal myomectomy. The outcomes is miscarriage rate

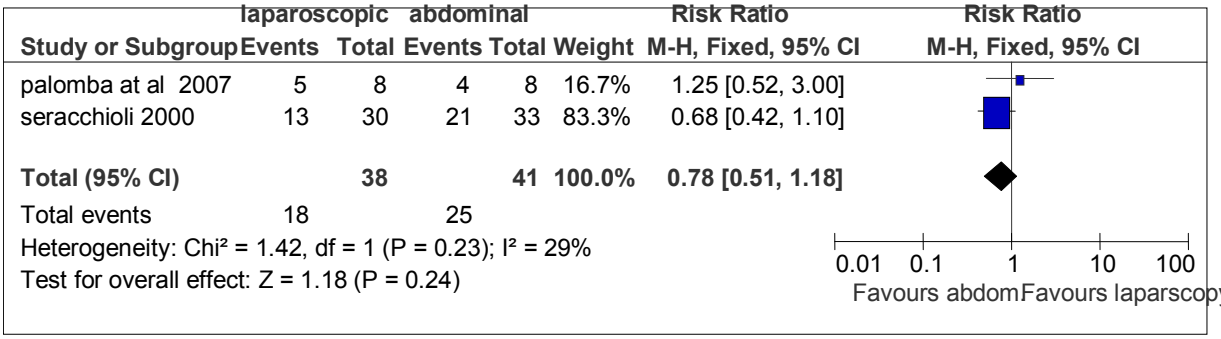


The forest plot is shown that there is no evidence of a difference in effect of each surgical procedure on live birth outcome. As the statistical result (95%CI is 0.46 to 3.40, I^2=0, p=0.66) which means there is no significant different. Also the RR is 1.25 which means that laparoscopic intervention when compared to abdominal myomectomy is increase the abortion rate by 25%. This result is not significant and it means that more studies or more participants are needed to clear the relationship and to clear the effect of laparoscopic intervention.

Caesarean Section Rate

It is calculated as the ratio between number of caesarean deliveries and total pregnancies.

Forest plot for comparison between laparoscopic and abdominal myomectomy. The outcomes is Caesarean section rate



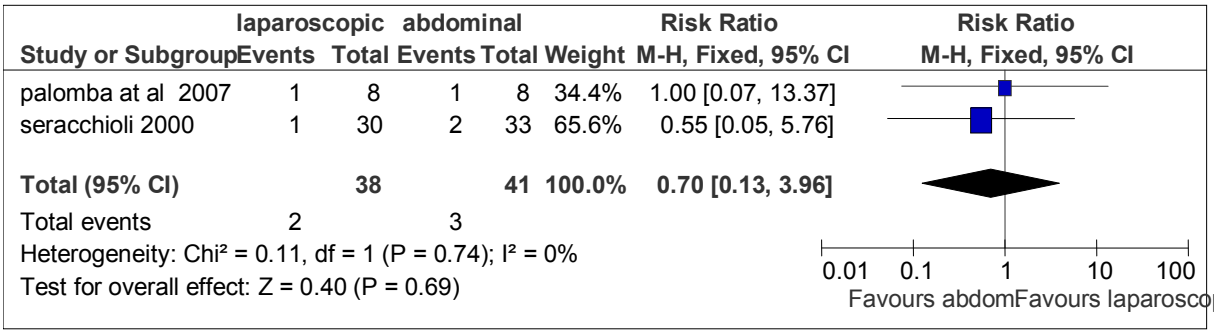
The forest plot is shown that there is no evidence of a statistically difference in effect of each surgical procedure on Caesarean section rate. As the statistical result (95%CI is 0.61 to 1.18, I^2=0, p=0.24) which means there is no significant different. Also the RR is 0.78 which means that there is decrease 22% of caesarean section in laparoscopic intervention when compared to abdominal myomectomy. This result demonstrates that more studies or more participants are needed to clear the relationship and to clear the effect of laparoscopic intervention.

The high rate of caesarean section, after both laparoscopy and abdominal procedures could be due to large uterine scar, the long duration of sterility and the age of the patient may all contribute in taking a decision for caesarean section delivery.

Preterm Delivery Rate

It is calculated as the ratio between number of preterm delivery and total pregnancies.

Forest plot for comparison between laparoscopic and abdominal myomectomy. The outcomes is Preterm delivery rate



The forest plot is shown that there is no evidence of a difference in effect of each surgical procedure on preterm delivery outcome. As the statistical result (95%CI is 0.13 to 3.96, I^2=0, p=0.70) which means there is no significant different. Also the RR is 0.78 which means that there is decrease 30% of preterm delivery in laparoscopic intervention when compared to abdominal myomectomy. This is meant that there is less preterm labour with laparoscopic surgery and more with laparotomy. This result demonstrates that more studies or more participants are needed to clear the relationship and to clear the effect of laparoscopic intervention.

The Heterogeneity Test

At the bottom of the forest plot graph on the left side,

the number concerned is the I^2 value. I^2 was developed recently and itrepresented as favoured and more reliable test for heterogeneity. I^2 ranges from 0 to 100%. Heterogeneity isused to measure the variability between studies, that's to say,it demonstratessome clarity as if the studies could be regarded as measuring the same phenomenon under investigation. If heterogeneity is present, this cannot be supposed and calls into question the validity of the review findings. There is other test in addition toI^2score; it is the chi-squared test also there is another test to examine the heterogeneity in RevManwhichis p value. When p value less than 0.05,it indicates that heterogeneity is presentand howcomparable studies in the meta-analysis are. Another practical visual guide to estimate heterogeneityis to eamin the overlap of the CIs, that's to say,the horizontal lines in the meta-analysis forest plot graph. Studies are considered homogeneous if CIs of all studies are overlapped.Evaluation of inter- and intra-study variationor comparability of studies is essential for the best choice of meta-analysis technique or model. If I^2 less or equal 25%, studies are considered homogeneous and If I^2 more or equal 75% then heterogeneity is regarded as very high.In the current analysis, all outcomes are associated with no heterogeneity, except the outcome of caesarean section rate were I^2 is 50% which mean there is heterogeneity.

Inference from the Meta-Analysis

From the above meta-analysis of the two studies it can be derived that there is no significant difference between laparoscopic myomectomy and abdominal myomectomy in terms of future effect on reported fertility outcome (live birth rate, clinical pregnancy rate, miscarriage rate, ongoing pregnancy rate, preterm labour rate and caesarean section rate).. In Palomba studygave a more favourable outcome to the laparoscopic group. This may be due to it is more recent trial and it conducted in more specialist laparoscopic centre with more skilled surgeon. This may lead to less post operative adhesions and the result better outcome. While Serracchioli study is older than Palomba study and it included patients underwent laparoscopic myomectomies in nineties. Which could be considered s the period ofthe beginning use of laparoscopy? For this inSerracchioli study found consistent favourable outcomes for the traditional abdominal myomectomy group.

All extracted data from the included studies has been uploaded meta-analysis. The study weight in the forest plot shows that the study of Seracchiolihas the higher weight thanPalomba study. That is because there were more participant in Seracchioli. It is clear that we still need more extensive trials before any conclusion.

Conclusion

There are some hypotheses which suggest a relationship between uterine fibroids and women infertility. They propose that leiomyomata may interfere with the movement of the sperm and transportation of the embryo as a result ofa modificationof the normal contractility movement of the uterus. Furthermore, when fibroids are present inthe locality of the uterine endometrium and cavity, they may cause vascular changes which affect endometrial trophism and subsequently the implantation of the embryo. Moreover,leiomyomata hasalso been associated with an increased rate of miscarriage and preterm labour and with an effect on the possibility of pregnancy within several IVF cycles.

Presently, surgical intervention to enucleatethe myomas is generally advised in women with unexplained sterility. The myomectomy procedure, regardless of the technique of surgery, is considered as the gold standard in patients wanting to conserve their uterus for conception.

In studies undertaken for IVF purposes, it was found that for patients who had previous had myomectomies the implantation and pregnancy ratewere slightly,but not significantly,higher than patients who still hadmyoma. Statistical significant was achievedin cases with large sized myomas or when the fibroid deformed the cavity of uterus. Thus, the size and location of fibroids are considered an important prognostic factor regarding their effect on fecundity.

Therefore, when surgical intervention is required, the question is which technique is best on to be implied:the laparotomy or laparoscopic approach.

Many clinicians agreed that the laparoscopic approach is preferable taking into account the many advantages of minimal invasive surgery over traditional laparotomy such as less blood loss, enhanced recovery and short hospital stays. However, regarding fertility outcomes, there is still some debateaboutwhether laparoscopic myomectomy produces better results.

According to the current meta-analysis of the two RCTPalomba and Seracchioli whichboth compared the two surgical approaches, there was no evidence to suggest a significant difference between laparoscopic and open myomectomy with regard to fecundity outcomes.

With regard to the quality of the evidence, despite the small number of studies, both of them supplied good evidence in relation to fertility outcomes e.g. live birth rate, pregnancy rate, miscarriage rate and late pregnancy follow up, preterm labour and caesarean section rates.

However, since there are currently only two studies available regarding this question, the evidence should be viewed with caution. Moreover, since neither study had a sample size calculation, they may have been underpowered.

Additionally, the comparison between laparoscopic and open approaches is difficult due to the significant variations in the practice of the surgery such as skill level, technique of the surgery and the intra-operativeuse of anti adhesion agents; all of these factors may affect fecundity outcomes. Therefore, a larger number of RCT studies are recommended.

In summary, untilmore studies are available, there is currently inadequate evidence to make anyfirm conclusions regarding the effects of myomectomy on fertility. Furthermore, with regard to the type of surgicalintervention, the current evidence, restrictedas it is by the small number of studies,proposes that there is no significant difference of fecundity outcomes betweenlaparotomicmyomectomy and laparoscopy.

Afinal search for new studies was done prior to submission whichensured that no new ones had been published duringthe preparation of thisanalysis.

Suggestions for further research: There is theneed for good quality randomised controlled studies to decide the role of enucleated myomasfor fertility treatment. Since fibroids are not a single entity but a wide spectrumof tumours, studies should includethe following points:

1. The initial preference would be for studies comparing surgical intervention with nointervention, following this for studiescomparing various types of surgicalprocedures. If adesirable effect of surgery isconcluded then the next step would be to focus on the types of surgicalintervention.

2. Studies should categorise outcomesaccording to the size and type ofmyomas (intramural, subserous and submucous) with cleardefinitions in the inclusion and exclusion criteria.

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