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CLINICAL ARTICLE

Impact of junctional zone adenomyosis on reproductive outcomes after first single embryo transfer with donated oocytes: A retrospective single-center cohort study

Andrea Etrusco[1] | Belén Moliner Renau[2] | Vittorio Agrifoglio[1] | Antonio Maiorana[3] | Juan Carlos Castillo Farfán[2,4] | Andrea Bernabeu García[2,4]

[1]AMBRA Fertility Center, Palermo, Italy

[2]Department of Reproductive Medicine, Instituto Bernabeu, Alicante, Spain

[3]Gynecologic and Obstetric Unit, ARNAS Civico Di Cristina Fatebenefratelli, Palermo, Italy

[4]Catedra de Medicina Comunitaria y Salud Reproductiva, Universidad Miguel Hernandez, Elche, Spain

Correspondence
Andrea Etrusco, AMBRA Fertility Center, 90138 Palermo, Italy.
Email: etruscoandrea@gmail.com

Abstract

Objective: To evaluate whether junctional zone (JZ) adenomyosis adversely affects assisted reproductive technologies (ART) outcomes in infertile women undergoing their first single embryo transfer (SET) using donor oocytes.

Methods: This retrospective single-center cohort study was conducted at Instituto Bernabeu (Alicante, Spain). A total of 240 infertile women undergoing their first SET with donor oocytes between December 2021 and June 2024 were included: 120 with isolated JZ adenomyosis diagnosed by two-dimensional (2D)–three-dimensional (3D) transvaginal ultrasound according to morphological uterus sonographic assessment (MUSA) criteria, matched to 120 controls without uterine abnormalities. Primary outcomes were live birth and miscarriage rates. Secondary outcomes included implantation rate and the relationship between adenomyosis severity and reproductive outcomes. Multivariable models were used to adjust for potential confounders.

Results: Women with JZ adenomyosis had significantly lower live birth rates than controls (34.16% vs 50.83%; $P=0.009$) and higher miscarriage rates (32.93% vs 11.11%; $P<0.001$), while implantation rates were comparable (68.33% vs 75.00%; $P=0.25$). JZ adenomyosis independently predicted reduced live birth (odds ratio [OR] 0.43, 95% confidence interval [CI]: 0.24–0.76; $P=0.004$) and increased miscarriage risk (OR 3.33, 95% CI: 1.42–7.82; $P=0.005$). Increasing disease severity was associated with a higher risk of miscarriage.

Conclusion: JZ adenomyosis is associated with significantly lower live birth rates and higher miscarriage rates after a first SET with donor oocytes, despite similar implantation rates. Comprehensive pre-ART ultrasound assessment of the JZ may improve counseling and support targeted strategies to optimize reproductive outcomes.

KEYWORDS
adenomyosis, assisted reproductive technologies, egg donation, infertility, junctional zone

1 | INTRODUCTION

Adenomyosis is a benign inflammatory condition of the myometrium, influenced by estrogens and common in women of reproductive age.[1] It is often accompanied by other conditions, such as endometriosis and leiomyomas,[2] and may manifest with symptoms such as chronic pelvic pain, abnormal uterine bleeding and infertility.[3,4] It can also reduce the effectiveness of assisted reproductive technologies (ART).[5]

The precise causes underlying adenomyosis are not yet fully known. One of the most widely accepted hypotheses suggests that the disease results from the invasion of endometrial glands and stroma, which migrate from the basal layer of the endometrium to the myometrium as a result of changes in the junctional zone (JZ).[6,7] It has been observed that, in the non-pregnant uterus, the JZ generates highly specialized contractile waves that are crucial not only for the maintenance of hemostatic balance during the menstrual cycle, but also for fundamental reproductive functions, such as sperm transport and proper implantation of the embryo.[8] Furthermore, once pregnancy is established, the JZ contributes to the complex mechanisms of placentation,[9] making its integrity a key element in reproductive health.

Transvaginal ultrasound (TVUS), supported by three-dimensional (3D) uterine reconstruction in the coronal plane, offers a unique non-invasive view to examine the JZ and is an indispensable tool in infertility workup, especially in the presence of suspected adenomyosis.[10]

However, the actual influence of JZ's involvement on reproductive outcomes remains a matter of lively debate. In fact, a retrospective study has shown that US features of adenomyosis, defined according to the morphological uterus sonographic assessment (MUSA) consensus—including interruption or irregularity of the JZ—do not seem to affect the reproductive outcomes of patients undergoing embryo transfers (ETs) from donated oocytes.[11] In contrast to this, some authors have recently reported in a large cohort of patients who underwent ET with their own oocytes, that features localized in the inner myometrium, in particular an interrupted JZ, are more likely to reduce the likelihood of live birth, whereas localizations in the outer myometrium are associated with an increased likelihood of live birth.[12] Consistent to this, a recent prospective observational study showed that in adenomyosis patients undergoing single embryo transfer (SET) with donated oocytes, JZ involvement was an important risk factor for miscarriage.[13] However, it should be noted that this study did not focus exclusively on patients with isolated JZ involvement, which may have led to an underestimation—or, conversely, overestimation—of the actual influence of coinvolvement of this structure on ART outcomes.

The relationship between the manifestations of adenomyosis and the outcomes of conventional ET cycles is particularly complex to interpret. The difficulty lies in distinguishing the possible negative effects of the pathology from those attributable to the use of autologous oocytes. In this context, oocyte donation assumes a fundamental role, as it makes it possible to mitigate the problems associated with oocyte incompetence by highlighting more clearly any uterine factors contributing to infertility.

Considering these premises, the aim of the present retrospective analysis was to assess reproductive outcomes in patients with adenomyotic involvement of the JZ, diagnosed by two-dimensional (2D)/3D-TVUS, undergoing the first SET in an oocyte donation cycle.

2 | MATERIALS AND METHODS

2.1 | Institutional review board approval

On April 15, 2025, the Institutional Review Board of the Instituto Bernabeu (reference MR62) approved this study and waived the requirement for informed consent.

2.2 | Design and population

This retrospective single-center matched cohort study involved 240 infertile patients with an age of up to 50 years and a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) not exceeding 30, who underwent their SET using donated oocytes at the Instituto Bernabeu in Alicante, Spain, between December 2021 and June 2024.

All the participants were recruited during the first visit where a comprehensive history was collected for each patient, including data on medical history, surgical procedures, and gynecologic and obstetrical history. Information included age, BMI, number of previous infertility treatments and ETs, and outcomes of previous pregnancies, such as miscarriages, live births, and mode of delivery. To refine the approach for the first egg donation SET at Instituto Bernabeu, protocols used in previous other centers were carefully analyzed.

Before beginning the endometrial preparation, each patient underwent 2D-3D TVUS evaluations during the luteal phase of the cycle. Both 2D and 3D TVUS scans were employed to diagnose adenomyosis according with the morphological uterus sonographic assessment (MUSA) consensus.[14]

2.2.1 | Inclusion and exclusion criteria

Only patients with solely JZ involvement (in addition to the presence of at least one MUSA direct feature in the inner myometrium) were included in the study group. To minimize the influence of factors other than JZ adenomyotic involvement, patients with concomitant endometriosis, uterine fibroids of any size or location, müllerian anomalies, any endometrial pathology, thin endometrium (<6 mm), hydrosalpinx, previous uterine surgery, untreated endocrine disorders, severe dyspermia, double embryo transfer, or any SET other than the first were excluded. Sperm DNA fragmentation testing was not systematically performed in all cases and was therefore not used as a formal eligibility criterion. Women with known thrombophilia or coagulation disorders

were also excluded; however, universal thrombophilia screening was not performed unless clinically indicated. The same exclusion criteria were applied to the control group, which consisted of patients without adenomyosis and was established by matching each patient in the study group with an age-matched control at a 1:1 ratio.

2.3 | Ultrasound examination and adenomyosis diagnosis

All TVUS examinations were performed by a single experienced operator (BMR) within the endometriosis unit of Instituto Bernabeu, using the Voluson E8/E10 system (GE Healthcare, Chicago, IL, USA) equipped with a 5–9 MHz transvaginal volumetric probe, performed during the first visit, with patients in the lithotomy position and bladder emptied.

A standardized protocol was followed: the uterus was enlarged to fill three-quarters of the screen, the scan angle was set at 180°, and the scanning speed was optimized for high image quality. The 3D volume was configured to extend at least 2–3 cm beyond the uterine margins, with 2D acquisitions performed at 180° harmonic frequencies and 3D scans using a 120° arch to enhance resolution.

Additional imaging modalities—including tomographic ultrasound imaging (TUI), multiplanar mode, and OmniView—were employed to visualize the uterine coronal plane and identify signs indicative of adenomyosis. The diagnosis was initially established using 2D scans in accordance with the MUSA consensus criteria and later confirmed with 3D reconstruction.

The US analysis, based on MUSA consensus, differentiated between direct signs (indicating the presence of ectopic endometrial tissue) and indirect signs (reflecting secondary myometrial changes). The use of 3D imaging, which enables evaluation of the JZ from multiple planes, further enhanced diagnostic accuracy.

According to established criteria,[14] a diagnosis of adenomyosis required the presence of at least one direct feature, either alone or alongside indirect features. For inclusion in this study, patients diagnosed with adenomyosis had to exhibit at least one direct feature identified in the inner myometrium (echogenic subendometrial lines and buds, hyperechoic islands and cysts) associated exclusively with JZ alterations (irregularities and/or interruption plus the eventually presence of direct signs affecting the integrity of the JZ); patients showing direct features in other locations were excluded. The extent of the disease was subjectively assessed based on the estimated proportion of the JZ affected by adenomyosis and classified as mild (<25% of JZ surface involvement) (Figure 1a), moderate (25%–50% of JZ surface involvement) (Figure 1b), or severe (>50% of JZ surface involvement) (Figure 1c), as described by Van Den Bosch et al.[14,15] The sum of volumes of the different JZ lesions was estimated when describing the extent of the disease. Regarding the classification, adenomyotic lesions were defined as focal when >25% of the circumference of the lesion was surrounded by normal inner myometrium and diffuse when <25% of the circumference of the lesion was surrounded by normal inner myometrium. As pointed by Van Den Bosch et al.,[14,15] in case of any doubts, classification was defined as diffuse.

2.4 | Characteristics of oocyte donors

Oocyte donors were healthy volunteers under 32 years of age, with a BMI below 30 and regular menstrual cycles ranging from 26 to 35 days. They were recruited in accordance with established clinical protocols and the legal requirements set by the Spanish Law on Assisted Human Reproduction (RD 9/2014), which included psychological evaluations, gynecologic examinations, and screenings for infectious and genetic conditions. Although the use of oral contraceptives prior to stimulation was not mandatory, donors were asked about recent unprotected intercourse and advised to take precautions to avoid pregnancy during the treatment.

2.5 | Endometrial preparation protocol

Endometrial preparation was carried out using both artificial cycle (AC) and modified natural cycle (mNC). Once the endometrium was

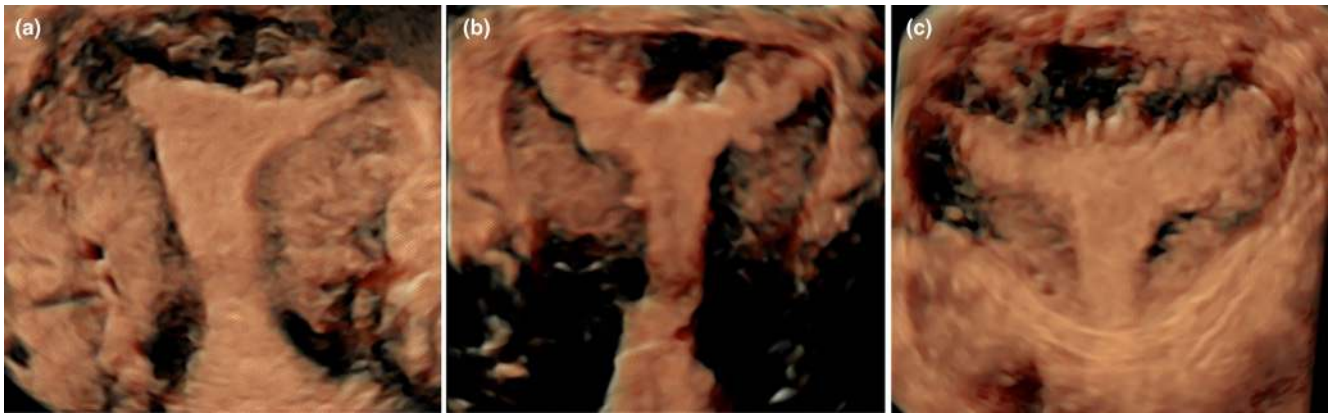

FIGURE 1 Extent of disease according to the estimated proportion of the junctional zone affected by adenomyosis. (a) Mild (<25% of the area of the junctional zone). (b) Moderate (25%–50% of the area of the junctional zone). (c) Severe (>50% of the area of the junctional zone).

prepared, a single high-quality blastocyst obtained at day 5 or 6 of development evaluated according to Gardner's classification system[16] was transferred. The ET protocol was documented, noting the endometrial preparation method, progesterone (P_4) levels on the day of ET, and whether fresh or frozen embryos were used.

2.5.1 | Modified natural cycle protocol

In cases with regular menstrual cycles, a mNC was applied. A baseline TVUS was conducted during the early follicular phase (days 1–3) to rule out any abnormalities. Follow-up monitoring around day 10 allowed for the evaluation of follicular growth. When a leading follicle measured between 17 and 22 mm and the endometrium presented a trilaminar pattern with a thickness of at least 7 mm, ovulation was induced with human chorionic gonadotropin (hCG). In these patients, vaginal P_4 supplementation (Cyclogest 400 mg, Gedeon Richter Iberica, Spain) was initiated 36 h after hCG administration, with the embryo transfer scheduled 7 days post-trigger. Serum β-hCG levels were measured 13 days after the ET, and a subsequent US at 5 weeks verified the presence of a gestational sac, while a fetal heartbeat detected at 12 weeks confirmed an ongoing pregnancy. Additionally, 3 days after the embryo transfer, serum P_4 levels were evaluated. In instances where P_4 was found to be below 9.2 ng/mL, patients received supplementary subcutaneous P_4 (Prolutex 25 mg; IBSA Pharma Limited, UK).[17]

2.5.2 | Hormonal replacement therapy protocol

For those undergoing AC, the process began with pituitary suppression using a single mid-luteal dose of a gonadotropin-releasing hormone agonist (Gonapeptyl 3.75 mg, Ferring, Saint-Prex, Switzerland). This was followed by a gradual estrogen regimen administered either through transdermal patches (Evopad 50 mcg, Janssen Pharmaceutica, Beerse, Belgium) or oral estradiol valerate (Progynova 2 mg, Bayer HealthCare Pharmaceutical, Whippany, Hanover, New Jersey, USA) over at least 12 days. Once US assessment confirmed an endometrial lining of 7 mm or more with a trilaminar structure, ET proceeded. Following confirmed fertilization, P_4 support (Cyclogest 400 mg every 12 h) was provided, with pregnancy monitoring comprising serum β-hCG testing 13 days after transfer, an US at 5 weeks to detect a gestational sac, and verification of a fetal heartbeat at 12 weeks. Hormonal support was maintained until the conclusion of the first trimester for confirmed pregnancies. Also in this case, 3 days post-ET, serum P_4 was measured, and if levels were below 9.2 ng/mL, additional subcutaneous progesterone (Prolutex 25 mg; IBSA Pharma Limited, UK) was administered.[17]

2.6 | Outcomes

The primary aim of this study was to determine whether involvement of the JZ by the adenomyosis affected the live birth rate (LBR) and miscarriage rate (MR) following the first SET. According to the International Glossary on Infertility and Fertility Care,[18] a live birth was defined as the complete delivery of an infant after at least 22 full weeks of gestation, with any sign of life. In the case of multiple pregnancies, each newborn was counted individually. The miscarriage was defined as the spontaneous loss of an intrauterine pregnancy before 22 full weeks of gestation. The secondary objectives were to investigate whether JZ adenomyosis was associated with a reduced implantation rate (IR) and whether the extent of disease led to poorer reproductive outcomes.

2.7 | Statistical analysis

A comprehensive statistical evaluation was performed using both descriptive and inferential approaches. Continuous data are expressed as the mean ± standard deviation (SD), while categorical data are summarized using frequencies and percentages. To compare continuous variables among groups, the student's *t*-test was applied, and for categorical variables, either the Chi-square or Fisher exact test was utilized as appropriate. In order to adjust for potential confounding factors, a multivariate logistic regression model was employed to pinpoint the independent variables that significantly affected the principal outcomes per SET. Relative risk (RR) along with its corresponding 95% confidence interval (CI) was also calculated. In every analysis, a *P* value below 0.05 was considered statistically significant.

A priori power analysis was conducted to determine the required sample size. Based on previous reports[13]—which did not show a reduction in the LBR but indicated a 17.3 percentage point increase in the MR in a setting comparable to our study—and setting an α error of 0.05 with an 80% power, a minimum of 102 subjects per group was deemed necessary. Our study surpassed this benchmark by including a total of 240 participants (120 in the control group and 120 in the group with JZ adenomyosis), ensuring adequate power to detect significant differences.

All statistical analyses were performed using R (version 4.2.0) and SPSS (version 23.0, Chicago, IL, USA).

3 | RESULTS

A total of 240 patients were included in the study, with 120 patients in each group. As shown in Table 1, baseline characteristics, including age (41.74 ± 3.70 vs 41.80 ± 4.17 years, $P = 0.91$), BMI (22.48 ± 6.35 vs 23.18 ± 5.12, $P = 0.35$), number of previous ovarian stimulations (2.98 ± 2.06 vs 2.57 ± 1.55, $P = 0.08$), and previous miscarriages (0.89 ± 1.22 vs 0.75 ± 4.05, $P = 0.72$), did not differ significantly between the control and adenomyosis groups. Similarly, the distribution of endometrial preparation protocols (AC: 65.00% vs 63.33%, $P = 0.79$; mNC: 35.00% vs 36.67%, $P = 0.79$), endometrial thickness, P_4 levels on the day of ET, and type of ET (fresh vs frozen, $P = 0.89$ for both) were comparable between groups.

Among patients diagnosed with adenomyosis, all cases involved the JZ exclusively. Within this group, the extent of JZ involvement

TABLE 1 Baseline characteristics of the included study population.

	No adenomyosis ($n=120$)	JZ adenomyosis ($n=120$)	*P* value
Patient characteristics			
Age, mean ± SD (years)	41.74 ± 3.70	41.80 ± 4.17	0.91
BMI, mean ± SD	22.48 ± 6.35	23.18 ± 5.12	0.35
Previous ovarian stimulation, mean ± SD (*n*)	2.98 ± 2.06	2.57 ± 1.55	0.08
Previous miscarriage, mean ± SD (*n*)	0.89 ± 1.22	0.75 ± 4.05	0.72
Embryo transfer and endometrial preparation			
Fresh ET, %	33.33% (40/120)	34.16% (41/120)	0.89
FET, %	66.67% (80/120)	65.83% (79/120)	0.89
AC, %	65.00% (78/120)	63.33% (76/120)	0.79
Endometrial thickness (AC), mean ± SD (mm)	8.69 ± 1.86	8.33 ± 1.33	0.08
P_4 ET day (AC), mean ± SD (ng/mL)	18.40 ± 11.56	20.57 ± 11.58	0.15
mNC, %	35.00% (42/120)	36.67% (44/120)	0.79
Endometrial thickness (mNC), mean ± SD (mm)	8.83 ± 1.92	8.52 ± 1.33	0.16
P_4 ET day (mNC), mean ± SD (ng/mL)	21.68 ± 11.20	20.56 ± 8.99	0.39

Note: BMI, calculated as weight in kilograms divided by the square of height in meters.

Abbreviations: AC, artificial cycle; BMI, body mass index; ET, embryo transfer; FET, frozen embryo transfer; JZ, junctional zone; mNC, modified natural cycle; P_4, progesterone; SD, standard deviation.

TABLE 2 ART outcomes per SET.

	No adenomyosis	Adenomyosis	*P* value
Implantation rate, %	75.00% (90/120)	68.33% (82/120)	0.25
Biochemical miscarriage rate%	15.83% (19/120)	11.67% (14/120)	0.35
Live birth rate, %	50.83% (61/120)	34.16% (41/120)	**0.009**
Miscarriage rate, %	11.11% (10/90)	32.93% (27/82)	**<0.001**

Note: Bold values denote statistical significance.

Abbreviations: ART, assisted reproductive technologies; SET, single embryo transfer.

was categorized as mild (<25% of JZ) in 35.83% of cases, moderate (25%–50% of JZ) in 33.33%, and severe (>50% of JZ) in 30.83%. Regarding the differentiation, all the mild JZ involvement and three moderate JZ involvement were judged as focal since >25% of the circumference of the lesion was surrounded by normal inner myometrium; 10 patients with moderate JZ involvement were classified as mixed types (focal + diffuse); 27 patients with moderate JZ involvement and all the severe JZ involvement were classified as diffuse since >75% of the surrounding inner myometrium resulted affected.

ART outcome analysis per SET showed that the IR was 75.00% in the control group compared to 68.33% in the adenomyosis group ($P=0.25$), and the biochemical miscarriage rate was 15.83% versus 11.67% ($P=0.35$). However, the LBR was significantly lower in the adenomyosis group (34.16%) than in the control group (50.83%, $P=0.009$), while the MR was significantly higher when JZ was affected (32.93% vs 11.11%, $P<0.001$) (Table 2).

Multivariate logistic regression analysis, which adjusted for age, endometrial preparation protocol, endometrial thickness, P_4 levels on the day of ET, and type of ET, demonstrated that JZ adenomyosis was independently associated with a decreased likelihood of live birth (odds ratio [OR] = 0.4272, 95% CI: 0.2389–0.7642, $P=0.004$) (Table 3) and an increased risk of miscarriage (OR = 3.3278, 95% CI: 1.4169–7.8155, $P=0.005$) (Table 4).

Subgroup analyses of patients with adenomyosis revealed that, when assessing the RR for maintaining an ongoing pregnancy versus miscarriage, the solely adenomyotic involvement of the JZ had an RR of 0.45 (95% CI: 0.22–0.88, $P=0.01$). With respect to the extent of JZ adenomyosis, the RR for ongoing pregnancy was 0.85 (95% CI: 0.40–1.78, $P=0.62$) in cases with mild involvement, 0.65 (95% CI: 0.33–1.27, $P=0.21$) in moderate cases, and 0.17 (95% CI: 0.04–0.67, $P=0.007$) in severe cases (Table 5). Conversely, analysis of the risk of losing the pregnancy showed RRs of 2.20 (95% CI: 1.10–4.41, $P=0.008$) for the evaluation of the localization of the adenomyosis (JZ only), 1.32 (95% CI: 0.43–4.05, $P=0.58$) for mild, 2.41 (95% CI: 1.05–5.55, $P=0.04$) for moderate, and 4.05 (95% CI: 1.78–9.12, $P=0.001$) for severe involvement of the JZ (Table 5).

4 | DISCUSSION

Our results showed that women with JZ adenomyosis underwent the first SET with donated oocytes presented a significantly lower

TABLE 3 Multivariate analysis assessing the effect of possible confounders on live birth per SET.

Variable	*B*	SE	*z*	Odds ratio	95% CI	*P* value
Adenomyosis	**−0.8504**	**0.2966**	**−2.8663**	**0.4272**	**(0.2389, 0.7642)**	**0.004**
Age	−0.0674	0.0354	−1.9055	0.9348	(0.8721, 1.0019)	0.07
Endometrial preparation (mNC or AC)	−0.0717	0.0819	−0.8758	0.9308	(0.7927, 1.0929)	0.38
Endometrial thickness	−0.0064	0.0124	−0.5197	0.9936	(0.9696, 1.0181)	0.60
P_4 day of the transfer	0.3223	0.2851	1.1307	1.3804	(0.7894, 2.4137)	0.26
ET type (fresh or FET)	0.1171	0.2873	0.4075	1.1243	(0.6401, 1.9747)	0.68

Note: Bold values denote statistical significance.

Abbreviations: AC, artificial cycle; B, beta coefficient; CI, confidence interval; ET, embryo transfer; FET, frozen embryo transfer; mNC, modified natural cycle; P_4, progesterone; SE, standard error; SET, single embryo transfer.

TABLE 4 Multivariate analysis assessing the effect of possible confounders on miscarriage per SET.

Variable	*B*	SE	*z*	Odds ratio	95% CI	*P* value
Adenomyosis	**1.2022**	**0.4356**	**2.7599**	**3.3278**	**(1.4169, 7.8155)**	**0.005**
Age	−0.0273	0.0488	−0.5606	0.9730	(0.8842, 1.0707)	0.57
Endometrial preparation (mNC or AC)	0.1704	0.1093	1.5588	1.1858	(0.9571, 1.4691)	0.12
Endometrial thickness	0.0134	0.0158	0.8470	1.0136	(0.9825, 1.0456)	0.40
P_4 day of the transfer	0.2405	0.3894	0.6176	1.2719	(0.5929, 2.7286)	0.54
ET type (fresh of FET)	−0.0428	0.3949	−0.1084	0.9581	(0.4418, 2.0777)	0.91

Note: Bold values denote statistical significance.

Abbreviations: AC, artificial cycle; B, beta coefficient; CI, confidence interval; ET, embryo transfer; FET, frozen embryo transfer; mNC, modified natural cycle; P_4, progesterone; SE, standard error; SET, single embryo transfer.

TABLE 5 Comparison of the relative risk of maintaining and losing pregnancy.

	Ongoing pregnancy (*n* = 41)	Miscarriage (*n* = 27)	RR	95% CI	*P* value
Maintaining pregnancy					
Location of the adenomyosis					
JZ only (*n* = 68)	41	27	**0.45**	**(0.22–0.88)**	**0.01**
Extent of adenomyosis					
Mild (<25% of JZ) (*n* = 30)	25	5	0.85	(0.40–1.78)	0.62
Moderate (25%–50% of JZ) (*n* = 18)	11	7	0.65	(0.33–1.27)	0.21
Severe (>50% of JZ) (*n* = 20)	5	15	**0.17**	**(0.04–0.67)**	**0.007**
Losing pregnancy					
Location of the adenomyosis					
JZ only (*n* = 68)	41	27	**2.20**	**(1.10–4.41)**	**0.008**
Extent of adenomyosis					
Mild (<25% of JZ) (*n* = 30)	25	5	1.32	(0.43–4.05)	0.58
Moderate (25%–50% of JZ) (*n* = 18)	11	7	**2.41**	**(1.05–5.55)**	**0.04**
Severe (>50% of JZ) (*n* = 20)	5	15	**4.05**	**(1.78–9.12)**	**0.001**

Note: Bold values denote statistical significance.

Abbreviations: CI, confidence interval; JZ, junctional zone; RR, relative risk.

LBR and a higher MR, with the relative risk of pregnancy loss increasing with the extent of JZ involvement by disease.

To our knowledge, this study represents the first work entirely dedicated to the analysis of the impact of JZ changes due to adenomyosis on reproductive outcomes in women undergoing ET derived from donated oocytes. The diagnosis of adenomyosis in the JZ was performed by a single experienced operator, TVUS and an in-depth evaluation of 3D reconstructions. Confirming the current evidence, our results indicate that the presence of JZ adenomyosis is a relevant risk factor for miscarriage, the severity of which varies depending

on the extent of the disease.[13] However, in contrary to them, we also show that invasion of the JZ by endometrial tissue may contribute to the reduction of LBR. The results of our study are therefore consistent with the editorial by Donnez and Dolmans,[19] in which, in addition to discussing whether and how adenomyosis affects ART outcomes, they point out that if women with adenomyosis have a higher MR, one would logically expect a lower LBR.

The JZ is a highly specialized area, located between the endometrium and inner myometrium, with a crucial role in the very early stages of reproduction.[20] Endowed with high sensitivity to sex hormones, the JZ coordinates uterine contractions and regulates blood perfusion, supporting the preparation of the uterus for embryo implantation.[21] During the implantation window, this region undergoes specific structural and functional modifications, in close cooperation with the endometrium, in order to create a suitable environment for trophoblastic adhesion and invasion.[8] In adenomyosis, on the other hand, endometrial tissue abnormally invades the myometrium, causing a thickening and disorganization of the JZ.[22] Moreover, the chronic inflammatory state characteristic of adenomyosis can alter the molecular and immunological signals that regulate endometrial development and the dialogue between uterus and embryo. On these premises, several in vitro and in vivo theories have been postulated that have related the damaging effects of adenomyosis to embryo implantation, including decreased levels of integrin alpha-1, integrin beta-1, and laminin gamma-1 subunit expression,[23] altered TGF- β1 expression[24] and altered HOXA-10 gene function during the implantation window,[25] altered endometrial-myometrial vascular growth,[26] and increased prostaglandin levels in ectopic endometrial epithelium.[27]

An important finding of our study is the dissociation between implantation and subsequent pregnancy maintenance. Although implantation rates were not significantly reduced, miscarriage rates were markedly higher and live birth rates lower in women with JZ adenomyosis.[13,28] This pattern suggests that JZ adenomyosis may not primarily compromise the earliest steps of embryo apposition and attachment, especially in donor-oocyte SET cycles in which embryo quality is expected to be high, but rather the post-implantation processes required to sustain early pregnancy.

A plausible explanation is that the altered JZ microenvironment allows initial implantation to occur but impairs decidualization, trophoblast invasion, and early placentation. The JZ is crucial for coordinated uterine peristalsis, local vascular regulation, and endometrial-myometrial cross-talk.[29] When distorted by adenomyosis, this region may exhibit abnormal contractility, chronic inflammation, progesterone resistance, altered cytokine signaling, and defective remodeling of the spiral arteries.[30] These abnormalities may be insufficient to prevent formation of a gestational sac, yet sufficient to compromise placental anchoring and perfusion during the following weeks, thereby increasing the risk of miscarriage.[31]

This interpretation is consistent with experimental and translational evidence showing impaired receptivity/decidualization signaling in adenomyosis, including reduced HOXA-10 and LIF expression, altered integrin and TGF-β pathways, and structural absence of pinopods in adenomyosis-derived endometrial models.[32] Together, these findings support the concept that adenomyosis-related reproductive failure may be expressed more strongly as defective pregnancy progression than as failed implantation per se. In other words, the biological impact of JZ adenomyosis may emerge after implantation, when stable maternal-fetal interface development and early placentation become critical.[19,33]

Thus, functional alterations in the JZ may contribute to poor reproductive outcomes, suggesting a correlation between adenomyosis and difficulty in achieving evolutionary pregnancies.

Indeed, consistent to our study, several authors had already observed increased MR and reduced LBR in patients with adenomyosis.[34–37] However, the MUSA consensus for diagnosis was not systematically adopted in many of these studies, compromising the uniformity of diagnostic criteria.[38,39] In addition, specific analysis of individual portions of myometrium involved by adenomyosis was often absent or relegated to a marginal role and conducted on small cohorts.

Studies that have attempted to assess the impact of US features defined by the MUSA consensus on reproductive outcomes have also reported mixed results; moreover, none have examined the effect of individual US features in isolation.[11,12]

Hence the need to focus attention on a very specific structure of the uterus—the JZ—which has long been recognized as playing a central role in the mechanisms of reproduction. Paradoxically, however, this region has never been the subject of systematic, in-depth study in a well-defined clinical setting, leaving many questions about its real impact on pregnancy outcomes unanswered until now.

A major strength of this study was the rigorous selection of participants, which minimized confounding variables by including only patients undergoing their first SET with donated oocytes. The exclusive focus on JZ adenomyosis, diagnosed by analysis of MUSA consensus US features using both 2D and 3D TVUS by a single experienced operator, further contributes to the robustness and reproducibility of the results. However, the fact that the analysis was conducted retrospectively and that the study was conducted in a single center may introduce bias and limit the generalizability of the results. In addition, although the extent of disease was classified, its subjective assessment may introduce some variability in classification. Moreover, although TVUS performed by an expert may give similar results to MRI, as not all centers have experienced sonographers, another criticism could be the fact that MRI was not used to confirm TVUS data. Finally, another limitation is that sperm DNA fragmentation was not systematically assessed in all couples and therefore could not be included in the multivariable models. However, severe male factor infertility was excluded based on routine semen analysis in order to reduce the potential impact of sperm-related confounding.

5 | CONCLUSIONS

The results of this study show how JZ adenomyosis can negatively affect reproductive outcomes in patients undergoing the first SET with donated oocytes. In particular, the presence of JZ involvement

was found to be associated with a significantly increased risk of miscarriage and decrease in the LBR. These observations suggest the importance of accurate US assessment of the JZ prior to treatment in order to identify patients at increased risk. A detailed classification of the extent and site of adenomyosis could also allow more personalized management and targeted therapeutic strategies, helping to improve both counseling and reproductive planning.

AUTHOR CONTRIBUTIONS

AE contributed to the conception and design of the study. BMR performed all ultrasound examinations, data acquisition and to data analysis and interpretation. AE and VA drafted the manuscript. AM, JCCF and ABG revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The dataset used and analyzed during the current study is partially available due to data loss that occurred after completion of the analyses. The available data supporting the findings of this study are retained by Dr. Belen Moliner and can be shared upon reasonable request. The results presented in this manuscript are based on the complete dataset as originally collected and analyzed prior to the data loss.

ORCID

Andrea Etrusco https://orcid.org/0000-0001-7414-4224

REFERENCES

1. Bergeron C, Amant F, Ferenczy A. Pathology and physiopathology of adenomyosis. *Best Pract Res Clin Obstet Gynaecol*. 2006;20:511-521. doi:10.1016/j.bpobgyn.2006.01.016
2. Khan KN, Kitajima M, Hiraki K, et al. Cell proliferation effect of GnRH agonist on pathological lesions of women with endometriosis, adenomyosis and uterine myoma. *Hum Reprod*. 2010;25:2878-2890. doi:10.1093/humrep/deq240
3. Etrusco A, Agrifoglio V, D'Amato A, et al. Efficacy and safety of hormone therapies for treating adenomyosis-associated pelvic pain: a systematic review and network meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne)*. 2025;16:1571727. doi:10.3389/fendo.2025.1571727
4. Vercellini P, Viganò P, Bandini V, Buggio L, Berlanda N, Somigliana E. Association of endometriosis and adenomyosis with pregnancy and infertility. *Fertil Steril*. 2023;119:727-740. doi:10.1016/j.fertnstert.2023.03.018
5. Cozzolino M, Tartaglia S, Pellegrini L, Troiano G, Rizzo G, Petraglia F. The effect of uterine adenomyosis on IVF outcomes: a systematic review and meta-analysis. *Reprod Sci*. 2022;29:3177-3193. doi:10.1007/s43032-021-00818-6
6. Tocci A, Greco E, Ubaldi FM. Adenomyosis and "endometrial-subendometrial myometrium unit disruption disease" are two different entities. *Reprod Biomed Online*. 2008;17:281-291. doi:10.1016/s1472-6483(10)60207-6
7. García-Solares J, Donnez J, Donnez O, Dolmans M-M. Pathogenesis of uterine adenomyosis: invagination or metaplasia? *Fertil Steril*. 2018;109:371-379. doi:10.1016/j.fertnstert.2017.12.030
8. Brosens I, Derwig I, Brosens J, Fusi L, Benagiano G, Pijnenborg R. The enigmatic uterine junctional zone: the missing link between reproductive disorders and major obstetrical disorders? *Hum Reprod*. 2010;25:569-574. doi:10.1093/humrep/dep474
9. Ni X, Su X, Shi Y, et al. Association between adenomyosis volume and adverse perinatal outcomes: multicenter cohort study. *Ultrasound Obstet Gynecol*. 2024;64:678-686. doi:10.1002/uog.29108
10. Exacoustos C, Luciano D, Corbett B, et al. The uterine junctional zone: a 3-dimensional ultrasound study of patients with endometriosis. *Am J Obstet Gynecol*. 2013;209:248.e1-248.e7. doi:10.1016/j.ajog.2013.06.006
11. Dason ES, Maxim M, Hartman A, et al. Pregnancy outcomes with donor oocyte embryos in patients diagnosed with adenomyosis using the morphological uterus sonographic assessment criteria. *Fertil Steril*. 2023;119:484-489. doi:10.1016/j.fertnstert.2022.12.021
12. Alson S, Henic E, Hansson SR, Sladkevicius P. Correlation of adenomyosis features to live birth rates after the first IVF/ICSI treatment, when using the revised morphological uterus sonographic assessment group definitions. *Acta Obstet Gynecol Scand*. 2024;103:2540-2553. doi:10.1111/aogs.14986
13. Cozzolino M, Cosentino M, Loiudice L, et al. Impact of adenomyosis on in vitro fertilization outcomes in women undergoing donor oocyte transfers: a prospective observational study. *Fertil Steril*. 2024;121:480-488. doi:10.1016/j.fertnstert.2023.11.034
14. Van den Bosch T, Dueholm M, Leone FPG, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) Group. *Ultrasound Obstet Gynecol*. 2015;46:284-298. doi:10.1002/uog.14806
15. Van den Bosch T, de Bruijn AM, de Leeuw RA, et al. Sonographic classification and reporting system for diagnosing adenomyosis. *Ultrasound Obstet Gynecol*. 2019;53:576-582. doi:10.1002/uog.19096
16. Gardner DK, Lane M, Stevens J, Schlenker T, Schoolcraft WB. Reprint of: blastocyst score affects implantation and pregnancy outcome: towards a single blastocyst transfer. *Fertil Steril*. 2019;112:e81-e84. doi:10.1016/j.fertnstert.2019.08.077
17. Labarta E, Mariani G, Rodríguez-Varela C, Bosch E. Individualized luteal phase support normalizes live birth rate in women with low progesterone levels on the day of embryo transfer in artificial endometrial preparation cycles. *Fertil Steril*. 2022;117:96-103. doi:10.1016/j.fertnstert.2021.08.040
18. Zegers-Hochschild F, Adamson GD, Dyer S, et al. The international glossary on infertility and fertility care, 2017. *Fertil Steril*. 2017;108:393-406. doi:10.1016/j.fertnstert.2017.06.005
19. Donnez J, Dolmans M-M. Uterine adenomyosis: is there an impact on in vitro fertilization outcomes? *Fertil Steril*. 2024;121:442-443. doi:10.1016/j.fertnstert.2023.12.027
20. Brosens JJ, de Souza NM, Barker FG. Uterine junctional zone: function and disease. *Lancet*. 1995;346:558-560. doi:10.1016/s0140-6736(95)91387-4
21. Ng EHY, Chan CCW, Tang OS, Yeung WSB, Ho PC. The role of endometrial and subendometrial vascularity measured by three-dimensional power Doppler ultrasound in the prediction of pregnancy during frozen-thawed embryo transfer cycles. *Hum Reprod*. 2006;21:1612-1617. doi:10.1093/humrep/dei502
22. Wang S, Duan H. The role of the junctional zone in the management of adenomyosis with infertility. *Front Endocrinol (Lausanne)*. 2023;14:1246819. doi:10.3389/fendo.2023.1246819

23. Li Y, Zhang D, Jin B, Xia L, Zhang A. Proteomic analysis of uterine tissues during peri-implantation period in mice with experimentally induced adenomyosis that treated with anti-NGF: implications for cell-cell adhesion and metabolic processes. *Reprod Sci*. 2021;28:207-217. doi:10.1007/s43032-020-00262-y
24. Kay N, Huang C-Y, Shiu L-Y, et al. TGF-β1 neutralization improves pregnancy outcomes by restoring endometrial receptivity in mice with adenomyosis. *Reprod Sci*. 2021;28:877-887. doi:10.1007/s43032-020-00308-1
25. Wang J, Huang C, Jiang R, et al. Decreased endometrial IL-10 impairs endometrial receptivity by downregulating HOXA10 expression in women with adenomyosis. *Biomed Res Int*. 2018;2018:2549789. doi:10.1155/2018/2549789
26. Shen M, Liu X, Zhang H, Guo S-W. Transforming growth factor β1 signaling coincides with epithelial-mesenchymal transition and fibroblast-to-myofibroblast transdifferentiation in the development of adenomyosis in mice. *Hum Reprod*. 2016;31:355-369. doi:10.1093/humrep/dev314
27. Ota H, Igarashi S, Sasaki M, Tanaka T. Distribution of cyclooxygenase-2 in eutopic and ectopic endometrium in endometriosis and adenomyosis. *Hum Reprod*. 2001;16:561-566. doi:10.1093/humrep/16.3.561
28. Benaglia L, Cardellicchio L, Leonardi M, et al. Asymptomatic adenomyosis and embryo implantation in IVF cycles. *Reprod Biomed Online*. 2014;29:606-611. doi:10.1016/j.rbmo.2014.07.021
29. Barbanti C, Centini G, Lazzeri L, et al. Adenomyosis and infertility: the role of the junctional zone. *Gynecol Endocrinol*. 2021;37:577-583. doi:10.1080/09513590.2021.1878131
30. Brosens I, Pijnenborg R, Benagiano G. Defective myometrial spiral artery remodelling as a cause of major obstetrical syndromes in endometriosis and adenomyosis. *Placenta*. 2013;34:100-105. doi:10.1016/j.placenta.2012.11.017
31. Norwitz ER. Defective implantation and placentation: laying the blueprint for pregnancy complications. *Reprod Biomed Online*. 2007;14(1):101-109. doi:10.1016/S1472-6483(10)61464-2
32. Stratopoulou CA, Rossi M, Beaussart C, et al. Generation of epithelial-stromal assembloids as an advanced in vitro model of impaired adenomyosis-related endometrial receptivity. *Fertil Steril*. 2025;123:350-360. doi:10.1016/j.fertnstert.2024.08.339
33. Stratopoulou CA, Cussac S, d'Argent M, Donnez J, Dolmans M-M. M2 macrophages enhance endometrial cell invasiveness by promoting collective cell migration in uterine adenomyosis. *Reprod Biomed Online*. 2023;46:729-738. doi:10.1016/j.rbmo.2023.01.001
34. Stanekova V, Woodman RJ, Tremellen K. The rate of euploid miscarriage is increased in the setting of adenomyosis. *Hum Reprod Open*. 2018;2018:hoy011. doi:10.1093/hropen/hoy011
35. Sharma S, Bathwal S, Agarwal N, Chattopadhyay R, Saha I, Chakravarty B. Does presence of adenomyosis affect reproductive outcome in IVF cycles? A retrospective analysis of 973 patients. *Reprod Biomed Online*. 2019;38:13-21. doi:10.1016/j.rbmo.2018.09.014
36. Neal S, Morin S, Werner M, et al. Three-dimensional ultrasound diagnosis of adenomyosis is not associated with adverse pregnancy outcome following single thawed euploid blastocyst transfer: prospective cohort study. *Ultrasound Obstet Gynecol*. 2020;56:611-617. doi:10.1002/uog.22065
37. Martínez-Conejero JA, Morgan M, Montesinos M, et al. Adenomyosis does not affect implantation, but is associated with miscarriage in patients undergoing oocyte donation. *Fertil Steril*. 2011;96:943-950. doi:10.1016/j.fertnstert.2011.07.1088
38. Costello MF, Lindsay K, McNally G. The effect of adenomyosis on in vitro fertilisation and intra-cytoplasmic sperm injection treatment outcome. *Eur J Obstet Gynecol Reprod Biol*. 2011;158:229-234. doi:10.1016/j.ejogrb.2011.04.030
39. Mijatovic V, Florijn E, Halim N, Schats R, Hompes P. Adenomyosis has no adverse effects on IVF/ICSI outcomes in women with endometriosis treated with long-term pituitary down-regulation before IVF/ICSI. *Eur J Obstet Gynecol Reprod Biol*. 2010;151:62-65. doi:10.1016/j.ejogrb.2010.02.047

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