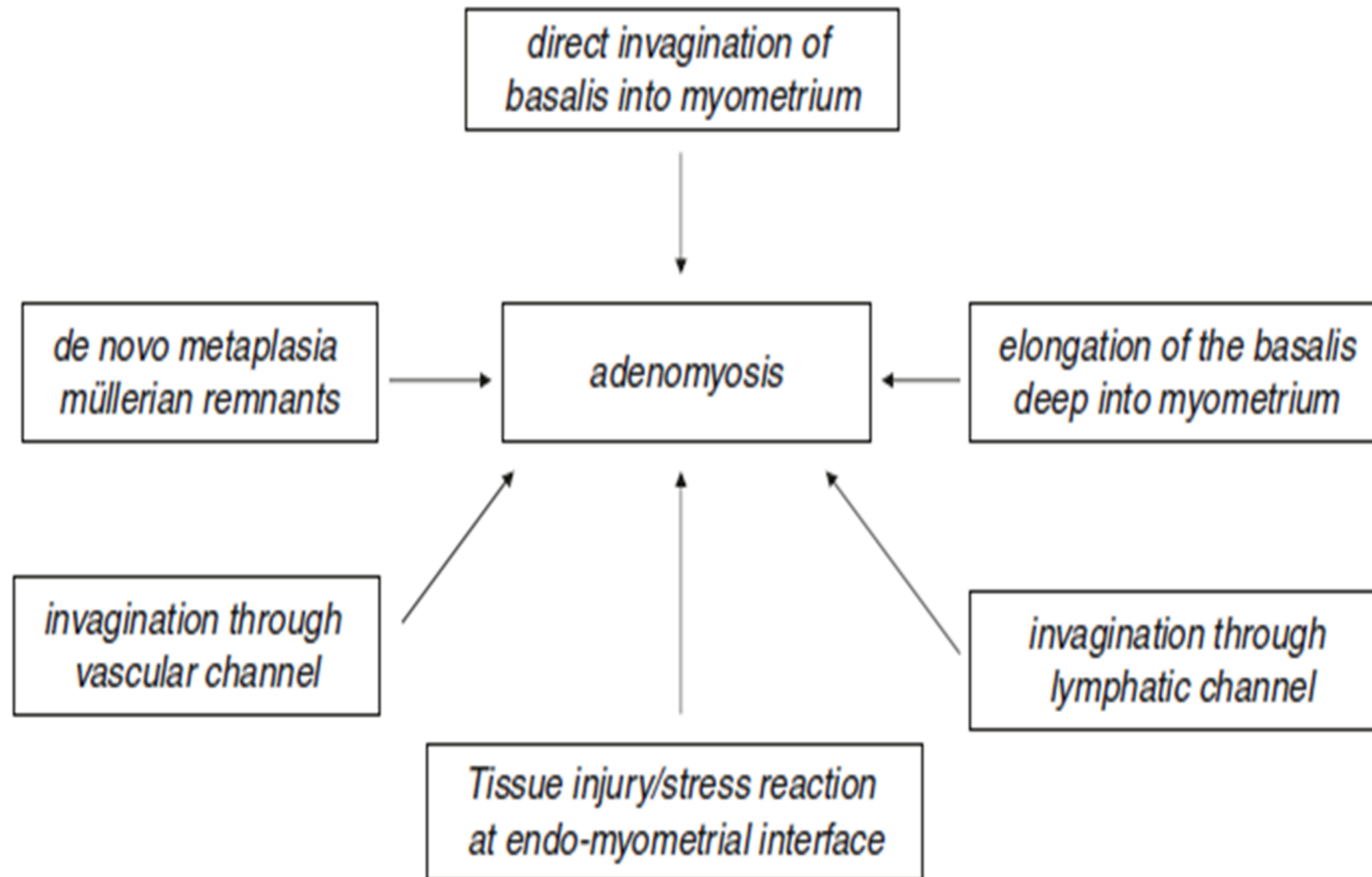
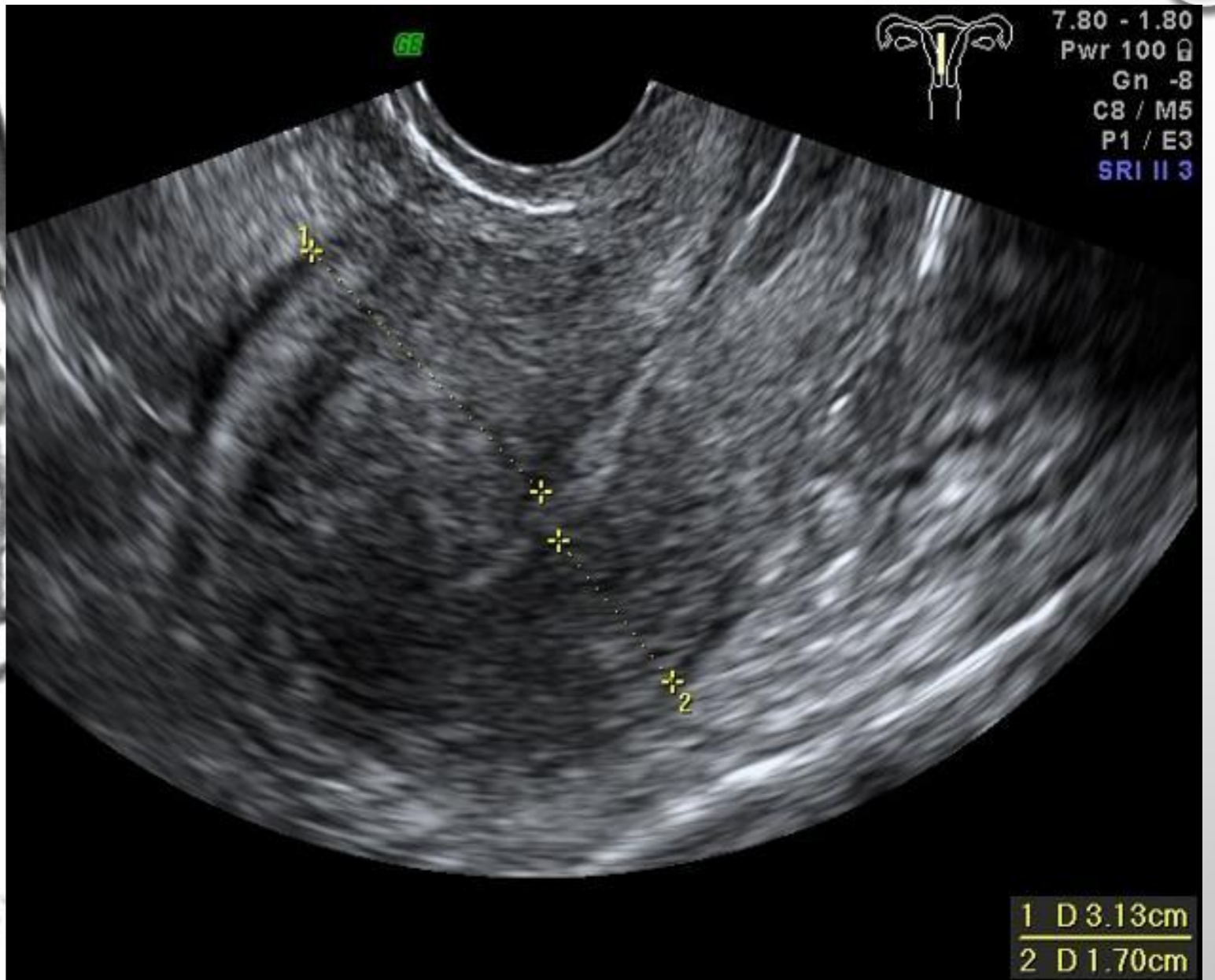


The background of the slide is a light gray gradient with several realistic water droplets of various sizes scattered across it. The droplets have highlights and shadows, giving them a three-dimensional appearance. The text is centered in the middle of the slide.

ADENOMYOSIS AND INFERTILITY





INTRODUCTION

- **ADENOMYOSIS (AD)** IS REGARDED AS A DISEASE OF THE ENDOMYOMETRIAL *JUNCTION* DEFINED BY THE PRESENCE OF **HETEROTOPIC ENDOMETRIAL GLANDS AND STROMA IN THE MYOMETRIUM.**
- 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 COEXIST 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).**

1. BENAGIANO G, BROSENS I, HABIBA M. STRUCTURAL AND MOLECULAR FEATURES OF THE ENDOMYOMETRIUM IN ENDOMETRIOSIS AND ADENOMYOSIS. HUM REPROD UPDATE. 2014;20:386-402.

2. VERCELLINI P, CONSONNI D, BARBARA G, BUGGIO L, FRATTARUOLO MP, SOMIGLIANA E. ADENOMYOSIS AND REPRODUCTIVE PERFORMANCE AFTER SURGERY FOR RECTOVAGINAL AND COLORECTAL ENDOMETRIOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS. REPROD BIOMED ONLINE. 2014;28:704-13.

- 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.

IMAGE DIAGNOSIS OF ADENOMYOSIS

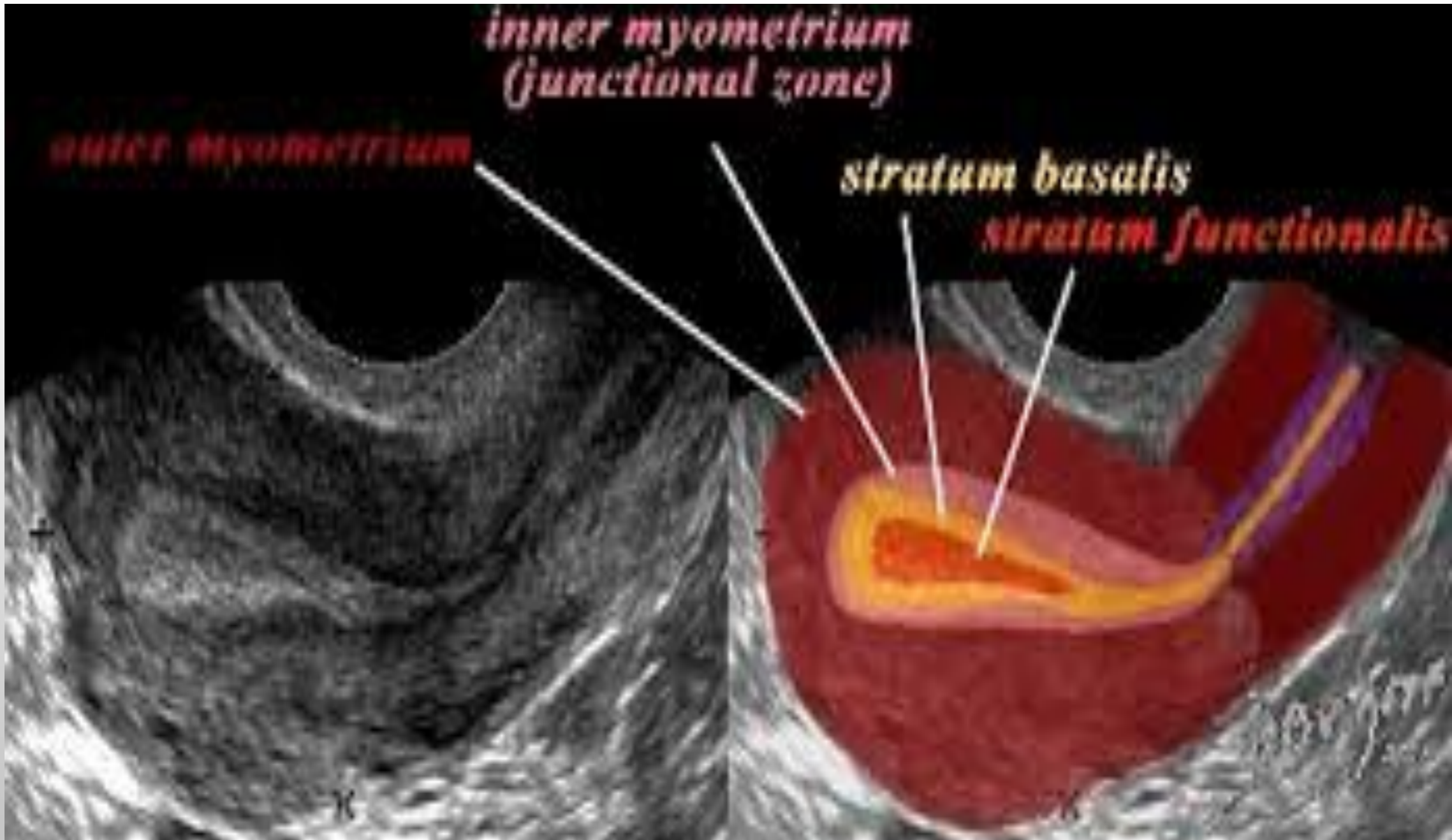
- **STUDIES OF AD AND FERTILITY ARE BUILT ON AN IMAGING DIAGNOSIS WITHOUT HISTOLOGIC VERIFICATION. A GREAT VARIATION IN THE INTERPRETATION AND USE OF IMAGE CRITERIA IS A LARGE CONFOUNDER IN THESE STUDIES.**
- **THE RELATIVE WEIGHT OF THE DIFFERENT FEATURES IN ESTABLISHING A CORRECT DIAGNOSIS REMAINS UNCLEAR, BUT MORE THAN ONE CRITERION AND OFTEN THREE CRITERIA ARE NEEDED FOR AN IMAGE DIAGNOSIS OF AD, AND THE UTERUS SHOULD ALWAYS BE SEARCHED FOR CLEAR FEATURES OF HETEROTOPIC ENDOMETRIUM.**
- **STUDIES WITH HISTOPATHOLOGIC CORRELATIONS SUGGESTED THAT AD IS STRONGLY SUSPECTED WHEN THE JZ MEASURES AT LEAST 12 MM IN THICKNESS ON MR IMAGES, BUT OTHER STUDIES HAVE USED A MAXIMAL THICKNESS OF 10 MM (JZMAX) AS A CUTOFF VALUE ABOVE WHICH JZ AD IS ASSUMED.**

IMAGE DIAGNOSIS OF ADENOMYOSIS

- IN A REVIEW BY **CHAMPANERIA ET AL.** THAT INCLUDED ONLY **STUDIES OF HIGH QUALITY WITH MICROSCOPIC VERIFICATION**, THE **POOLED SENSITIVITY AND SPECIFICITY** WITH 95% CONFIDENCE LIMITS FOR **TRANSVAGINAL ULTRASOUND** WERE **72%** AND **81%**, AND FOR **MRI 77%** AND **89%**, 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 (MAXIMUM JZ THICKNESS OF ≥ 8 AND < 12 MM)
- THE EFFECT ON **PERISTALSIS, UTERINE CONTRACTION, AND FERTILITY CAN DIFFER** IN CONCORDANCE WITH THE **VARIATION IN MORPHOLOGIC CHANGES**, BUT THERE IS ***NO CONSENSUS ON A CLASSIFICATION SYSTEM REGARDING THE EXTENT OF THE DISEASE BASED ON IMAGE MORPHOLOGY.***
- **FERTILE WOMEN** SEEM TO HAVE A **REGULAR, THIN JZ** (MEDIAN JZMAX 5.2).
- **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).**



JUNCTIONAL ZONE

- **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, AND 10% HAD A SEVERE IMPACT, WITH A PSEUDO T-SHAPED UTERUS.**
- **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.**
- **MUSCULAR PERISTALSIS IN THE JZ IS IMPORTANT IN THE TRANSPORT OF OOCYTE AND SPERM.**
- **DYSPERISTALSIS WAS DEMONSTRATED IN WOMEN WITH DIFFUSE AD AND ENDOMETRIOSIS, AND A THICKENED JZ WAS RELATED TO DYSPERISTALSIS.**

EFFECT OF ADENOMYOSIS ON REPRODUCTIVE OUTCOME

- MANY ENDOMETRIAL RECEPTIVITY MARKERS ARE ALTERED IN THE ADENOMYOTIC ENDOMETRIUM, ALTHOUGH **NONE** OF THESE HAS **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.

EXTENT OF JZ CHANGE RELATED TO OUTCOME

- IN A STUDY BY **YOUM ET AL.**, THE PRESENCE OF AN **INCREASED MYOMETRIAL THICKNESS WITHOUT SIGNS OF AD** WAS RELATED TO **LOWER BIRTH RATES. PREGNANCY RATES** IN WOMEN **WITH AD** WERE **LOWER** THAN IN THESE WOMEN WITHOUT AD.

- IN A PROSPECTIVE STUDY, 152 WOMEN HAD MRI PRIOR TO IN VITRO FERTILIZATION (IVF). 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 VS. >7 MM WAS 63 VS. 26%. IN THE GROUP WITH JZMAX <10 VS. >10 MM, PR WAS 63 VS 14%. IMPLANTATION FAILURE RATE WAS 96% IN PATIENTS WITH AN AVERAGE JZ THICKNESS >7 MM AND A MAXIMAL JZ >10 MM, COMPARED WITH 38% IN OTHER PATIENT GROUPS.

(MAUBON A, FAURY A, KAPPELLA M, POUQUET M, PIVER P. UTERINE JUNCTIONAL ZONE AT MAGNETIC RESONANCE IMAGING: A PREDICTOR OF IN VITRO FERTILIZATION IMPLANTATION FAILURE. J OBSTET GYNAECOL RES. 2010;36:611-8.)

- MOREOVER, CHANGES IN THE JZ EVEN WITH A THICKNESS <12 MM (JZ HYPERPLASIA) MAY HAVE AN ADVERSE EFFECT ON IMPLANTATION; HOWEVER, MORE STUDIES ARE NEEDED.

Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis

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Objective: To systematically review and summarize the existing evidence related to the effect of adenomyosis on fertility and on in vitro fertilization (IVF) clinical outcomes, and to explore the effects of surgical or medical treatments.

Design: Meta-analysis.

Setting: Not applicable.

Patient(s): An electronic-based search was performed with the use of the following databases: Pubmed, Embase, Ovid Medline, Cochrane Central Register of Controlled Trials, and Google Scholar, identifying all related articles up to November 2016. We included 11 comparative studies that evaluated the clinical outcomes of IVF treatments in women with (519 patients) and without (1,535 patients) adenomyosis diagnosed with the use of magnetic resonance imaging or transvaginal ultrasound. We also separately evaluated four articles comparing fertility outcomes in two groups of infertile adenomyotic patients untreated and treated surgically or medically with the use of GnRH agonist (GnRHa).

Intervention(s): None.

Main Outcome Measure(s): Primary outcome: clinical pregnancy rate after IVF. Secondary outcomes: rates of implantation, ongoing pregnancy, live birth, miscarriage, and ectopic pregnancy. The summary measures were expressed as odds ratio (OR) and 95% confidence interval (CI).

Result(s): The rates of implantation, clinical pregnancy per cycle, clinical pregnancy per embryo transfer, ongoing pregnancy, and live birth among women with adenomyosis were significantly lower than in those without adenomyosis. The miscarriage rate in women with adenomyosis was higher than in those without adenomyosis. It appears that surgical treatment or treatment with GnRHa increases the spontaneous pregnancy rate in women with adenomyosis.

Conclusion(s): Adenomyosis has a detrimental effect on IVF clinical outcomes. Pretreatment with the use of long-term GnRHa or long protocol could be beneficial. (Fertil Steril® 2017;108:483–90. ©2017 by American Society for Reproductive Medicine.)

Key Words: Adenomyosis, adenomyoma, infertility, meta-analysis, in vitro fertilization

PREGNANCY RATES RELATED TO ADENOMYOSIS

- **11 OBSERVATIONAL STUDIES ON CLINICAL OUTCOME OF IVF (TABLE 1) AND FOUR RETROSPECTIVE STUDIES EVALUATING THE EFFECTS OF SURGICAL OR MEDICAL TREATMENT OF ADENOMYOSIS ON FERTILITY (TABLE 2).**
- **OF THE 11 STUDIES ON IVF OUTCOME, FIVE WERE PROSPECTIVE COHORT STUDIES AND SIX WERE RETROSPECTIVE COHORT STUDIES.**
- **11 STUDIES (2,054 PATIENTS) INCLUDED IN THE META-ANALYSIS, CONSISTING OF 519 PATIENTS WITH AND 1,535 WITHOUT ADENOMYOSIS.**

TABLE 1

Main characteristics of the included studies on adenomyosis and its effect on IVF treatment outcomes.

Authors	Study design	Study population	Age	No. of patients with adenomyosis	No. of patients without adenomyosis	Method of diagnosis	Treatment protocol	No. of IVF cycles
Ballester et al. (2012) (20)	Prospective multicenter study	Infertile women with colorectal endometriosis and no previous surgery for deep infiltrating endometriosis or adenomyosis undergoing IVF/ICSI treatments	23–42, median 33	21	54	MRI	<ul style="list-style-type: none"> • Long protocol with GnRHa • Short protocol with GnRHa • Antagonist protocol 	1–3
Benaglia et al. (2014) (26)	Prospective cohort study	Infertile women undergoing first IVF/ICSI treatment	≤42	49	49	TVUS	<ul style="list-style-type: none"> • Long protocol with GnRHa • Short protocol with GnRHa • Antagonist protocol 	1
Chiang et al. (1999) (29)	Prospective cohort study	Infertile women undergoing TVUS before IVF treatment	Mean 36	19	144	TVUS	<ul style="list-style-type: none"> • Long protocol with GnRHa • Short protocol with GnRHa 	1
Costello et al. (2011) (27)	Retrospective cohort study	Infertile women for various causes undergoing first IVF/ICSI treatment	18–42	37	164	TVUS	Long protocol with GnRHa	1
Martinez Conejero et al. (2011) (30)	Retrospective cohort study	Infertile women undergoing oocyte donation cycle	39–42, mean 40.5	152 patients, 328 cycles	147 patients, 331 cycles	TVUS	Oocyte donation protocol with HRT	1–3
Maubon et al. (2010) (25)	Prospective cohort study	Infertile women undergoing pelvic MRI before IVF treatment	21–43, mean 33	39	113	MRI	<ul style="list-style-type: none"> • Long protocol with GnRHa • Antagonist protocol 	1–3
Mijatovic et al. (2010) (28)	Retrospective cohort study	Infertile women with surgically proven endometriosis undergoing first IVF/ICSI cycle after long-term GnRHa treatment	Mean 33	20	54	TVUS	≥3 mo GnRHa (mean 5 mo, range 3–26 mo)	1
Salim et al. (2012) (22)	Prospective cohort study	Infertile women undergoing first IVF/ICSI cycle	Mean 34	19	256	TVUS	Long protocol with GnRHa	1
Thalluri et al. (2012) (24)	Retrospective cohort study	Infertile women undergoing first IVF/ICSI treatment and single transfer of a good-quality embryo	≤39	38	175	TVUS	Antagonist protocol	1

TABLE 1

Continued.

Authors	Study design	Study population	Age	No. of patients with adenomyosis	No. of patients without adenomyosis	Method of diagnosis	Treatment protocol	No. of IVF cycles
Yan et al. (2014) (21)	Retrospective cohort study	Infertile women undergoing IVF/ICSI treatment with adenomyosis diagnosed by TVUS	≤42, mean 34	77	77	TVUS	<ul style="list-style-type: none">• Long GnRHa protocol• Short GnRHa protocol• Ultrashort agonist protocol• Mild stimulation	1
Youm et al. (2011) (23)	Retrospective cohort study	Infertile women undergoing IVF for various causes	≤40	48 ^a (73 cycles)	302 (397 cycles)	TVUS	Short GnRHa protocol	1–2

Note: GnRHa = gonadotropin-releasing hormone agonist; ICSI = intracytoplasmic sperm injection; HRT = hormone replacement therapy; IVF = in vitro fertilization; MRI = magnetic resonance imaging; TVUS = transvaginal ultrasound.

^a Only the group with thickness >2.5 cm was considered in this meta-analysis.

Younes. Adenomyosis and IVF treatment outcomes. *Fertil Steril* 2017.

TABLE 2**Studies evaluating the effects of treatment of adenomyosis on fertility/IVF outcome.**

Authors	Study design	Study population	Patient group A (n)	Patient group B (n)	Method of diagnosis	Treatment	Outcome
Al Jama et al. (2011) (40)	Retrospective cohort study	Infertile patients with adenomyosis	18 patients treated with surgery + GnRHa	22 patients treated with GnRHa alone	TVUS and MRI	6 courses of GnRHa	Spontaneous pregnancy within 3 y
Wang et al. (2009) (41)	Retrospective cohort study	Patients with adenomyosis and unexplained infertility	28 treated with surgery ± GnRHa therapy	37 treated with 6 mo GnRHa alone	TVUS and pathology	Surgery vs. 6 mo GnRHa	Spontaneous pregnancy within 3 y
Niu et al. (2013) (38)	Retrospective cohort study	Infertile women with adenomyosis undergoing frozen-embryo transfer	194 treated with GnRHa and HRT	145 treated with HRT alone	TVUS	3.75 mg leuprolide acetate, 28 days later 1.875 mg, and 21 days later plus HRT; or HRT alone	Clinical pregnancy after 1 cycle
Park et al. (2016) (39)	Retrospective cohort study	Infertile women with adenomyosis undergoing fresh- or frozen-embryo transfer	87 women/105 cycles with GnRHa treatment before fresh transfer	116 women/147 cycles without GnRHa treatment before fresh transfer	TVUS	Goserelin 3.75 mg for 2–3 months	Clinical pregnancy after 1–2 IVF cycles

Note: Abbreviations as in Table 1.

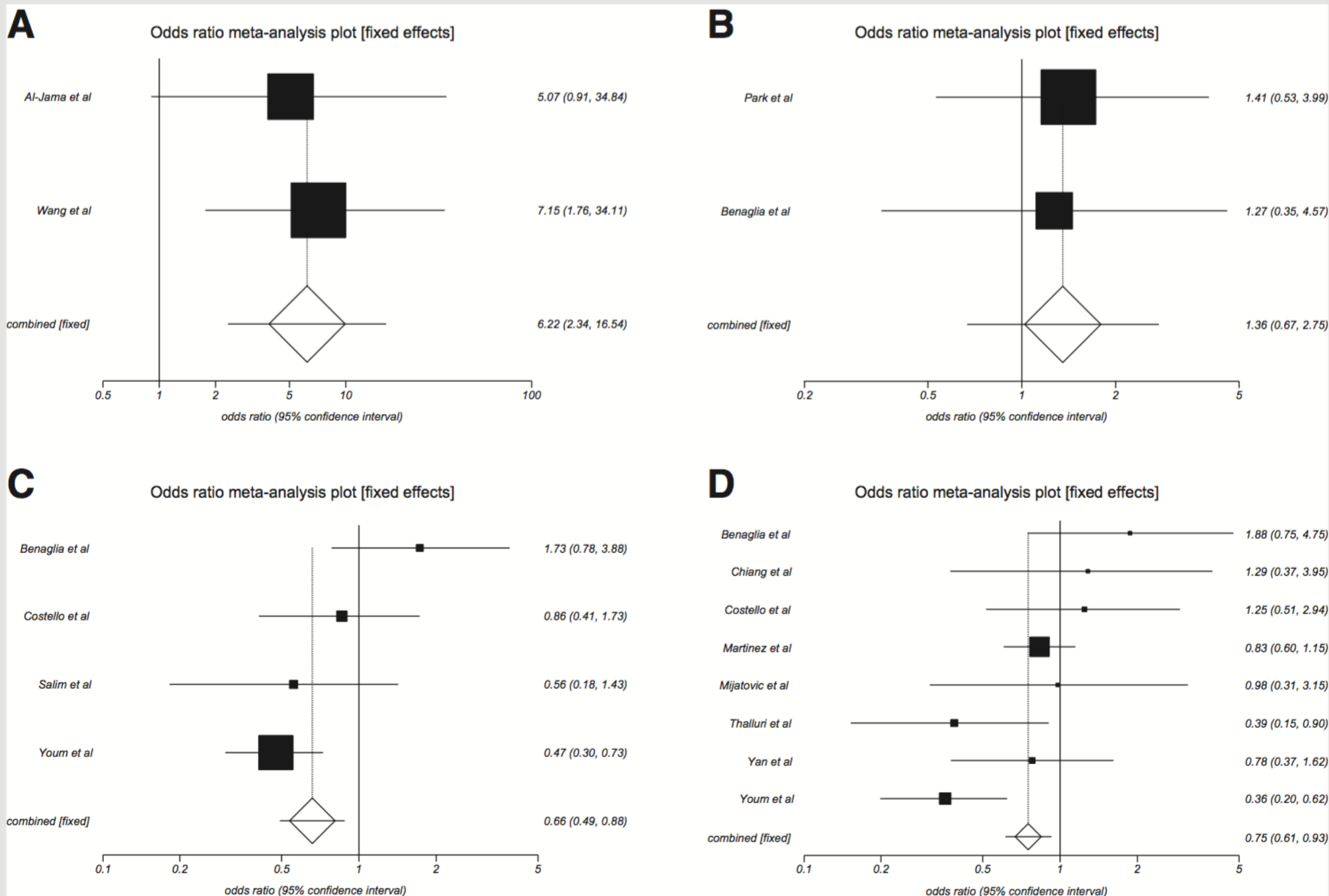
Younes. Adenomyosis and IVF treatment outcomes. *Fertil Steril* 2017.

- ***SPONTANEOUS PREGNANCY RATE AFTER SURGERY:***
COMBINED TREATMENT WITH THE USE OF CONSERVATIVE SURGERY AND GNRHA VERSUS GNRHA TREATMENT ALONE (2 STUDIES):
SURGERY IS ASSOCIATED WITH **INCREASED PREGNANCY RATE** (FIG. 1A; OR 6.22, 95% CI 2.34–16.54). HOWEVER, THE **NUMBER OF SAMPLES** IN THE STUDIES WERE **SMALL**.

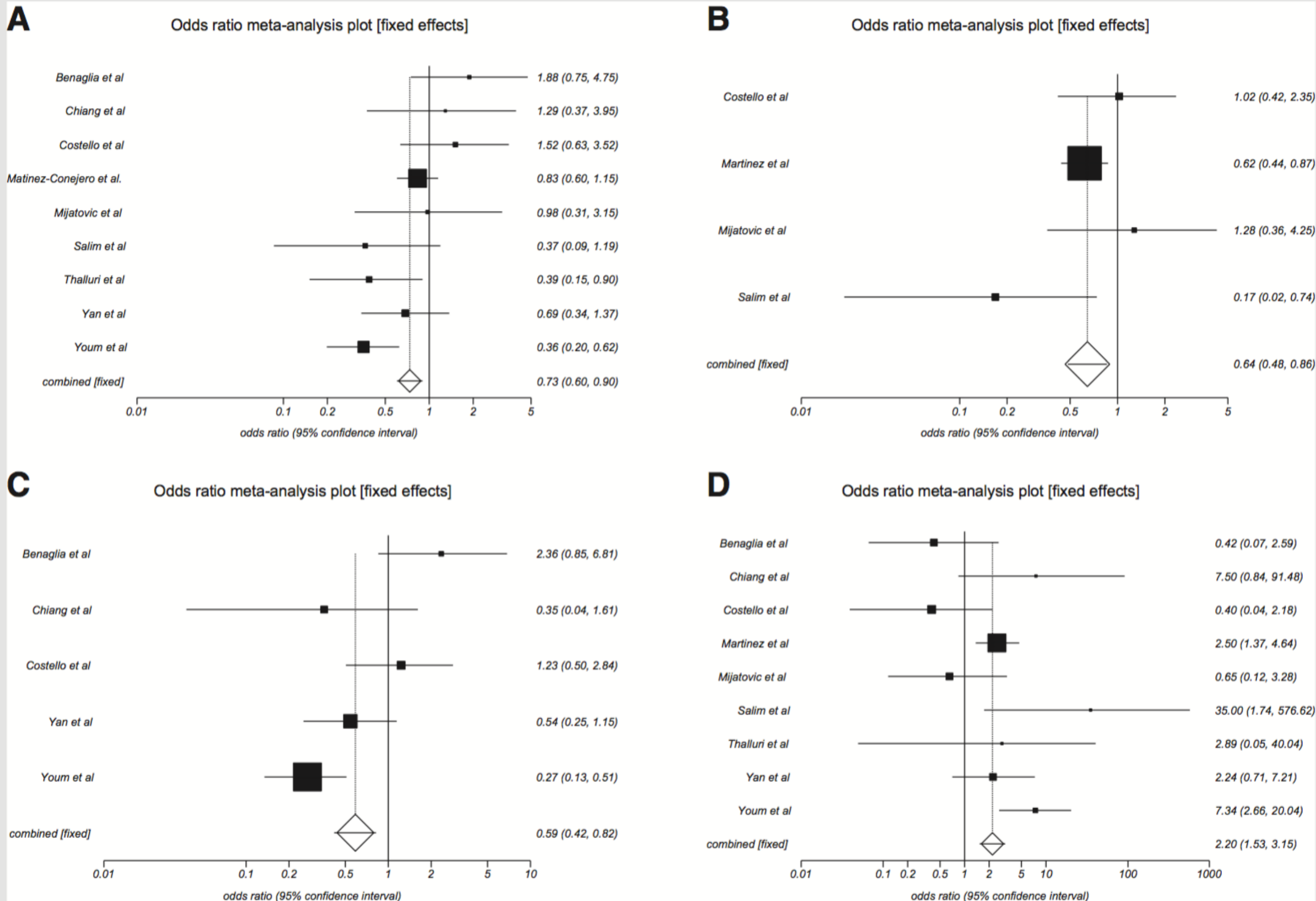
- **FOCAL VERSUS DIFFUSE ADENOMYOSIS:** TWO STUDIES COMPARED THE EFFECTS OF FOCAL VERSUS DIFFUSE ADENOMYOSIS ON IVF OUTCOME. THE POOLED RESULTS GAVE AN OR OF 1.36 FAVORING FOCAL ADENOMYOSIS; HOWEVER, THE CIS WERE 0.67–2.75 (FIG. 1 B).

- ***IMPLANTATION AND PREGNANCY OUTCOME:*** THE RATES OF IMPLANTATION, CLINICAL PREGNANCY PER CYCLE, CLINICAL PREGNANCY PER EMBRYO TRANSFER, ONGOING PREGNANCY, AND LIVE BIRTH AMONG WOMEN WITH ADENOMYOSIS WERE **SIGNIFICANTLY LOWER** THAN AMONG THOSE WITHOUT ADENOMYOSIS (FIGS. 1C, 1D, AND 2). THE **MISCARRIAGE RATE** IN WOMEN WITH ADENOMYOSIS WAS **HIGHER** THAN IN THOSE WITHOUT ADENOMYOSIS (FIG. 2D; OR 2.2, 95% CI 1.53–3.15). **LIVE BIRTH RATE PER CYCLE** WAS REPORTED IN **FIVE STUDIES**. THE PRESENCE OF ADENOMYOSIS WAS ASSOCIATED WITH A **41% DECREASE IN LIVE BIRTH RATE** (FIG. 2C; OR 0.59, 95% CI 0.42–0.82).

- **EFFECTS OF GNRHA PRETREATMENT BEFORE IVF:** THE EFFECTS OF GNRHA TREATMENT BEFORE IVF IN WOMEN WITH ADENOMYOSIS WERE EVALUATED IN TWO STUDIES. ONE STUDY COMPARED COMBINED GNRHA WITH ADD-BACK OR ADD-BACK TREATMENT ALONE BEFORE FROZEN-EMBRYO TRANSFER AND ANOTHER COMPARED GNRHA VERSUS NO TREATMENT BEFORE FRESH- EMBRYO TRANSFER.
- THE RESULTS SHOWED THAT PRETREATMENT WITH GNRHA APPEARS TO BE BENEFICIAL TO THE PREGNANCY RATE.



(A) Cumulative spontaneous clinical pregnancy rate in women who underwent surgery for adenomyosis and who did not (favoring surgery). **(B)** Clinical pregnancy rates after fresh-embryo transfer in women with diffuse (*left of vertical line*) and focal adenomyosis (*right of vertical line*). **(C)** Implantation rates in women without and with adenomyosis. **(D)** Clinical pregnancy rate per embryo transfer in women without and with adenomyosis.



(A) Clinical pregnancy rate per cycle in women without and with adenomyosis. (B) Ongoing pregnancy rate per cycle in women without and with adenomyosis. (C) Live birth rate per cycle in women without and with adenomyosis. (D) Miscarriage rate in women without and with adenomyosis.

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

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Key words

Adenomyosis, infertility, assisted reproduction, pregnancy, obstetric outcome, surgery

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Abstract

This review includes an analysis of the clinical studies evaluating reproductive outcome and adenomyosis, and 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 have suggested that adenomyosis has a negative impact on reproductive outcome, although there are substantial variations between studies. Few 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, a lack of strict image diagnosis, and the absence of a classification of the extent of disease. Selection of the 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.

- **PRETERM DELIVERY:**
- **TWO RECENT REVIEWS 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 PREECLAMPSIA, PRETERM BIRTH, AND CESAREAN SECTION** IN ANOTHER RECENT STUDY THAT INCLUDED A TOTAL BIRTH COHORT OF 82 793 SINGLETON PREGNANCIES; 1 213 OF THESE WOMEN HAD ENDOMETRIOSIS .
- **HOWEVER, THE EFFECT OF CONCOMITANT AD ON PREGNANCY COMPLICATIONS HAS NOT BEEN EVALUATED IN ANY LARGE STUDY. TWO STUDIES** HAVE EXAMINED THE RELATION BETWEEN AD AND PRETERM BIRTH AND REPORTED AN **INCREASED RISK OF PRETERM BIRTH IN AD** (TABLE 2).

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 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)

^aAdjusted odds ratio (OR), age, body mass index (kg/m²), previous preterm delivery and smoking.

^bSmall-for-gestational age (33.3 vs. 10.4%), fetal malpresentation (27.8 vs. 8.3%), and cesarean delivery (58.3 vs. 24.3%).

TREATMENT OF ADENOMYOSIS IN THE INFERTILE PATIENTS

- ***MEDICAL THERAPIES:*** TREATMENT OPTIONS ARE DESCRIBED IN A RECENT REVIEW. **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.**

CYTOREDUCTIVE SURGERY

- **UTERINE-SPARING OPERATIVE TREATMENT OF AD IS FEASIBLE AND CAN BE EFFICACIOUS IN CAREFULLY SELECTED WOMEN <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

- **HYSTEROSCOPIC TREATMENT OF MYOMETRIAL CYSTS BY ULTRASOUND-GUIDED INCISION, EXCISION OR COAGULATION: NO STUDIES** EVALUATING THE BENEFIT OF THIS TREATMENT **ON FERTILITY**
- **HIGH-INTENSITY FOCUSED ULTRASOUND (ULTRASOUND-GUIDED OR MAGNETIC RESONANCE-GUIDED) AND UTERINE ARTERY EMBOLIZATION: THE EFFICIENCY OF BOTH** TECHNIQUES WITH REGARD TO THE RELIEF OF SYMPTOMS OF AD IS **DEPENDENT ON ACHIEVING NECROSIS** IN THE INVOLVED **ADENOMYOTIC TISSUE**, AND THE **CHALLENGE IS TO CONTROL THE SIZE AND LOCATION OF THE NECROSIS. NO LARGER STUDIES ON PREGNANCY OUTCOME** AND ONLY CASES OF PREGNANCY ARE REPORTED.
- **AT PRESENT, THESE TECHNIQUES** HAVE THEREFORE **NOT** BEEN **RECOMMENDED FOR WOMEN WITH AD AND A WISH TO CONCEIVE.**

Uterine adenomyosis and *in vitro* fertilization outcome: a systematic review and meta-analysis

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STUDY QUESTION: Is adenomyosis associated with IVF/ICSI outcome in terms of clinical pregnancy rate?

SUMMARY ANSWER: In a meta-analysis of published data, women with adenomyosis had a 28% reduction in the likelihood of clinical pregnancy at IVF/ICSI compared with women without adenomyosis.

WHAT IS KNOWN ALREADY: Estimates of the effect of adenomyosis on IVF/ICSI outcome are inconsistent.

STUDY DESIGN, SIZE, DURATION: A systematic literature review and meta-analysis were conducted. A Medline search was performed to identify all the comparative studies published from January 1998 to June 2013 in the English language literature on IVF/ICSI outcome in women with and without adenomyosis. Two authors independently performed the literature screening, scrutinized articles of potential interest, selected relevant studies and extracted data. Studies were categorized based on research design.

PARTICIPANTS, SETTING, METHODS: Of the 17 articles assessed in detail, 9 were finally selected based on diagnosis of adenomyosis at magnetic resonance imaging or transvaginal ultrasonography. The quality of studies was evaluated by means of the Newcastle-Ottawa scale. A total of 1865 women were enrolled in the 9 selected studies, 665 of whom in 4 prospective observational studies, and 1200 in 5 retrospective studies. The dichotomous data for clinical pregnancy and secondary outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CIs) and were combined in a meta-analysis using the random-effects model. The heterogeneity Cochrane's Q and the I^2 statistics were calculated. Egger's approach to testing the significance of funnel plot asymmetry was also used.

MAIN RESULTS AND THE ROLE OF CHANCE: The clinical pregnancy rate achieved after IVF/ICSI was 123/304 (40.5%) women with adenomyosis versus 628/1262 (49.8%) in those without adenomyosis. The RR of clinical pregnancy ranged from 0.37 (95% CI, 0.15–0.92) to 1.20 (95% CI, 0.58–2.45), with a significant heterogeneity among studies ($I^2 = 56.8\%$, $P = 0.023$). Pooling of the results yielded a common RR of 0.72 (95% CI, 0.55–0.95). A funnel plot showed no indication of asymmetry among studies (Egger's test, $P = 0.696$). In a meta-regression model, no association was observed between prevalence of endometriosis and the likelihood of clinical pregnancy. Three studies reported the pregnancy rate per cycle. The common RR was 0.71 (95% CI, 0.51–0.98; $I^2 = 78.1\%$, $P = 0.010$). The RR observed in a study with donated oocytes was 0.90 (95% CI, 0.75–1.08). The number of miscarriages per clinical pregnancy was reported in seven studies. A miscarriage was observed in 77/241 women with adenomyosis (31.9%) and in 97/687 in those without adenomyosis (14.1%). The RR of miscarriage ranged from 0.57 (95% CI, 0.15–2.17) to 18.00 (95% CI, 4.08–79.47) ($I^2 = 67.7\%$, $P = 0.005$). Pooling of the results yielded a common RR of 2.12 (95% CI, 1.20–3.75).

LIMITATIONS, REASONS FOR CAUTION: Qualitative and quantitative heterogeneity among studies was high. At sensitivity analysis, I^2 statistic regarding the main outcome was reduced under the 50% threshold removing one trial, but the resulting confidence interval crossed unity. Also the confidence interval of the common RR of the four studies reporting only one IVF/ICSI cycle included unity. Only part of the studies could be included in the assessment of secondary outcomes.

WIDER IMPLICATIONS OF THE FINDINGS: Adenomyosis appears to impact negatively on IVF/ICSI outcome owing to reduced likelihood of clinical pregnancy and implantation, and increased risk of early pregnancy loss. Screening for adenomyosis before embarking on medically

assisted reproductive procedures should be encouraged. The potentially protective role of long down-regulation protocols needs further evaluation. In future studies on the association between adenomyosis and IVF/ICSI outcome, a matched case–control design should be adopted, live birth should be the default primary outcome and only the results regarding the first cycle should be considered.

STUDY FUNDING/COMPETING INTEREST: None.

- THE PRESENCE OF **UTERINE ADENOMYOSIS** IS **STRONGLY ASSOCIATED WITH POST-OPERATIVE REPRODUCTIVE OUTCOME.**
- **COEXISTENCE OF UTERINE ADENOMYOSIS IN ADDITION TO DEEP ENDOMETRIOSIS** WAS ASSOCIATED WITH **A 68% REDUCTION IN THE LIKELIHOOD OF PREGNANCY.**
- **CAUTION!** THE **QUALITY OF THE ASSESSED STUDIES** WAS **SUBOPTIMAL,** AND **CONFOUNDING AND SELECTION BIAS** CANNOT BE EXCLUDED.

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.

- 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.

CONCLUSION

- **SURGERY REDUCES SYMPTOMS AND HAS BEEN SUCCESSFUL IN A FEW SERIES, BUT MAY INCREASE THE RISK OF RUPTURE.**

CONCLUSION

- 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.
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