PROFESSOR MARGIT DUEHOLM (Orcid ID : 0000-0002-2577-7903)

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Uterine adenomyosis and infertility, review of reproductive outcome after in vitro fertilization and surgery

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Margit Dueholm

Department of Gynecology and Obstetrics, Aarhus University Hospital, Aarhus, Denmark

Corresponding author:

Margit Dueholm

Department of Gynecology and Obstetrics, Aarhus University Hospital, Palle Juhl Jensensvej 100, 8200 Aarhus N, Denmark
Mail: dueholm@dadlnet.dk

Conflict of interest

None

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Abstract

This review includes: a) analysis of the clinical studies evaluating reproductive outcome and adenomyosis, and b) a review of studies on reproductive outcome and surgical treatment options for adenomyosis. Strict diagnostic criteria and classification of disease are needed for an image diagnosis of adenomyosis. Studies of in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) populations and women with surgically treated deep endometriosis suggested that adenomyosis has a negative impact on reproductive outcome, although there are substantial variations between studies. Little data are available on the relation between the extent of disease and impact on reproductive outcome, but a correlation appears to exist. Case series seem to confirm a positive effect of gonadotropin-releasing hormone analog treatment and surgery on reproductive outcome, but there are no controlled trials. Evidence is impaired by the poor quality of many studies, deficient strict image diagnosis, and the absence of a classification of the extent of disease. Selection of the most optimal evidence-based treatment options for adenomyosis in the fertility clinic is difficult because of a lack of evidence regarding the relation between fertility and the degree and composition of adenomyosis. Adenomyosis may reduce implantation so severely that surgical or other treatment options should be recommended, but the benefit of these treatment options needs to be verified. Referral of women with adenomyosis and recurrent miscarriage and repeated failure of assisted reproductive technology to centers with a special interest in adenomyosis research and treatment may be critical.

Keywords:
adenomyosis, infertility, assisted reproduction, pregnancy, obstetric outcome, surgery

Key message:

Reproductive outcome seems to be reduced in women with adenomyosis, but data on any effective treatment to improve reproduction is limited. Surgery could be effective, but should only be performed in centers specializing in adenomyosis research and treatment.

Abbreviations:

AD adenomyosis

ART assisted reproductive technology

IVF in vitro fertilization

ICSI intracytoplasmic sperm injection

TVS transvaginal ultrasonography

3D-TVS 3D-ultrasonography

MRI magnetic resonance imaging

JZ junctional zone

JZmax maximal thickness of junctional zone

PR pregnancy rate

Introduction

Adenomyosis (AD) is regarded a disease of the endo-myometrial junction defined by the presence of heterotopic endometrial glands and stroma in the myometrium. Migration of endometrial cells into the myometrium is accompanied by a varying degree of muscular hypertropia. AD should be understood as a two-component disease consisting of an element of ectopic endometrial glands and stroma and a second element of muscular change (hypertropia, hyperplasia, and fibrosis).

The diagnosis of AD is made by histopathology. The increased resolution of transvaginal ultrasonography (TVS), 3D-ultrasonography (3D-TVS) and magnetic resonance imaging (MRI) has made it possible to perform an image diagnose of AD, and to clearly display the endo-myometrial junction. The inner myometrium adjacent to the endometrium, or junctional zone (JZ), is normally displayed as a thin hypoechoic zone by TVS and a low signal band adjacent to the endometrium by MRI.

Adenomyosis of the uterus is most often diagnosed in the classical form in the fourth or fifth decades of life, based on the classical symptoms of dysmenorrhea and menorrhagia. The classical form of AD is described without endometriosis. However, recent studies have revealed that AD can the coexistence with endometriosis in younger women, indicating a common pathogenesis (1), and AD has been suggested to cause implantation failure in younger women with endometriosis (2). Infertility is a less frequent complaint in the classic form, but because more women delay their pregnancy until their late 30s or 40s, the relation between AD and infertility is becoming increasingly relevant.

The impact of AD on fertility is evaluated by imaging. This review will analyze the relation between infertility and AD and review studies on reproductive outcome and surgical treatment options for AD in infertile patients.

Material and methods:

We conducted a PubMed search using the keywords: AD OR adenomyoma OR junctional zone AND infertility OR assisted reproduction, IVF, pregnancy OR obstetric outcome, AD AND treatment (surgery, treatment, GnRH, gonadotropin-releasing hormone). In all, 726 abstracts were reviewed, and articles on the subject were retrieved, read, and searched for additional references, resulting in 277 articles being retrieved and indexed. Studies on fertility outcome and AD and surgery for AD were systematically retrieved. Data on fertility outcome and AD were displayed by funnel plots and a simple pooled analysis (fixed model), see Figure 1. In the presence of heterogenecity ($I^2 \geq 50\%$), pooled values for random effects models are given in the figure legend. No sensitivity or regression analysis or analysis of study quality was performed because a meta-analysis including most of the studies has already been done (2, 3).

Image diagnosis of adenomyosis

Studies of AD and fertility are built on an imaging diagnosis without histologic verification. A great variation in the interpretation and use of image criteria is a large confounder in these studies. In a general gynecologic clinic, a single diagnostic ultrasound criterion was present in 21% of women, while three were seen in 14% (4). In women with at least four sonographic

criteria of AD (8.4% of the women), there was a relation between the numbers of sonographic criteria and the symptoms of menorrhagia (5). This important study indicates the presence of a high number of unspecific image changes in the myometrium which are not AD and underlines the importance of strict criteria for image diagnosis.

Image features of AD comprise features of heterotopic endometrial tissue and accompanying myometrial hypertrophy. TVS, 3D-TVS, and MRI features of AD (6) are given in Table 1. Signs of ectopic endometrium are highly specific, while signs of muscular changes are less specific both by TVS and MRI (7). Changes in the JZ can be visualized by MRI or 3D-TVS, and JZ thickness and irregularity are signs of AD. The efficiency of 3D-TVS has been shown in a single study to be slightly more efficient than 2D-TVS for the diagnosis of AD (8).

The relative weight of the different features in establishing a correct diagnosis remains unclear, but more than one criterion and often 3 criteria are needed for an image diagnosis of AD, and the uterus should always be searched for clear features of heterotopic endometrium (9, 10).

Studies with histopathologic correlation suggested that AD is strongly suspected when the JZ measures at least 12 mm in thickness on MR images (7, 10, 11), but others have used a maximal thickness of 10 mm (JZmax) as a cutoff value beyond which JZ AD is assumed(12).

In a review by Champaneria et al.(13) that included only studies of high quality with microscopic verification, the pooled sensitivity and specificity with 95% confidence limits (95% CI) for transvaginal ultrasound were 72% (65–79) and 81% (77–85), respectively, and for MRI were 77% (67–85) and 89% (84–92), respectively. Thus, the use of imaging gives 23–28% false negative results and 11–19% false positive results in highly selected symptomatic women scheduled for hysterectomy. The use of imaging for the diagnosis of AD in an infertile population has clear shortcomings. Image characteristics of AD and the diagnostic efficiency of imaging techniques may be different in infertile populations in which the proportion of women with minimal disease may be more pronounced.

Junctional zone

Smooth muscle changes in the JZ may precede AD. These changes could be regarded as stage 0 AD, with microtraumas in the endo-myometrial boarder that may develop into AD. The smooth muscle change in the JZ may be seen as a disease in itself, an endometrial−subendometrial myometrium unit disruption(14), and Gordts (15) proposed that the junctional changes with a maximum JZ thickness ≥8 mm and <12 mm- JZ be classified as hyperplasia , or what could be called "stage 0" of the disease.

The muscular changes and morphology in AD vary widely and range from slight localized expansion of the JZ to massive myometrial hyperplasia and fibrosis, which could be expected to change the plasticity and tonus of the uterus as well as the contour of the endometrial cavity (16). The effect on peristalsis, uterine contraction, and fertility could differ in concordance with the variation in morphologic changes (16), but there is no consensus on a classification system regarding the extent of the disease based on image morphology (6, 15).

Fertile women seem to have a regular, thin JZ (median JZmax 5.2). No women had AD in a 3D study of JZ thickness in 82 consecutive fertile women 6–12 months after first delivery, and only 12% had JZmax thickness values of 8.0 to 12.0 mm (17).

Features of AD and JZ changes should be especially searched for in the infertile subgroup of women with recurrent miscarriage and repeated failure of assisted reproductive technology (ART). JZ thickness (JZmax) was thicker in a group with recurrent miscarriage compared to controls (5.8 ± 0.7 vs. 5.0 ± 1.1 mm)(18).

AD was diagnosed in 38% of women with recurrent miscarriage and 35% of women with repeated failure of ART using 3D-TVS. A morphologic evaluation of the endometrial cavity showed moderate distortion in 23% of women with AD, while 10% had a severe impact, with a pseudo T-shaped uterus (16).

A thickened and irregular JZ is seen in women with endometriosis. A JZ thickening (JZmax of >10 mm) on MRI was reported in 79% of women with laparoscopic evidence of peritoneal endometriosis (12) . Three other studies (19-21) reported lower prevalence's of 27%, 35%, and 38%, respectively, using strict JZ changes for the diagnosis of AD, as explained in Table 1. Thus, AD seems to be present in one-third of women with surgically treated endometriosis. Moreover, the presence and depth of infiltration of AD was related to the extent of endometriosis (20). Muscular peristalsis in the JZ is important in the transport of oocyte and

sperm. Uterine contractions are hormone dependent and may be visualized and assessed by ultrasound and seem to affect implantation by assisting in sperm transport (22).

Muscular changes in the JZ may reflect an altered peristalsis (23). Dysperistalsis was demonstrated in women with diffuse AD and endometriosis, and a thickened JZ was related to dysperistalsis (23).

Effect of adenomyosis on reproductive outcome

Many endometrial receptivity markers are changed in the adenomyotic endometrium (1, 24, 25). Although none of these have proven to be predictive of implantation in humans.

No studies have examined natural conception in women with AD, but a negative influence of AD on spontaneous conception is seen in baboons, even in the absence of endometriosis. There is a strong correlation between AD and endometriosis in baboons. (26)

Extent of JZ change related to outcome

Imaging allows the diagnosis of JZ changes. In a study by Youm et al., the presence of an increased myometrial thickness without signs of AD was related to lower birth rates. The increased myometrial thickness was most likely attributed to a thickened JZ, which in turn affected fertility. Pregnancy rates in women with AD were lower than in these women without AD (27).

In a prospective study, 152 women had MRI prior to in vitro fertilization (IVF) (28). An increase in JZ thickness was significantly correlated with implantation failure at IVF. The pregnancy rate (PR) in the group with average JZ thickness (AJZ) <7 mm compared to >7 mm was 63% vs 26%. In the group with JZmax <10 mm compared to >10 mm, PR was 63% vs 14%. Implantation failure rate was 96% in patients with an average JZ thickness greater than 7 mm AND a maximal JZ superior to 10 mm, versus 38% in other patient groups.

These studies indicate an increase in adverse implantation outcome in relation to the extent of JZ change and AD. Moreover, changes in the JZ even with a thickness <12 mm (JZ hyperplasia) may have an adverse effect on implantation, but more studies are needed.

Pregnancy rates, miscarriage, delivery rate, and preterm delivery related to adenomyosis

Pregnancy rate

The effect of AD on IVF/intracytoplasmic sperm injection (ICSI) outcome has been described in a total of 11 studies. Four studies were case-control studies (29-32), and seven cohort studies (27, 28, 33-37). Additionally, the effect of AD on pregnancy rate (PR) (both spontaneous and ART pregnancy) after surgery for rectovaginal and colorectal endometriosis is described in five trials (38-42). One study (43) was not included because it comprised some of the same women included in (38). A distinction between classical AD without endometriosis and AD associated with endometriosis in IVF/ICSI studies was not possible, and it was not possible to extract additional data regarding the extent of AD and outcome.

One case-control study was performed in an oocyte donation population (30). This study only reported PR per cycle and could not be included in the pooled PR per woman. The PR per cycle was not reduced; however, the miscarriage rate was significantly higher in the AD group.

Figure 1 displays the pooled and individual PRs related to AD in women who underwent surgery for deep endometriosis (rectovaginal and colorectal) and in infertile women who underwent IVF/ICSI. Sub analyses for cohort studies, case-control studies, and deep endometriosis surgery are displayed.

In cohort studies, PRs were reduced in women with AD. Pooling the results yielded a common RR of 0.73 (95% CI 0.64–0.82). In concordance, the common PR in women who underwent surgery for deep endometriosis was reduced (RR 0.37 (95% CI 0.21–0.67)). The age of patients was either similar or adjusted for in most studies (27-29, 31, 32, 34, 36, 37, 40). In one study in which AD women had higher PRs, AD patients were slightly older (33), while the age distribution was not described in the other studies (35, 38, 39, 41, 42).

Notably, the overall PR was not reduced in case-control studies. Selection bias could mask the effect of AD in two case-control studies using retrospective identified cases and controls. One had lower PRs among women with AD (31), while another only included 19 women with AD and a large control group of 144 (29). Benaglia (44) performed a prospective case-control study and only included 49 asymptomatic women with AD and compared them to 49

matched controls. They used the criteria proposed by Naftelin (4), which only required one criterion for the diagnosis of AD in contrast to the usual inclusion of three criteria. Thus, discrete sonographic changes in asymptomatic women may not affect fertility.

A meta-analysis in 2014 (3) concerned the effect of AD on IVF/ICSI outcome. This analysis included nine studies in a pooled analysis and all the presented studies in IVF/ICSI women except two recent case-control studies (31, 32). Based on a total of 1865 women, 306 of which were diagnosed with AD, the authors concluded that AD adversely affects both the probability of clinical pregnancy and increases the risk of early pregnancy loss. The adverse impact of AD on fertility in deep endometriosis is also described in another review (2).

In two of the cohort studies (34, 35), all the women had endometriosis. No association between endometriosis and PR was found. However, PR was also reduced in women with AD (RR 0.53 (95% CI 0.37–0.77)) when all data were pooled from seven studies (34, 35, 39-42) in 381 women with deep endometriosis, including 102 with AD.

Live birth rates, miscarriage, and preterm delivery.
The adverse effect of AD on live births rates is demonstrated in Figure 2A. Four studies reported crude live birth rates (29, 31, 33, 34) and showed a pooled RR of 0.69 (95% CI, 0.56–0.85).

Seven studies reported the number of miscarriages in IVF/ICSI studies, which was 32% in women with AD and 14% in women without AD, with a common RR of 2.12 (95% CI, 1.20–3.75) (Figure 2B). An association between AD and miscarriage was also found.

Two recent reviews (45, 46) concluded that endometriosis is likely associated with spontaneous miscarriage, preterm birth, and small-for-gestational-age babies. In addition, women with endometriosis were at increased risk of pre-eclampsia, preterm birth, and cesarean section in another recent study that included a total birth cohort of 82,793 singleton pregnancies; 1213 of these women had endometriosis (47). However, the effect of concomitant AD on pregnancy complications has not been evaluated in any large study. Two studies (48, 49) have examined the relation between AD and preterm birth and reported an increased risk of preterm birth in AD, see Table 2.

In summary, an increasing amount of data indicates decreased implantation and increased early abortions in the presence of AD. However, several women with AD conceived. Based on the present sparse data, the rate of successfully pregnancies may be related to the extent of AD.

Treatment of adenomyosis in the infertile patients

Medical therapies

Treatment options are described in a recent review (50). Continuous use of oral contraceptive pills, high-dose progestins, and selective progesterone receptor modulators can temporarily improve the symptoms. Moreover, use of a levonorgestrel-releasing intrauterine device, danazol, aromatase inhibitors, and GnRH-a may temporarily induce regression of AD.

Gonadotropin-releasing hormone analog (GnRH-a) treatment.

GnRH-a treatment with add-back estrogen therapy is used for AD and has resulted in reports of several pregnancies (50). GnRH-a treatment decreases the size and demarcation of adenomyotic lesions, as demonstrated by MRI (51), and treatment has a positive effect on endometrial implantations markers (52).

AD was not associated with a lower PR in the pooled data from two studies (33, 35) in which a long protocol (GnRH-a) was adopted. However, both studies were retrospective, and other factors may also have contributed to the difference.

Recently, Niu (53) compared outcomes in AD patients undergoing frozen embryo transfer after long-term preparation of the endometrium with GnRH-a therapy before hormone replacement therapy. In the group of GnRH-a pre-treated women, clinical pregnancy, implantation, and ongoing PRs were significantly higher than in women not pre-treated with GnRH-a.

In another study of women with AD, a similar trend of higher PRs was seen after pretreatment with GnRH-a, especially with regard to frozen embryo transfer. PR was highest in frozen-thawed transfer cycles, but the difference was not significant (54).

These studies indicate some beneficial effect of GnRH-a analog therapy in AD. The therapy may produce a window of time with improved implantation. Women with AD are often in their late reproductive years, with reduced ovarian reserve. In these women, the negative effect of time for surgery or GnRH-a should be weighed against reduced PR without GnRH-a pretreatment. Oocyte retrieval for frozen embryo transfer before therapy for AD could be an option in older women, but more studies are needed

Cytoreductive surgery

Operative techniques include laparoscopic or an open approach with either partial or total excision of AD. The adenomyotic tissue may be approached with a classic myomectomy technique including the same steps as used in myomectomy. The adenomyotic tissue is dissected and excised either by diathermia or scalpel, and the uterine walls are sutured in several layers, often with different closure techniques, to restore the thickness of the myometrium. These closure techniques include overlapping the remaining seromuscular layer (flaps) in double or triple layers (55). Suturing is done with U-sutures, figure of eight, or interrupted sutures. Incision may be transverse or longitudinal, wedge-shaped, or a transverse H incision(56). In several studies (55, 57-60), a combined medical (GnRH-a) and surgical treatment was applied.

Pregnancy outcome after cytoreductive surgery is reported in Figure 3. This figure covers reported studies (all are case series; case reports are not included) (56-64) of women trying to conceive after cytoreductive surgery for AD. Some women received ART, while others conceived without fertility treatment. Two not included studies (65, 66) comprised women most likely included in another study (58).

In all, 160 pregnancies, 126 deliveries, and 33 miscarriage have been reported in 338 women with AD (PR 47%, delivery rate 37%, percent miscarriage 10%) (Figure 3). After surgery, the delivery rate and PR were only slightly higher than in women with AD who underwent IVF/ICSI (Figures 1 &2A). However, all the largest surgical studies comprised older women with a median age over 38 years (58, 61-63), often with failed ART, repeated abortions, and infertility for several years, while women treated with IVF/ICSI (Figure 1) had a lower mean age of 33–35 years.

In a detailed review from 2014, the outcome of AD surgery was reported to be efficient for symptomatic relief of symptoms, and the delivery rate was higher (50%) than presented in

Figure 3 (67). This review included the first 147 of the 338 infertile women with surgically treated AD that have been reported to date. These first reported studies comprised mostly complete excision of localized AD in younger women. Recent additional studies include women with extensive AD (63) and older women (62). Kishi (62) included 27 women more than 40 years old, i.e. women with a very low PR, and concluded that cytoreductive surgery had no impact on fertility outcome in women over the age of 40.

Wang (66) compared 28 women who had surgery and 37 women who had only GnRH-a treatment and found a higher delivery rate (33% vs 8%) in the surgery group. He also compared GnRH-a combined with surgery and surgery alone (Figure 3) and found no difference in delivery outcome, but the medical-surgical group was older than the surgery group (58).

Uterine rupture during pregnancy is one of the main shortcomings after uterine surgery for AD and was reported in two cases after extensive surgery (63). In another study, two of 23 pregnancies after cytoreductive surgery had rupture in the second trimester. In five women with myometrial thickness <7mm only two had normal pregnancies. The authors concluded that the optimum wall thickness for conception and prevention of rupture after cytoreductive surgery may range from 9 to 15 mm(68).

Thus, uterine-sparing operative treatment of AD is feasible and can be efficacious in carefully selected cases <40 years old, but the risk of uterine rupture after surgery and the limited evidence of improved outcome should reserve surgery to centers in which well-designed studies are performed and the benefit is validated.

Other methods

A technique that involves hysteroscopic treatment of myometrial cysts by ultrasound-guided incision, excision, or coagulation has been described. However, there are no studies evaluating the benefit of this treatment on fertility (69).

High-intensity focused ultrasound (ultrasound guided or magnetic resonance guided) and uterine artery embolization are other treatment options reported to be efficient for the treatment of symptomatic AD (70, 71). The efficiency of both techniques with regard to the relief of symptoms of AD is dependent on achieving necrosis in the involved adenomyotic

tissue (71, 72), and the challenge is to control the size and location of the necrosis. Consequently, the myometrial tissue is affected, which may reduce the strength of the uterine wall and induce a risk of rupture in pregnancy. No larger studies on pregnancy outcome and only cases of pregnancy are reported (73, 74) after these procedures for AD. At present, these techniques have therefore not been recommended for women with AD and a wish to conceive.

Conclusion

In clinical studies, reduced implantation, early pregnancy loss, and preterm birth are related to AD. Even a thickened JZ (junctional zone hyperplasia or stage 0 AD) may decrease implantation, but the presented evidence is poor because only heterogeneic studies of moderate quality are available, and more studies are needed to reach a definitive conclusion. Moreover, the present absence of strict image criteria and image classification of the extent of AD impairs results. A selection of the most optimal evidence-based treatment options for AD in the fertility clinic is difficult because of the lack of evidence on the degree of change that causes AD to interfere with fertility and the degree and composition of AD that may reduce implantation so severely that surgical or other treatment options should be recommended. Surgery reduces symptoms and has been successful in a few series, but may increase the risk of rupture. However, there are no effective treatment options that do not interfere with conception, and there is an urgent need for the evaluation of the role of surgery or other treatment possibilities. Therefore, women with AD and recurrent miscarriage or repeated failure of ART should be referred to the few centers with special interest in AD research and treatment, and surgery should only be performed in these centers until the benefit of surgery and other treatment options is known.

At present, GnRH-a pretreatment before natural conception is suggested in women without diminished ovarian reserve. In women with diminished ovarian reserve, immediate IVF or ICSI with long protocol or oocyte retrieval can be followed by frozen embryo transfer after GnRH-a treatment is performed. There is limited evidence for an improved outcome after surgery, and surgery should only be an option for symptomatic women with repeated IVF/ICSI failure in validated studies (75). Based on the present data, we cannot give strong evidence-based recommendations on treatment options in women with AD and infertility.

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Table 1. Image features for the diagnosis of adenomyosis.

	Transvaginal ultrasound (TVS)	Magnetic Resonance Imaging (MRI)
Ectopic endometrium		
	Myometrial cysts, anechoic lacunae,	Hyperintense cystic areas (T2W images)
	Sub-endometrial linear striation	
	Indistinct endo-myometrial junction	Irregular abrupt endometrial outline
	Hyperechoic spots	Hemorrhagic content is seen as high signal intensity spots (T1W images)
	Trans-lesion vascularity	
Muscular hypertropia		
	Globally enlarged or asymmetric myometrium	
	a heterogeneous myometrium and indistinct myometrial mass	
	Fan-shaped echo shading in the myometrium (TVS)	
	3D-TVS OR MRI	
	A maximal junctional zone thickness >12 mm (76)	
	An irregular junctional zone (JZdiff >4 mm) (difference between maximum and minimum thickness)(10)	
	Without the presence of leiomyomas Ratio JZmax/myometrial thickness >40%(7).	

T2-weighted sequences (T2W images); T1-weighted sequences (T1W images);
3D-transvaginal ultrasonography (3D-TVS)

Table 2. Adenomyosis and risk of preterm delivery.

	Adenomyosis and risk of preterm delivery or preterm rupture of membranes (PROM)		
Study	Study description	Preterm OR (95%CI)	PROM OR (95%CI)
Juang 2007	pregnant women with a pre-pregnancy pelvic image reports. Adenomyosis diagnosed by MRI or ultrasound based on established criteria. Retrospective case control. Cases: 104 preterm, 16 had adenomyosis vs 208 not preterm, 19 had adenomyosis	1.84[a] (1.3–4.3)	1.98 [a] (1.4–3.2)
Mochimaru 2015	36 from a database of 10,413. Controls selected from 8332 without adenomyosis. Diagnosis based on MRI or ultrasound criteria of enlarged uterus 36 women with adenomyosis vs 144 controls selected from 8332 without adenomyosis	5.0 (2.2-11.4)[b]	5.5(1.7-17.7)

[a]Adjusted Odds ratio (OR), age, body mass index (kg/m2), previous preterm delivery and smoking. [b]Small-for-gestational age (33.3% vs 10.4%), fetal malpresentation (27.8% vs 8.3%), and cesarean delivery (58.3% vs 24.3%).

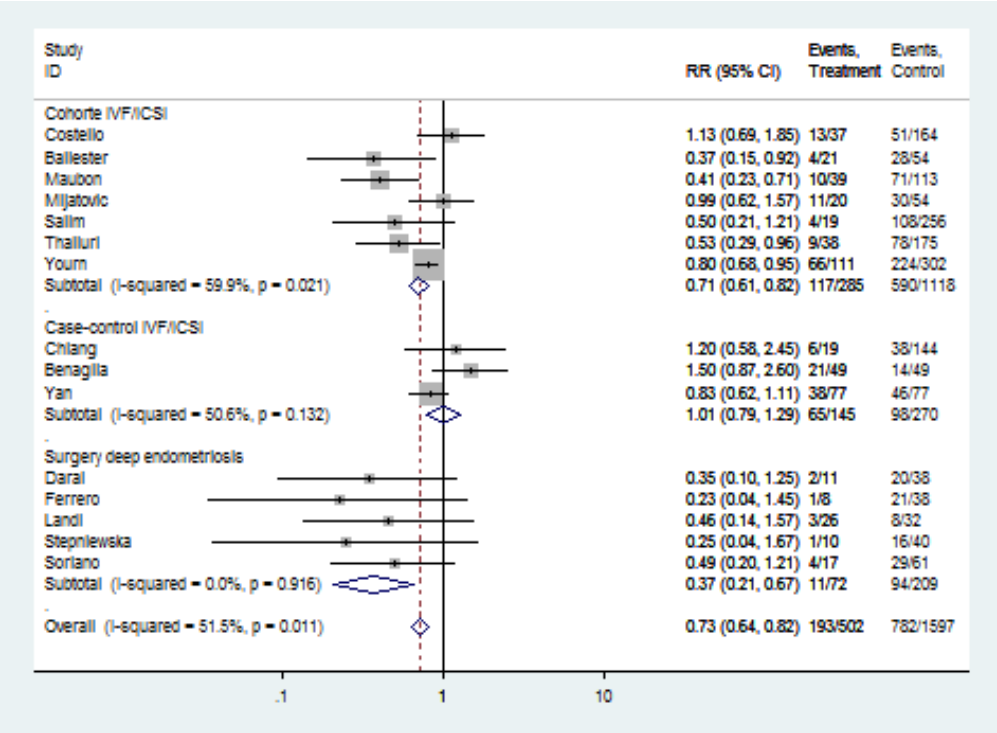

Figure 1. Clinical pregnancy and adenomyosis. Studies that evaluated the pregnancy rate per women in infertile women with or without adenomyosis undergoing IVF/ICSI. Studies are grouped in case-control studies and cohort studies. Studies on women who underwent surgery for deep endometriosis (with and without ART) are included. Funnel plots showing individual and combined effect size estimates and 95% confidence intervals (CIs). Horizontal lines indicate 95%CIs; boxes show the study specific weight; the diamond represents the combined effect size for groups and overall; dashed line indicates the overall estimate based on a fixed effects model. Heterogenecity was seen in both cohort and case-control IVF/ICSI studies, but not in women with deep endometriosis after surgery. In cohort studies, random effect analysis RR (95% CI) was: 0.69 (0.51–0.92) and in case-control studies:1.07 (0.7–1.6). Prospective studies were: Maubon, 2010 (28); Ballester, 2012 (34); Salim, 2012 (36) ; Benaglia, 2014 (32); Darai, 2010 (38); and Ferrero, 2009 (39). Diagnostic criteria for AD were based on MRI findings of abnormal myometrial and JZ thickness in two IVF studies: Ballester, 2012 (34); Maubon, 2010 (28). TVS in nine IVF/ICSI studies: Costello, 2011 (33); Chiang, 1999 (29); Martinez-Conejero, 2011 (30); Mijatovic, 2010 (35); Salim, 2012 (36); Thalluri, 2012 (37); Youm, 2011 (27); Yan, 2014 (31); Benaglia, 2014 (32).In studies of women scheduled for endometriosis surgery, diagnosis was based on MRI in one study: Landi 2008 (40), TVS in two: Stepniewska, 2010 (41); Soriano, 2016 (42) and both

techniques in two: Darai, 2010 (38); Ferrero, 2009 (39).TVS findings of AD characteristics including (asymmetrically) thickened endometrium, cysts, striations, heterogeneity. The numbers of ultrasound criteria used varied.

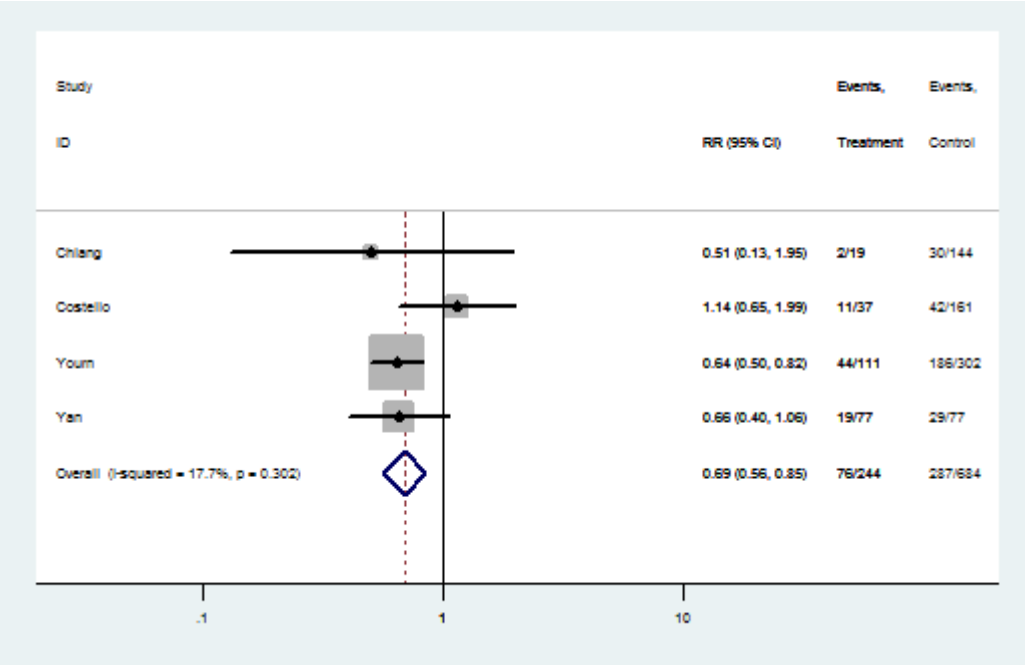

Figure 2A. Birth rate and adenomyosis. Studies that evaluated the live birth rate in infertile women with or without adenomyosis undergoing IVF/ICSI. Funnel plots showing individual and combined effect size estimates and 95% confidence intervals (CIs). Horizontal lines indicate 95%CIs; boxes show the study specific weight; the diamond represents combined effect size; dashed line indicates the overall estimate based on a fixed effects model.

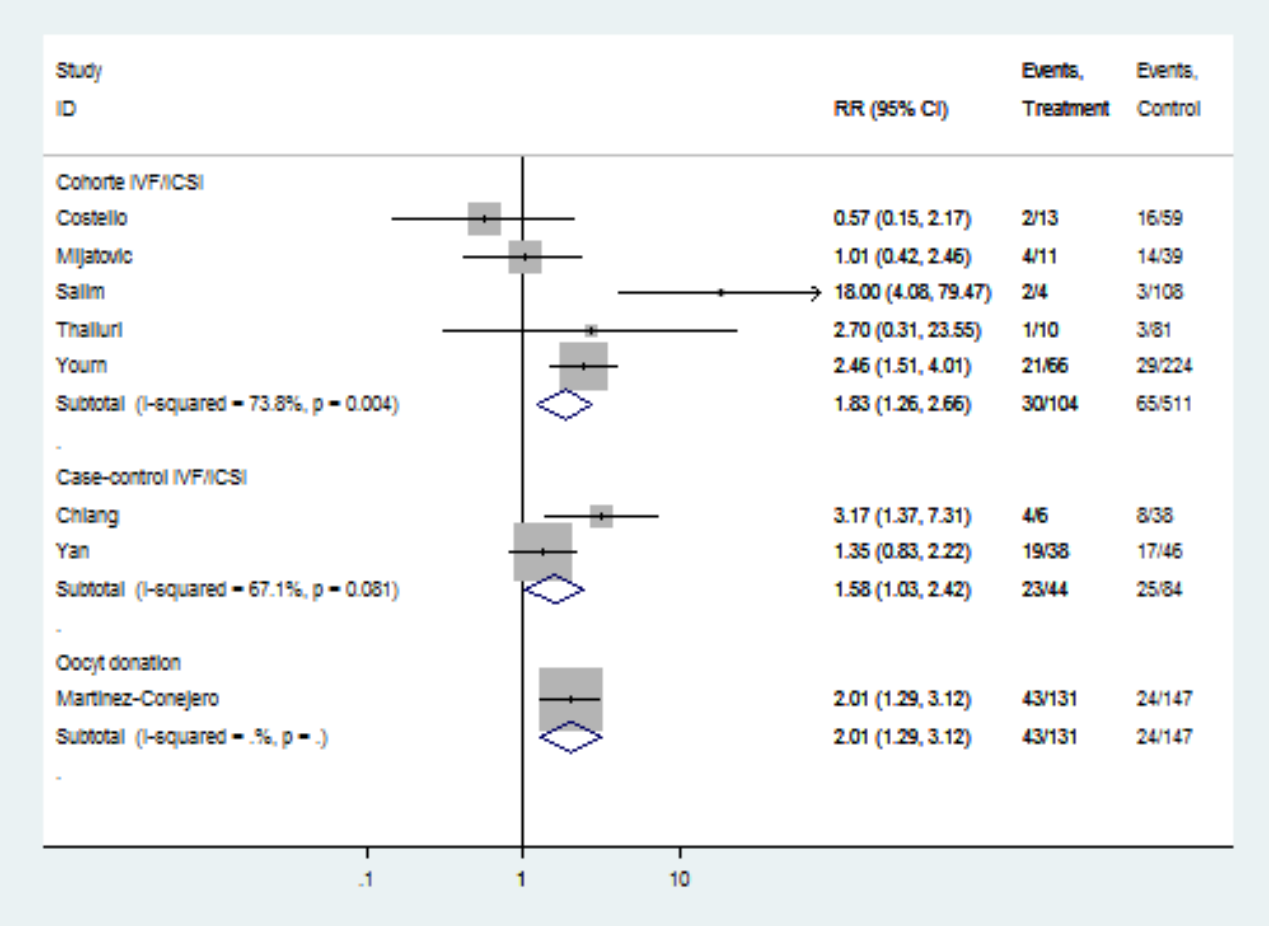

Figure 2B. Miscarriage and adenomyosis. Studies that evaluated the rate of miscarriage per woman in infertile women with or without adenomyosis. Studies on women undergoing IVF/ICSI are grouped in cohort studies and case control studies. Data from studies on women who underwent surgery for deep endometriosis (with and without ART) could not be extracted. Funnel plots showing individual and combined effect size estimates and 95% confidence intervals (CIs). Horizontal lines indicate 95% CIs; boxes show the study specific weight; the diamonds represent combined effect size for the groups. Heterogenecity was seen in both cohort and case-control IVF/ICSI studies. In cohort studies, random effect analysis RR (95% CI) was 2.2(0.8–5.6), in case-control studies 1.9(0.8–4.5) and overall without Martinez-Conejero (95% CI) 2.04(1.1–3.7).

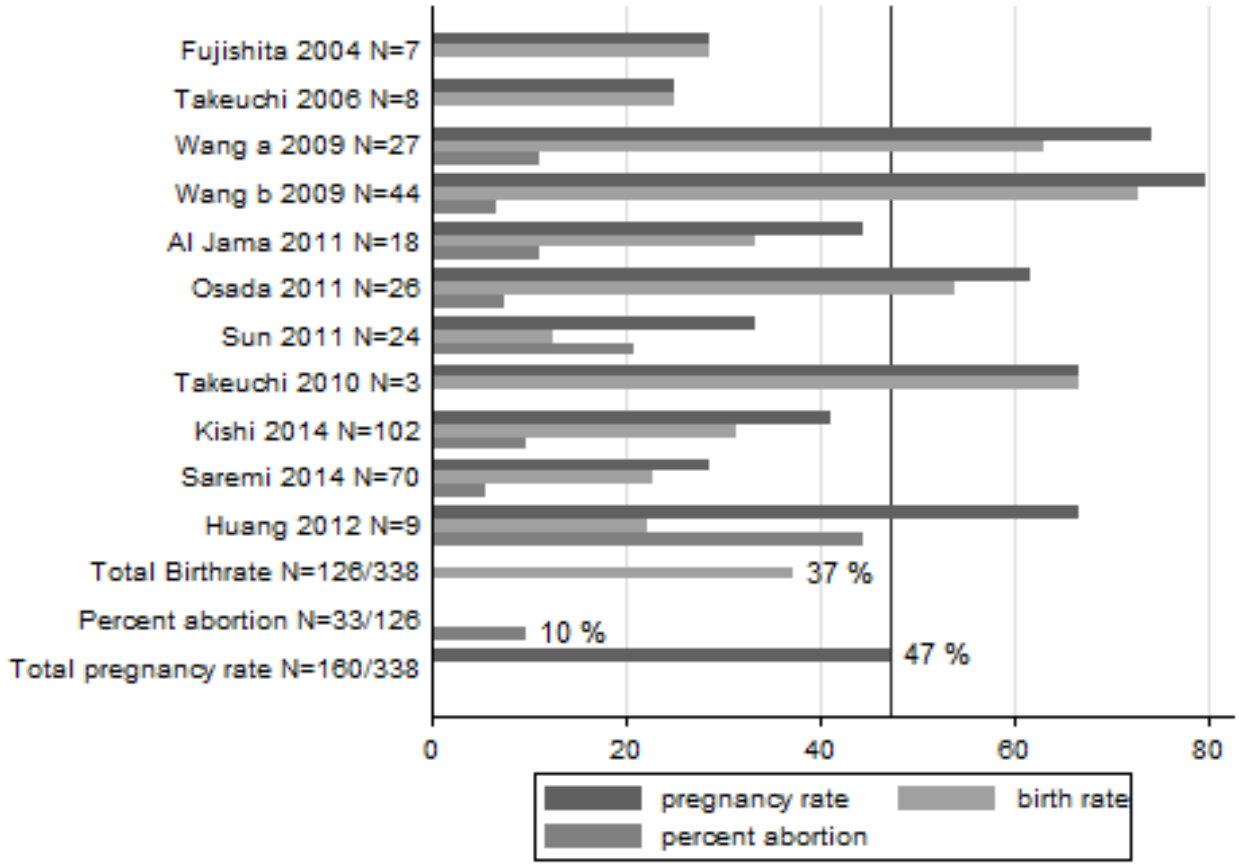

Figure 3. Pregnancy rate, rate of abortion, and birth rate in studies on cytoreductive surgery for adenomyosis, where analysis of reproductive performance was described.