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PII: S1553-4650(17)31361-4
DOI: https://doi.org/10.1016/j.jmig.2017.12.020
Reference: JMIG 3380

To appear in: *The Journal of Minimally Invasive Gynecology*

Received date: 19-10-2017
Revised date: 2-12-2017
Accepted date: 23-12-2017

Please cite this article as: Justin Tan, Sophie Moriarty, Omur Taskin, Catherine Allaire, Christina Williams, Paul Yong, Mohamed A. Bedaiwy, Reproductive Outcomes after Fertility-Sparing Surgery for Focal and Diffuse Adenomyosis: a Systematic Review, *The Journal of Minimally Invasive Gynecology* (2018), https://doi.org/10.1016/j.jmig.2017.12.020.

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Reproductive Outcomes after Fertility-Sparing Surgery for Focal and Diffuse Adenomyosis: A Systematic Review

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Conflict of Interests: None declared.

Funding sources: None.

Prior publications: None.

Clinical trial registry number: N/A.

IRB: N/A

Word count: 3961 words

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ABSTRACT

Among the variety of treatment options to improve reproductive outcomes for infertile women with adenomyosis (AD), uterine conserving surgery has demonstrated varying success. Hence, we conducted a systematic review around the topic of fertility-sparing surgery across 18 studies and 1396 infertile women with focal and diffuse AD. Patients with focal AD demonstrated mean pregnancy and miscarriage rates of 52.7% (range:14.3-77.5%) and 21.1% (range:0-44.4%), respectively, while patients with diffuse AD had a mean pregnancy and miscarriage rate of 34.1% (range:9.4-100%) and 21.7% (range:12.5-33.3%), respectively. Uterine rupture and preterm birth was observed in 6.8% (3/44) and 4.5% (2/44) of pregnant patients with diffuse AD vs. 0% (0/35) and 10.9% (12/110) of patients with focal AD, respectively. No significant differences were observed between natural conception vs. ART with or without GnRHa pre-treatment. Overall, patients with focal AD appeared to have higher pregnancy rates after conservative surgery compared to diffuse AD, while a higher incidence of uterine rupture was reported after surgery for diffuse AD. However, significant heterogeneity precludes any direct comparison and prospective controlled trials are required to further elucidate the benefits of fertility preserving surgery over medical or expectant management for AD-related infertility. In view of the debatable benefits of conservative surgery and the possible increase in adverse pregnancy outcomes particularly in cases of diffuse adenomyosis, clinicians should consider surgery on a case-by-case basis as it may be appropriate for women with concurrent AD-associated pelvic pain or menorrhagia, younger infertile women who have failed medical management or older women with infertility despite ART, and those with a history of recurrent pregnancy loss or implantation failure.

Keywords: Adenomyosis; fertility-sparing surgery; systematic review

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INTRODUCTION

Adenomyosis is a complex disease process that manifests in a multitude of ways. Among reproductive age women, numerous theories have discussed the possible causes of infertility including an impaired uterine system of sperm transport, uterine dysperistalsis (resulting in reduced embryo implantation), abnormal concentrations of free radicals in the uterine environment, and altered endometrial vascularization and decidualization [1-3]. Anatomically, the disease process occurs due to the presence of heterotopic endometrial stroma and glands within the myometrium that leads to junctional zone dysfunction (JZ) and subsequent smooth muscle hyperplasia and hypertrophy [4]. AD often presents concurrently with endometriosis and leiomyomas, with a co-prevalence rate of 6-22% and 35-55%, respectively. Similarly, AD has been found on MRI in 77% of infertile women with endometriosis compared to 22% of those without endometriosis [5]. Unlike endometriosis and uterine fibroids, however, AD exhibits a unique quality in the varying extent of disease, ranging from diffuse myometrial hypertrophy encasing the uterus to more discrete focal lesions known as adenomyomas. Given the myriad of possible presentations and concurrence with other gynecologic treatments, diagnosis and treatment of AD has proven exceptionally difficult.

Population estimates suggest that approximately 20% of cases of AD involve women under 40 years old, while 80% of cases are diagnosed among women in the fourth or fifth decades of life [6]. Depending on individual patient goals for symptom-relief or improved fertility, the range of available treatments range from conservative medical management, fertility-sparing surgery, or definitive hysterectomy [7,8]. Although definitive hysterectomy offers curative results among women with AUB and pelvic pain who have completed childbearing, fertility-sparing options such as hormonal therapy with gonadotropin-releasing hormone agonists (GnRH-a) and conservative surgical procedures have variable rates of success [9-13]. Specifically in regards to uterine-conserving surgical options to improve fertility outcomes, a recent review of available options emphasized the paucity of good quality evidence and importance of further research to optimize treatment options and improve reproductive outcomes among women with AD who wish to preserve their fertility [14].

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Several recent systematic reviews and meta-analyses have investigated the relationship between adenomyosis, surgery, pelvic pain, and infertility. Vercellini et al [15] examined the effect of adenomyosis on IVF/ICSI outcomes with and without GnRHa pre-treatment and demonstrated that women with AD had a significantly lower clinical pregnancy rate (relative risk [RR]: 0.72; 95% confidence interval [CI]: 0.55-0.95) and twofold increased risk of miscarriage (RR: 2.12; 95% CI: 1.20-3.75) after IVF compared to those without AD. However, no assessment of pregnancy outcomes after surgery or through natural conception are discussed. Conversely, Younes et al [16] conducted a systematic review of post-surgical outcomes for adenomyosis that were mainly indicated for treatment of menorrhagia and dysmenorrhea, although in a subgroup analysis of fertility outcomes after surgery, they noted significant heterogeneity between studies and concluded that surgery is effective for symptom relief in 75% of cases and may also improve fertility outcomes. Similarly, Dueholm et al [17] included a sub-analysis of reproductive outcomes after cyto-reductive surgery among 338 women with AD and noted a slightly higher pregnancy rate (PR) and live birth rate (LBR) after IVF/ICSI in patients who underwent surgery. However, once again, the authors noted significant heterogeneity between included studies, adverse pregnancy outcomes were not discussed, and no comparison was made between focal and diffuse adenomyosis.

The primary purpose of this systematic review was to evaluate reproductive outcomes after conservative surgery for both focal and diffuse adenomyosis specifically in patients desiring fertility. In doing so, we have taken a different approach to previous reviews which primarily investigated the role of conservative surgery for relieving symptoms (pain, dysmenorrhea) associated with adenomyosis [16] or the effect of adenomyosis on reproductive outcomes after ART [15,17,18]. Ultimately, we hypothesize that good reproductive outcomes may be achieved through both natural conception and IVF after fertility-sparing surgery for adenomyosis. Since focal AD is well circumscribed and more amenable to complete excision, pregnancy outcomes may be improved after surgical cytoreduction compared to patients with diffuse AD. Furthermore, adverse pregnancy events are likely to be higher among patients with diffuse AD due to the presence of more extensive disease that may compromise uterine function and integrity during pregnancy.

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METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines 6 [19].

Three databases were reviewed: Ovid MEDLINE 1946 to present, EMBASE 1947 to July 25th 2017 and Evidence-Based Medicine Reviews (EMBR). The following subject headings and key words were searched: AD OR adenomyos* OR adenomyom* OR junctional zone AND fertility OR infertility OR pregnan* OR concepti* OR IVF OR assisted reproduct* OR obstetric outcome OR reproductive outcome AND surger* OR operati* OR adenomyomectom* OR cytoreductive.

All original research articles including randomized and non-randomized controlled trials, cohort studies, patient series and case reports were included. All included studies reported reproductive outcomes after NC or ART in infertile couples with focal or diffuse AD. Additional studies were extracted from the references in the full text articles. Articles were restricted to English only and we also considered published abstracts from conferences.

The search produced a total of 875 results: 248 from MEDLINE, 592 from EMBASE and 35 from EMBR. An additional study was included from the reference list of a previous review [20]. Following duplicate removal, 723 remained and each title and abstract was reviewed by two reviewers. Subsequently, 124 full texts were selected for full review and an additional 106 excluded, leaving 16 studies that were included for quantitative analysis and an additional two studies included for qualitative analysis. Reasons for exclusion included: case reports, non-English articles, systematic reviews, and studies that failed to report fertility outcomes, those pertaining to endometriosis instead of AD, and also studies that did not include uterine-conserving surgery as an intervention. Two reviewers (SM and OT) independently searched and reviewed the retrieved articles and results were compared. Any disagreement was resolved by discussion. Two specific studies excluded were Nishida et al [21] due to a short 3-month follow-up which precluded their ability to report fertility outcomes, and Dai et al [22] which did not exclusively enroll patients desiring fertility-conserving surgery. In addition, two studies were excluded from quantitative

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comparison, Tamura et al [23] and Chang et al [24], because they included duplicate patients from other studies that were already included in this review.

The following data was retrieved from all articles: study design, year of publication, diagnostic method, surgical technique, pregnancy rate and miscarriage rate after surgical treatment, and complications if applicable. As outlined in Supplemental Table 1, the Cochrane Collaboration's Risk of Bias Tools for Non-Randomized Studies was used to evaluate the methodologic quality and potential risk of bias of included studies.

In agreement with previous reviews, statistical analysis was deemed unsuitable for quantitative interpretation of this data due to the heterogeneity of the studies involved. With respect to quantitative comparisons, pregnancy rate was calculated according to the number of unique women who became pregnant, thereby excluding cases where a woman achieved more than one pregnancy. Conversely, live birth and miscarriage rates were calculated according to the total number of pregnancies rather than the number of unique pregnant women.

RESULTS

This review included 18 studies for qualitative analysis: 10 retrospective [9,11,20-23,25-29] and 8 prospective studies [12,13,22,24,30-33] with a combined cohort of 1396 women with AD who underwent uterine preserving surgery (Figure 1). As was previously explained, two studies were treated separately given the overlap in study groups; among the 16 remaining studies (Table 1), mean age of the study population was 34.1-years-old (range 20-51), and mean follow-up post-surgery was 44 months (range 3-120). Eight studies included patients with focal AD, seven studies among women with diffuse AD, and one study included patients with both types of AD. Most of the studies diagnosed AD by TVUS or MRI and in the majority of cases, observed adenomyotic lesions were located in the posterior wall of uterus. 5 studies involved laparoscopic approaches to surgery, while 12 others reported surgical intervention by laparotomy (Table 2).

Reproductive outcomes following conservative surgery alone for focal and diffuse AD are summarized in Figure 2. Overall, PR appeared to be better in the focal AD group following surgery

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compared to the diffuse AD group (52.7% vs 34.1%) and miscarriage rates were comparable (21.1% vs 21.7%). However, due to the significant heterogeneity between studies and lack of appropriate control groups, any direct comparison would be unreliable. Among studies that assessed surgical intervention alone, similar outcomes were observed between the focal and diffuse AD groups (PR: 49.1% vs. 38.5%, MR 27.6% vs. 16.2%, respectively) as shown in Figure 2. However, among studies that evaluated the effects of combined surgery and medical treatment, focal AD yielded improved PR, LBR, and MR compared to diffuse AD (67.1%, 61.3%, 11.6% vs. 17.6%, 9.8%., 33.3%, respectively). Interestingly, among studies that reported reproductive outcomes after medical treatment alone [9,23,28,29,32], reproductive outcomes appeared to be worse compared to women who underwent surgery. More specifically, women with focal AD demonstrated a PR of 14.3% (5/35) and MR of 40% (2/5) compared to 10% (6/60) and 33.3% (2/6) in the diffuse AD group.

As shown in Figure 3, similar PR were observed after NC (range: 9.4% to 46.4%) and ART (range: 28.6% to 33.3%) for diffuse AD. Similarly, PR in cases of focal AD ranged from 14.3% to 77.5% after natural conception, while only one study reported focal AD pregnancy outcomes after ART [27]. None of the studies reported information regarding the number of cycles required to achieve pregnancy among patients undergoing ART.

Although case reports that discussed adverse obstetrical outcomes after surgery for AD were excluded, 8 studies that met eligibility criteria also reported various perinatal outcomes among patients with focal and diffuse AD. Based on the limited number of patients, uterine rupture was observed in 3/44 (6.8%) of pregnant patients after conservative surgery for diffuse AD while no reported cases of uterine rupture were observed in the focal AD group. Similar rates of ectopic pregnancy, placenta accreta, preterm birth, and retained placenta were observed between groups (Table 3).

DISCUSSION

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Management of women with adenomyosis-associated subfertility is highly controversial and there remains an overall lack of consensus regarding the value of conservative surgery with or without medical management to improve reproductive outcomes [6]. Previous systematic reviews and meta-analyses have demonstrated an increased miscarriage rate and poor pregnancy outcomes with AD [15-17]. Oftentimes, these findings have been correlated to the extent and degree of abnormal uterine myometrium in AD that is functionally distinct both in terms of cell density and immunohistochemistry from that of normal uteri [34]; for instance, adverse IVF/ICSI outcomes and increased miscarriage rates in AD have been observed with a myometrial thickness of more than 2.5 cm on TVUS [35]. Hence, it would appear plausible that surgical removal of adenomyosis would reduce the deleterious effects of the disease [36]. Indeed, surgery has proven effective for control of symptoms related to adenomyosis and probable AD-related infertility [16,17,37]. Since focal adenomyosis is often well circumscribed and confined to a limited portion of the uterus, complete excision and maximal cytoreduction is typically easier; hence, the beneficial effect of fertility-sparing surgery should be more pronounced than for diffuse AD.

Our review of the currently available evidence identifies many areas of heterogeneity between studies that report reproductive outcomes after surgery for AD-related infertility. Beyond the intrinsic variability among patients with AD, the absence of standardized surgical techniques and differences in surgeon skill and experience further contribute to this heterogeneity. Nevertheless, this review highlights several important takeaways (Table 4) regarding the reproductive outcomes after fertility-sparing surgery for focal and diffuse AD.

Focal vs. Diffuse Adenomyosis

To the best of our knowledge, this is the first systematic review that evaluates differences in reproductive between focal and diffuse adenomyosis after fertility-sparing surgery. Overall, our results demonstrated higher mean pregnancy and live birth rates, yet similar miscarriage rates in cases of focal vs. diffuse AD after conservative surgery. Although significant heterogeneity between studies limits the overall validity of such a comparison (Supplemental Figure 1), these results offer avenues for further study as it is possible that the type and extent of disease (focal vs.

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diffuse) would influence treatment outcomes. Furthermore, there is preliminary evidence that improved pregnancy outcomes after fertility-conserving surgery may depend on the size of adenomyotic lesions being resected, particularly those causing intrauterine cavity distortion among patients with a concurrent history recurrent implantation failure [11,37,38]. Other specific criteria that may influence the benefits of surgery include patient age, as Kishi et al [11] found a significant difference in fertility outcomes after surgical intervention among women <39 years old compared to >40, with pregnancy rates of 48% and 22.2% and miscarriage rates of 13.9% and 83.3% respectively. Finally, among patients with concurrent dysmenorrhea or menorrhagia along with infertility, conservative surgery may be a cost-effective treatment option for patients since surgery has been shown to aid in symptom reduction [37]. In this way, surgery could be individualized and considered for specific patients where it has the potential to be beneficial.

ART, NC, & Pre-treatment with GnRHa

Although not addressed in prior systematic reviews, our study also demonstrates that acceptable and comparable pregnancy rates can be achieved through both NC and ART after fertility-conserving surgery for focal and diffuse AD. In a recent meta-analysis, Younes et al [18] demonstrated that focal AD was associated with improved IVF outcomes compared to diffuse AD (OR 1.36), although the results were not statistically significant. Park et al [39] also reported higher clinical pregnancy rates in focal AD compared to diffuse type after surgery in infertile women undergoing ART. However, these prior studies did not assess whether pregnancy outcomes after ART were improved over conservative expectant management. Conversely, the results of our review are consistent with a recent retrospective survey by Tamura et al [23], which showed no statistical difference in post-operative pregnancy rates after ART compared with infertility treatments other than ART in cases of both focal and diffuse AD; interestingly, however, they also demonstrated significantly lower miscarriage rates in the focal adenomyosis group.

Overall, significant variability in reproductive outcomes have been reported after ART among patients with adenomyosis [15,17,18]. Based on the included studies in this review (Supplemental Figure 2), this variability in outcomes observed can likely be attributed to significant heterogeneity

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in patient age, duration/type of infertility, and coexistence of other disorders such as endometriosis and leiomyoma. Nevertheless, most included studies reported a high miscarriage rate after surgery in women with both focal and diffuse AD. Ultimately, any operative intervention that compromises the integrity uterine cavity may contribute to adverse pregnancy outcomes; hence, this is a topic that warrants further research in prospective studies.

As shown in Figure 2, a combination of surgery and GnRHa pre-treatment appeared to improve pregnancy and live birth rates compared to surgery alone in cases of focal adenomyosis; conversely, surgery alone yielded the highest pregnancy rates among cases of diffuse adenomyosis. Since the GnRH receptor is found in adenomyotic lesions [40], it is plausible that the anti-proliferative and anti-inflammatory effects of GnRH on the myometrium and apoptosis induction would be more beneficial in cases of extensive diffuse disease compared to focal AD, although the heterogeneity between studies precludes any definitive conclusion. Younes and Tulandi [18] found that GnRHa prior to IVF yielded improved pregnancy outcomes, yet Tamura et al [23] found similar pregnancy and miscarriage rates among infertile women who were pre-treated with GnRHa prior to ART compared to women without any treatment (52.6% and 52.2% vs 41.4% and 34.0%, respectively) [23]. Interestingly, Tamura et al [23] also noted a slightly improved pregnancy and miscarriage rate after medical pre-treatment in cases of focal compared to diffuse AD.

Obstetrical Complications & Timing after Surgery

Pregnancy-related uterine rupture rates after conservative surgery for AD are sparsely reported in the literature, yet most likely depend on a variety of factors including the extent of disease, amount of AD that is surgically resected, and specific surgical technique [16]. In general, diffuse AD involves a greater proportion of the myometrium and is less well circumscribed than focal AD, hence it is less amenable to maximal cytoreduction and surgical excision may confer an increased risk of compromised uterine integrity. Indeed, uterine rupture was reported in 3 of 44 pregnant cases (6.8%) reported after conservative surgery for diffuse AD, while no cases were reported among cases of focal AD (Table 3). However, varying surgical techniques and extent of disease

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limit the comparability of adverse outcomes among included studies and further prospective studies are required to more accurately assess the incidence of uterine rupture after surgical removal of AD. Until more reliable evidence is available, surgeons should generally adopt a more conservative approach for women who wish to preserve their fertility since diligent reconstruction and careful avoidance of removing normal myometrial tissue are essential to ensure sufficient wall integrity that can sustain future pregnancy [46]. Although successful pregnancies have been reported as early as 3 months after surgery for AD [20,47], further research is also necessary to determine the optimal waiting time based on individual patient characteristics to ensure adequate healing before attempting to conceive.

It is also important to recognize a possible association between adenomyosis and various perinatal complications including miscarriage, preterm delivery, preterm premature rupture of membranes, small-for-gestational age, and fetal malpresentation [41-44]. Indeed, Tamura et al [43] conducted a multicenter retrospective survey and concluded that pregnancy complications were related to the size of adenomyotic lesion and more diffuse AD was associated with higher rates of pregnancy-induced hypertension and uterine infection compared to women with focal AD. However, they found no overall difference in pregnancy complications among women with AD who received no pre-treatment compared to those who were treated medically or surgically. Notwithstanding, it is possible that the mere presence of adenomyosis may impair uterine function and lead to a pro-inflammatory state that adversely affects pregnancy outcomes [43,45]. In this way, surgical removal of adenomyotic tissue may alleviate certain complications, but this must be counterbalanced by the inherent disadvantages of creating a possibly defective uterine wall.

Limitations & Future Considerations

While many previous studies address the benefits of surgery for treatment of adenomyosis, this systematic review specifically compared the effect of surgery on reproductive outcomes among patients desiring fertility with focal and diffuse AD. Overall, we included a large cohort of studies including 258 women with focal AD and 176 women with diffuse AD. However, over half of the included studies (56.3%) were retrospective and observational case series, each with small

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sample sizes and lacking matched controls. Significant variations in surgical techniques (Table 2) and surgeon ability to preserve healthy myometrium in cases of conservative fertility-preserving surgery further limited comparability between studies. Unfortunately, no randomized controlled trials exist on the topic of reproductive outcomes after both medical and surgical treatment for patients with focal and diffuse AD.

All studies were limited by heterogeneity in patient selection, imaging criteria used to diagnose AD, and lack of reporting of important clinical variables. For instance, the gold standard non-invasive technique for diagnosing adenomyosis and ruling out other pathology is magnetic resonance imaging (MRI) [48,49], yet over 40% of included studies used TVUS alone for diagnosis which may not have the resolution of identifying mild AD or co-occurring factors such as endometriosis, thereby potentially misclassifying many patients as normal. Furthermore, maternal age, ovarian response to medication, and embryo quality were also not adjusted for and may explain discrepancies in the reported results among studies reporting ART outcomes. Finally, significant clinical variables such as average time from surgical intervention to conception and number of ART cycles required for successful pregnancy were rarely reported. Among the 3 studies that evaluated reproductive outcomes after surgery, the average time-to-conception was 44.4 months, with the observation that fertility rates decrease substantially within the first 12 months after surgery. Nevertheless, the follow-up period among most studies was inadequate and the availability of this data would greatly influence whether NC or ART should be recommended following surgery for AD.

CONCLUSION

Based on a review of the currently available evidence, the benefits of conservative surgical management for improving fertility outcomes in patients with focal and diffuse AD appear to vary greatly based on individual patient and provider characteristics. Patients with focal AD may experience improved pregnancy rates and fewer adverse pregnancy outcomes after conservative surgery compared to those with diffuse AD, although further research is required to support this finding and there remains insufficient evidence to support the routine use of conservative surgery

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in either group to improve reproductive outcomes over expectant or medical management. Our results also demonstrate that there is insufficient evidence to support the use of ART over expectant management after fertility-sparing surgery. Nonetheless, clinicians may benefit from differentiating cases of focal and diffuse adenomyosis to better counsel patients about the risks and benefits of specific treatment strategies.

Until well-controlled large-scale studies are available on AD-associated infertility, surgical management should be tailored on a case-by-case basis for each patient's presentation and goals of treatment. In view of the debatable benefits of conservative surgery if fertility is desired and the risk of adverse pregnancy outcomes, medical treatment should remain the first-line option for patients to preserve fertility and relieve symptoms. Conservative surgery may be a reasonable option both for younger patients with concurrent dysmenorrhea or menorrhagia, or in cases of repeated implantation failure, repeated pregnancy loss, and refractory infertility or adenomyosis despite previous treatments; however, further research is required to definitively evaluate the benefits of conservative surgery in each of these populations. Finally, surgeons should be cautious to balance maximum cytoreduction while also conserving adequate tissue to maintain uterine integrity and patients should be appropriately counseled about the potential increased risk of adverse pregnancy events such as uterine rupture, particularly in cases of significant resection for diffuse adenomyosis. Given the complexity of the disease process and the co-occurrence of many confounding conditions such as endometriosis, adenomyosis is a uniquely challenging condition to study and future research should seek to focus on whether specific patient characteristics can be identified to better inform clinical decision making and maximize treatment benefit.

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Figure 1. PRISMA flow diagram showing the search for studies.

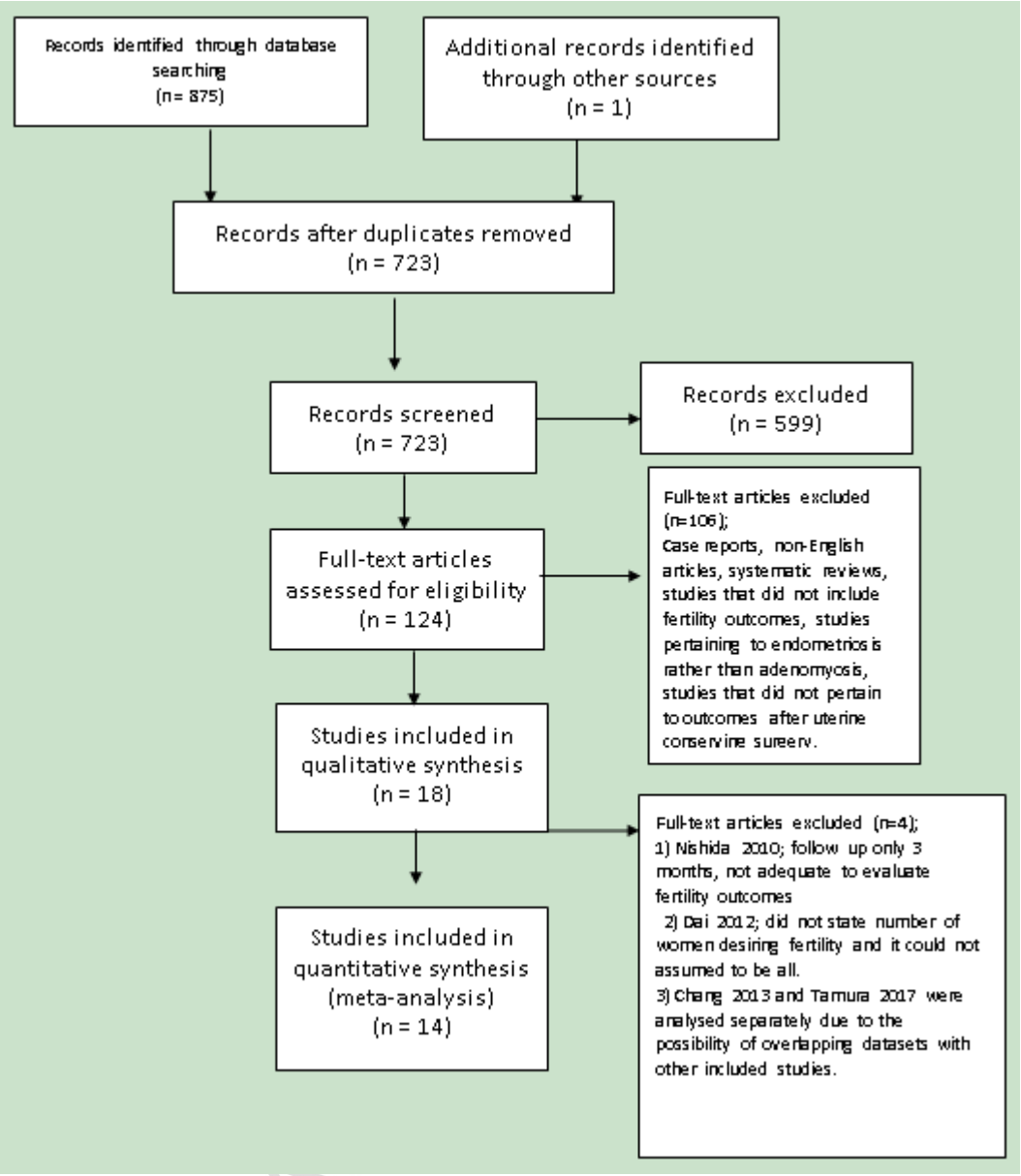

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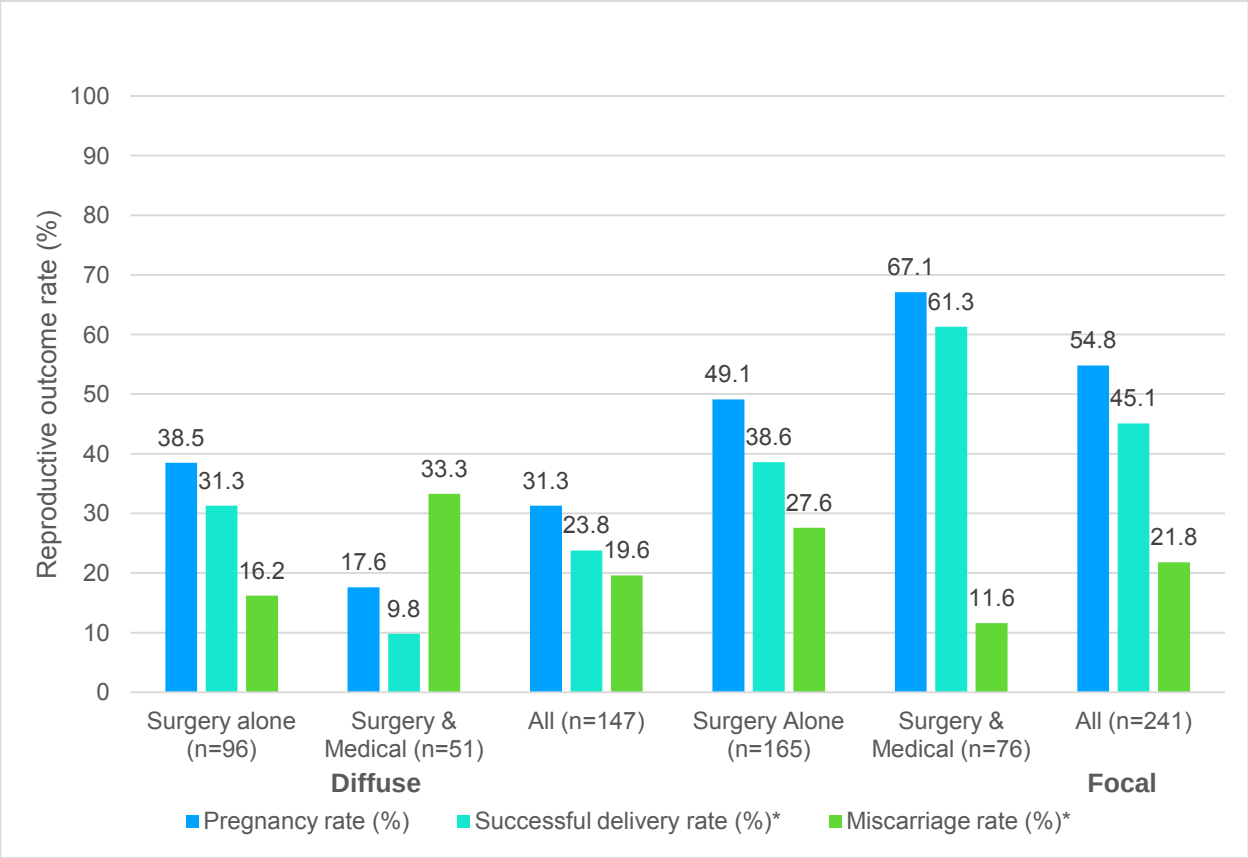
Figure 2. Mean fertility outcomes following surgery alone vs combined surgery & medical treatment for women diffuse and focal adenomyosis.



*Excludes Guy 2016 as that study does not give successful delivery and miscarriage numbers.

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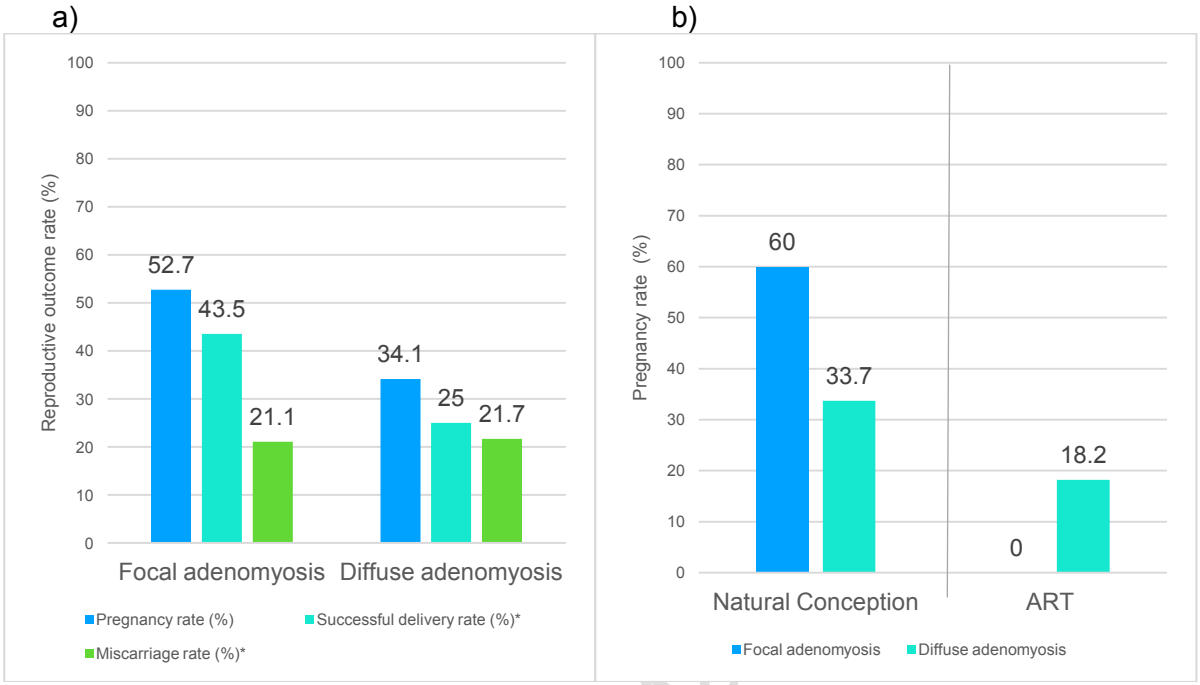
Figure 3: Mean reproductive outcomes for focal vs diffuse adenomyosis. (a) Total (b) Natural conception vs ART.



*Excludes Guy 2016 which did not provide successful delivery and miscarriage outcomes.

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512 **Table 1:** Overview of studies reporting pregnancy outcomes for focal and diffuse adenomyosis after fertility preserving surgery.

Author	Study design	No. of patients (n)	Mean age +- SD (years) (range)	Mean Follow up (months) (range)	Method of diagnosis	Any other pathology
Focal AD						
Fedele et al. 1993	Retrospective	28	35.1	53.2 +- 23.5	N/A	Endometriosis 6 (21.4%) Mullerin anomalies 5 (17.8%) Myomas 7 (25.0%)
Takeuchi et al. 2006	Prospective	14	36 (28-39)	-	TVUS & MRI.	Endometriosis n=9 (64.3%)
Wang et al. 2009 'comparison'	Prospective nonrandomized study.	165	38.3	24	TVUS & AbdUS/AbdUS only	No.
Takeuchi et al. 2010	Prospective long-term follow up	9	25.2 (20-30)	35.9	TVUS & MRI	Endometriosis n=5. Endometrioma n=1.
Al Jama et al. 2011	Non-randomized retrospective	18	38.1 +- 0.9	36	MRI + TVUS	N/A
Dai et al. 2012	Prospective	86	38 (27-48)	24.77 (6-60)	TVUS	N/A
Kishi et al. 2014	Retrospective cohort study	102	37.6	24 (9-60)	MRI	Endometriosis 66 (64.7%)
Guy et al 2016 Surgery + medical Surgery only	Retrospective	 27 25	 35.9 +-7.4 36.5 +-7.93	24	US not specified	No, those with other diseases excluded.
Chang et al. 2013 *	Prospective	56	38.3 +- 4.6	36	TVUS & AbdUS/AbdUS only	No. Those with other diseases were excluded.
Diffuse AD						
Hadisaputra et al 2006	Prospective	10	37.7 +-7.7 (range 32-48)	N/A	TVUS	N/A
Rajuddin et al 2006 Surgery	Retrospective	32	35.3+-0.7 (28-50)	N/A	TVUS	N/A
Wang et al. 2009 'is the'	Retrospective non-randomized	28	34.3 +- 2.1	36	TVUS	N/A
Nishida et al. 2010	Retrospective clinical study	44	37.1 (range 29-45)	3	MRI	Yes, but unknown what and prevalence.
Osada et al. 2011	Prospective case control	104	37.6	>120	MRI & TVUS	-

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Huang et al. 2012	Retrospective	9	34.2 (range 31-37)	62-83	TVUS	-
Saremi et al. 2014	Prospective	103	37.46	24 (20-50)	TVUS & AbdUS & HSP	Leiomyoma n=N/A
Both focal and diffuse AD						
Fujishita et al 2004 Classic method 'H' method	Retrospective	11 T 5 6	32.3 30.4 33.8	45.6 (range 23-69)	TVUS and/or MRI	-
Total (n) ** **Mean **** **Range ****	Restrosepctive 9 (56.3%) Prospective 7 (43.8%)	815 n/a 9-165	647.0 34.1 20-51	571.5 44.0 3->120	TVUS 7 (43.8%) MRI 2 (12.5%) TVU and/or MRI 1 (12.5%) TVUS & MRI 5 (31.3%) US not specified 1 (12.5%) N/A 1 (12.5%)	
Tamura et al. 2017* **Focal and Diffuse AD**	Retrospective multicenter study (response rate 16.5%)	84	34.8 +-4.2	N/A	TVUS only or TVUS & MRI.	No, other those with endometriosis and leiomyoma were excluded.

CS; caesarean section. NVD; normal vaginal delivery. TVUS; transvaginal ultrasound scan. AbdUS; abdominal ultrasound scan. MRI; magnetic resonance imaging. NC; natural conception. ART; assisted reproductive techniques. U; unknown whether ART or natural conception. T; total.
*Contains patients from previously published studies.
** Where applicable, only for women undergoing surgery, not medical only.

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519 **Table 2.** Further details of included studies.

Author	Surgical technique used	Pathologic confirmation	Lesion size	Lesion location	Other treatments	Operative complication	Symptoms pre-surgery
Focal AD							
Fedele et al. 1993	Adenomyomectomy according to microsurgical principles. All other coexisting pathologies (eg. endometriosis) were treated at time of surgery.	Yes	Range: 2-15	Subserosal (n=4; 14.3%) Intramural (n=23; 82.1%) Submucous (n=1; 3.6%)	No	-	Recurrent abortion (n=6; 21.4%) Primary infertility (n=7; 25.0%) Secondary infertility (n=4; 14.2%)
Takeuchi et al. 2006	Laproscopic adenomyomectomy	-	4.7	Ant wall (n=6; 42.9%) Post wall (n=8; 57.1%)	GnRH-a pre-op (n=9; 64.3%) COCP pre-op (n=1; 7.1%)	None	Dysmenorrhea (n=14;100%) Menorrhagia (n=8; 57.1%) Infertility (n=8; 57.1%) (median period 47 months)
Wang et al. 2009 'comparison'	Adenomyomectomy. Minilaprotomy, ultraminilaprotomty and laproscopic techniques.	Yes	-	Anterior wall (n=25; 15.2%) Posterior wall (n=121; 73.3%) Fundal (n=19;11.5%)	± GnRH-a 6 months post-op	-	Only included if 20-45 years old. Significantly different age and lesion diameters between groups.
Takeuchi et al. 2010	Laparoscopic enucleation of the cyst (form of adenomyomectomy)	Yes	3.2	' Right side' (n=6) ' left side' (n=3)	GnRH-a (n=3; 33.3%) Oral contraceptive (n=3; 33.3%)	None	Pelvic pain (n=6; 66.7%) Dyspareunia
Al Jama et al. 2011	Adenomyomectomy via microsurgical technique	Yes	Uterus max diameter 10.4 +- 7.3	' Most in anterolateral wall'	GnRH-a 6 months post op.	-	Infertility length 11.4±2.7 years
Dai et al. 2012	Laparotomy adenomyomectomy.	Yes	-	-	No	Endometrial perforation (n=35; 40.7)	Dysmenorrhea. Menorrhagia (n=34; 39.5%)
Kishi et al. 2014	Laproscopic adenomyomectomy	Yes	-	Anterior wall (n=34; 33.3%) Posterior wall (n=78; 76.5%) Both walls (n=20; 19.6%)	No	Placenta accreta (n=2; 2.0%) Threatened preterm delivery (n=2; 2.0%)	Recurrent miscarriage, infertility.
Guy et al 2016	Laparoscopic Adenomyomectomy.	-	-	-	±Gestrinone 3ms	-	-
Chang et al. 2013 *	Ultramini- or mini-laparotomy adenomyomectomy.	Yes	-	Anterior wall (n=18; 32.1%) Posterior wall (n=30; 53.6%) Fundal (n=8; 14.3%)	6 month course GnRH-a post op.	Uterine perforation (n=17; 30.4%)	Women aged 20-45. Desired fertility and no ART post-op.
Diffuse AD							
Hadisaputra et al 2006	Laparoscopic resection	N/A	153.42g (15-799)	N/A	GnRH-a 3months post op.	-	Dysmenorrhea (n=10; 100%) Menorrhagia (n=6; 60%) Pelvic pain (n=3; 30%)
Rajuddin et al 2006	Cytoreductive.	Yes	Volume 28.9±3.8mm3	-	GnRH-a 4wk pre+post-op Aromatase 3months	-	Length of infertility 86.9±85 months

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Wang et al. 2009 'is the'	laparotomy cytoreductive microsurgical technique.	Yes	Uterine size 10.17±0.92	-	GnRH-a 6months post-op (n=15; 53.6%)	Uterine perforation (30%)	' unexplained infertility' severe dysmenorrhea
Nishida et al. 2010	Laparotomy. Asymmetric dissection of uterus sacrificing a fallopian tube. No tourniquets. Concurrent peri-uterine adhesiolysis (n=13), myomectomy (n=8), chocolate cystectomy (n=8).	Yes	-	-	N/A	Transfusion 7 (15.9%)	Dysmenorrhea (100%)
Osada et al. 2011	Mini-laparotomy cytoreductive technique via ' triple-flap' method. Tourniquet applied to uterine vessels.	Yes	-	Ant wall (n=38; 36.5%) Post wall (n=44; 42.3%) Both (n=22; 21.2%)	N/A	Haematoma <1cm diameter 6 (5.8)	Prev IVF (n=57), embryo transfer (n=45), miscarried (n=17). Other ART (n=11), miscarried (n=3) Anemia (n=94; 90.4%) Dysmenorrhea (n=104; 100%) Menorrhagia (n=104; 100%)
Huang et al. 2012	Microscopic cytoreductive + GnRH-a postoperatively	-	-	-	GnRH-a for 6 months post-operatively in all.	None	>3 year history of infertility (n=9; 100%. Dysmenhorea (n=9; 100%) Menorrhagia (n=8; 88.9%
Saremi et al. 2014	Uterine artery tourniquet used. Cytoreductive via Laparotomy.	-	-	Ant and post wall (n=3; 2.9%)	No	Asherman's (n=4; 3.8%) Uterine rupture (n=2; 1.9%)	Infertility (n=57; 55.3%) Recurrent miscarriage (n=9; 8.7%) IVF failure (n=17; 16.5%) Menorrhagia (n=20; 19.4%)
Focal & Diffuse AD							
Fujishita et al 2004	Laparotomy. Cytoreductive ' H' technique and indigo-carmine catheter to assess endometrial perforation or classic cytoreductive.	-	-	-	No	Uterine perforation (n= 3; 27.3%)	' most' had dysmenorrhea menorrhagia and infertility
Tamura et al. 2017 * Both AD	Doesn't describe techniques used.	-	-	-	N/A	-	All women were to have ' infertility treatment'.

CS; caesarean section. NVD; normal vaginal delivery. TVUS; transvaginal ultrasound scan. AbdUS; abdominal ultrasound scan. MRI; magnetic resonance imaging. NC; natural conception. ART; assisted reproductive techniques. U; unknown whether ART or natural conception. T; total.
*Contains patients from previously published studies.

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524 **Table 3.** Pregnancy outcomes following surgery for focal and diffuse adenomyosis.

Author	Patients desiring fertility (n)	Women becoming pregnant (n) (% as proportion of women desiring fertility)	Successful deliveries (n) (% as proportion of women desiring fertility)	Term deliveries (n) (% as proportion of women desiring fertility)	Miscarriages/abortions (n) (% as proportion of total pregnancies)	Preterm deliveries (n) (% as proportion of women desiring fertility)	Obstetric outcomes	Delivery method	Birth weight (g)
Focal AD									
Fedele et al. 1993 Total	18	13 (72.2%) women (18 pregnancies)	9 (50%)	9 (50%)	8 (44.4%)	1 (5.6%)	1 preterm = neonatal death. 1 ectopic.	CS 3 (33.3%) NVD 6 (66.7%)	-
Natural conception	17	12 (70.6%)	9 (52.9%)	9 (52.9%)	7 (1 an ectopic) (41.4%)	1 (5.9%)	-	-	-
ART	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100%)	0	-	-	-
Fujishita et al 2004 total Natural conception	6	1 (16.7%)	1 (16.7%)	1 (16.7%)	0	0	-	CS 1	-
Takeuchi et al. 2006 Natural conception	14	2 (14.3%)	1 (50.0%)	1 (50.0%)	0	0	Live female; 1 (50.0%) Ongoing pregnancy at follow up; 1 (50.0%)	NVD 1	2856
Wang et al. 2009 'conservative' Natural conception	71	55 (77.5%)	49 (69.0%)	42 (59.2%)	6 (10.9%)	7 (9.9%)	-	-	-
Surgery alone	27	20 (74.1%)	17 (63.0%)	15 (55.6%)	3 (15.0%)	2 (7.4%)	-	-	-
Surgical-medical	44	35 (79.5%)	32 (72.7%)	27 (61.4%)	3 (8.6%)	5 (11.4%)	-	-	-
Takeuchi et al. 2010 Natural conception	3	2 (66.7%) (3 preg but 2 to 1 woman)	3 (100.0%) (3 preg in total)	3 (100.0%)	0	0	-	NVD 2 CS 37wks 1	-
Al Jama et al. 2011 Natural conception Surgical medical	18	8 (44.4%)	6 (33.3%)	6 (33.3%)	2 (25.0%)	0	Ectopic; 1 (9.1%) Retained placenta following NVD; 1 (9.1%)	CS 6 NVD 1 w/ retained placenta	-
Kishi et al. 2014 Total Unknown NC/ART	*** 102	*** 42 (41.2%)	*** 32 (31.4%)	-	*** 10 (23.8%)	*** 4 (3.9%)	Preterms; Placenta accreta 2 (2.0%) 2 (2.0%) threatened preterm labours delivered wks 35 & 36.	CS all.	-
Guy et al 2016 Natural conception							-	-	-
Surgery + medical	14	8 (57.1%)	N/A	N/A	N/A	N/A			
Surgery	12	5 (41.7%)	N/A	N/A	N/A	N/A			

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Totals surgery All Natural ART Unknown	 **258** 155 1 102	 **136 (52.7%)** 93 1 42		**	** **26 (19.1%)** 15 1 10	**	-	-	
Chang et al. 2013 * Natural conception	56	23 (41.1%) (27 pregnancies).	15 (26.8%)	13 (23.2%)	12 (44.4%); 7 elective (25.9%) 4 spont (14.8%) 1 ectopic (3.7%)	2 (3.6%)	1 ectopic pregnancy 2 preterm	-	-
Tamura et al.2017* Unknown ART/NC	*** 23	*** 9 (39.1%)	-	-	*** 0 (0.0%)	-	-	-	-
Diffuse AD									
Fujishita et al 2004 Natural conception	 1	 1 (100%)	-	-	-	-	Pregnancy ongoing at follow up	-	-
Hadisaputra et al 2006 Natural conception	10	3 (30.0%)	1 (10.0%)	1 (10.0%)	1 (33.3%) (5 wks)	1 (10.0%) 30 wks neonatal death	PROM 1 (10.0%)	CS 1	3500
Rajuddin et al 2006 Natural conception	32	3 (9.4%)	2 (6.3%)	N/A	1 (33.3%)	N/A	-	N/A	-
Wang et al. 2009 'is the' Natural conception Surgery +/- medical	28	13 (46.4%)	9 (32.1%)	-	4 (30.8%)	-	-	-	-
Osada et al. 2011 total	26	16 (61.5%)	14 (53.8%)	-	2 (12.5%)	0	0	CS 14	-
Natural conception	-	4	4	-	0	0	0	-	-
ART	-	12	10	-	2 (16.7%)	0	0	-	-
Huang et al. 2012 total	9	3 (33.3%)	2 U (22.2%) ***	-	1 U (33.3%) ***	-	-	CS 2	-
Natural conception	3	1 (33.3%)	N/A	-	N/A	-	-	-	-
ART	6	2 (33.3%)	N/A	-	N/A	-	-	-	-
Saremi et al. 2014	70	21 (30.0%)	16 U (22.9%) ***	17 U (24.3%) ***	4 U (19.0%) ***	1 U (1.4%) ***	Uterine rupture 2 (9.5%); 37 wks (still birth) & 32 wks (baby survived)	CS 17.	-
Natural conception	21	7 (33.3%)	N/A	N/A	N/A	N/A	-	-	-
ART	49	14 (28.6%)	N/A	N/A	N/A	N/A	-	-	-
Totals following surgery All Natural	 **176** 95 55	 **60 (34.1%)** 32 28	 **44 (25.0%)** 16 10	- **	 **13 (21.7%)** 6 2	 **	Uterine rupture 2 PROM 2	CS in all studies that specify	-

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ART Unknown	26	-	18 ***		5 ***				
Tamura et al. 2017* unknown ART/NC	61	*** 24 (39.3%)	-	-	*** 10/31 (32.3%)	-	-	-	-

CS; caesarean section. NVD; normal vaginal delivery. TVUS; transvaginal ultrasound scan. AbdUS; abdominal ultrasound scan. MRI; magnetic resonance imaging. NC; natural conception. ART; assisted reproductive techniques. U; unknown whether ART or natural conception. T; total.
*Contains patients from previously published studies.
** poorly reported so cannot be accurately calculated.
*** unknown if ART/NC; where the study reported pregnancy/delivery/miscarriage rates but did not specify whether in women with ART or with natural conception (NC).

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533 Table 4. **Summary conclusions & topics for future research.**

1. Management of women with adenomyosis-associated subfertility is highly controversial and there remains an overall lack of consensus regarding the value of conservative surgery and/or medical management to improve reproductive outcomes.

2. Based on currently available evidence, conservative surgery should not be routinely recommended if fertility is desired. It may be considered on a case-by-case basis for patients with concurrent AD-associated pelvic pain or menorrhagia, younger infertile women who have failed medical management or older women with infertility despite ART, and those with a history of recurrent pregnancy loss (RPL) or recurrent implantation failure (RIF).

3. There is insufficient evidence to recommend ART over expectant management after conservative surgery for both focal and diffuse adenomyosis given similar pregnancy rates observed.

4. Patients with adenomyosis are at increased risk of adverse perinatal outcomes including preterm birth, PPROM, pre-eclampsia, and spontaneous miscarriage.

5. Patients with diffuse adenomyosis may be an increased risk of antepartum or intrapartum uterine rupture after cytoreductive surgery compared to patients with focal adenomyosis after adenomyomectomy. This is likely related to the volume of tissue resected. However, the overall risk of uterine rupture is unknown and requires further study.

6. Reproductive surgeons should be cognizant to balance maximal cytoreduction while also conserving adequate uterine tissue to minimize the risk of adverse pregnancy outcomes.

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Supplemental Figures and Tables

Supplemental Figure 1: Reproductive outcomes following surgery for diffuse and focal AD.

*Denotes missing data for successful delivery and/or miscarriage rate.

Supplemental Figure 2: Pregnancy rate for focal vs. diffuse AD after natural conception and ART.

Supplemental Table 1: Methodologic quality assessment of nonrandomized studies for potential risk of bias using the Cochrane Collaboration's Risk of Bias Tools for Non-Randomized Studies.

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