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Women with combined adenomyosis and endometriosis on MRI have worse IVF/ICSI outcomes compared to adenomyosis and endometriosis alone: A matched retrospective cohort study

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ABSTRACT

Study objectives: To assess the effect of adenomyosis, endometriosis and combined adenomyosis and endometriosis, diagnosed on MRI, on IVF/ICSI outcomes versus male subfertility controls.
Study Design: This single-centre matched retrospective cohort study was carried out at Catharina Hospital in Eindhoven, The Netherlands. The study group consisted of infertile women undergoing their first, fresh embryo transfer during IVF/ICSI, with adenomyosis only (N = 36), endometriosis only (N = 61), and combined adenomyosis and endometriosis (N = 93) based on MRI. The control group consisted of IVF/ICSI patients undergoing treatment due to male subfertility (N = 889). 1:2 case-control matching based on age during IVF/ICSI, parity and number of embryos transferred was performed. Odds ratios were calculated for biochemical pregnancy, ongoing pregnancy and live birth rate versus matched male subfertility controls, and were corrected for embryo quality.
Results: Only the combined adenomyosis and endometriosis group showed a significantly reduced OR for biochemical pregnancy (p = 0.004, OR 0.453 (95% CI :(0.284–0.791)), ongoing pregnancy (p = 0.001, OR 0.302 (95% CI: (0.167–0.608)) and live birth (p = 0.001, OR 0.309 (95% CI: (0.168–0.644)) compared to matched male subfertility controls.
Conclusions: The lower (ongoing) pregnancy and live birth rates in the combined adenomyosis and endometriosis women can be attributed to more severe disease in these women, ultimately resulting in increased chances for failed implantation and miscarriage. This highlights the importance of screening for adenomyosis in endometriosis patients, and identifies these women target for additional (hormonal) treatment prior to IVF/ICSI.

Introduction

Adenomyosis is a common benign uterine disorder characterised by invasion of the endometrium into the myometrium and is thought to arise from the junctional zone (JZ). Adenomyosis is often found in conjunction with endometriosis and may share aetiological mechanisms, such as metaplasia of mullerian remnants [1].

Historically, adenomyosis was thought of as a disease affecting multiparous women, however with the advent of improved imaging techniques, it is also increasingly being linked to reproductive failure and infertility alongside endometriosis [2,3]. Adenomyosis may have a higher prevalence in sub-fertile populations than expected, with a reported prevalence as high as 32% in infertile women [4–6].

Several theories exist to explain why women with adenomyosis may have reduced fertility. First, through disruption of the JZ, adenomyosis affects uterine contractions and thereby spermatozoa transport and embryo implantation due to the alterations in the JZ [7,8]. The junctional zone is believed to be vital for uterine contraction initiation and modulation in the menstrual cycle [9,10]. Alterations in the function and receptivity of the endometrium have also been reported in

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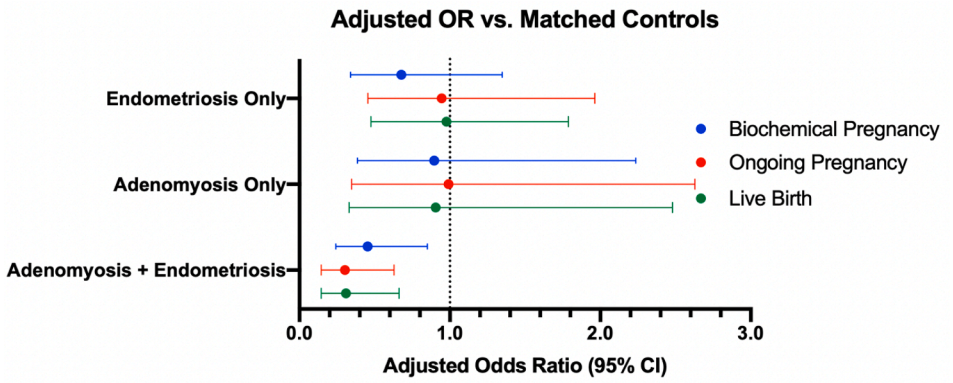

Fig. 2. Forest plots of biochemical pregnancy, ongoing pregnancy and live birth after matching. The forest plots depict the OR for a biochemical pregnancy, ongoing pregnancy and live birth for the study subgroups and full study group (all study subgroups together). Detailed values can be found in Appendix E.

adenomyosis patients [11–13]. Abnormal inflammatory responses have additionally been described, leading to embryo toxicity [14]. Finally, anatomical changes of the uterine cavity are also thought to have an influence on embryo implantation [12].

Many women with adenomyosis also have (other forms of) endometriosis, which makes it difficult to assess whether the influence on infertility is due primarily to adenomyosis, endometriosis or a combination of both [15]. It can be hypothesised, that when the two conditions occur together, the whole reproductive process is affected, with endometriosis affecting oocytes and fertilisation, and adenomyosis embryo implantation and the ongoing pregnancy [16]. Few studies exist which have simultaneously investigated the separate *and* combined effect of endometriosis and adenomyosis on fertility outcomes. Moreover, despite magnetic resonance imaging (MRI) reported to be the most accurate and reproducible non-invasive diagnostic method for adenomyosis and endometriosis with a sensitivity of up to 88% and specificity of up to 91% [17,18], few studies have included patients diagnosed by this method, favouring self-reported diagnosis or diagnosis by transvaginal ultrasound (TVUS, [16]).

We suggest that there is therefore a need to investigate how fertility outcomes are affected by the presence of only endometriosis, only adenomyosis or both, as visualized on MRI. As such, we carried out a retrospective cohort study comparing IVF/ICSI outcomes in women with MRI-diagnosed adenomyosis and/or endometriosis, compared to matched male infertility controls.

Materials and methods

Study design and setting

This single-centre retrospective cohort study was set at the Catharina Hospital in Eindhoven, The Netherlands, a regional referral centre between the years of 2008 and 2020.

Participants

Patients were women aged 18 to 42 years undergoing their first, fresh embryo transfer during IVF/ICSI. After meeting the local IVF/ICSI treatment eligibility requirements (see Appendix F), women in our centre received the same standard treatment. Pituitary downregulation was initiated with a recombinant GnRH agonist (Decapeptyl, Ferring Pharmaceuticals, Hoofddorp, the Netherlands), followed by ovarian stimulation using either recombinant follicle stimulating hormone (Gonal-F, *Merck KGaA, Darmstadt, Germany*) or human menopausal gonadotrophin (Menopur, Ferring Pharmaceuticals, Hoofddorp, the Netherlands; Fostimon, Goodlife Pharma, Lelystad, the Netherlands) at a standard starting dose of 150 IE/mL. Oocytes were fertilised on the same day as oocyte retrieval, either by IVF or ICSI (see Appendix F). Embryo transfer (single or double) took place three days after oocyte retrieval, after administration of human chorionic gonadotrophin (HCG, Pregnyl, *Merck KGaA, Darmstadt, Germany*) boost. Selection of the best quality (cleavage-stage) embryos was carried out according to local and alpha scoring criteria (see Appendix E). Luteal support was initiated with intravaginal progesterone (Utrogestan, *Besins Healthcare, Utrecht, the Netherlands*). See Appendix F for full details of local IVF/ICSI treatment protocol.

Study group

The study group included IVF/ICSI patients diagnosed with adenomyosis, endometriosis or both in the period of 2008 to 2020 on MRI. MRI consisted of T2-weighted images in axial, coronal and sagittal planes as well as axial T1-weighted images. Slight variations in protocol existed, however without significant implications for diagnostic quality. MRI criteria for the presence of adenomyosis were: focal or diffuse JZ thickening > 12 mm, JZ/myometrium ratio > 40%, and/or presence of high signal intensity myometrial foci on T1/T2 corresponding to an adenomyotic cyst (>2mm in diameter). MRI criteria for endometriosis were any of the following: presence of a solid (invasive) hypointense lesion (with or without high signal intensity foci on T1/T2) outside the uterine cavity corresponding to adhesive endometriosis plaques; hyperintense (multiple) ovarian cysts on T1, or one or more cysts with high T1 signal intensity and shading on T2 corresponding to haemorrhagic endometriomas.

All pelvic MRIs carried out in women of a fertile age during the study period were re-evaluated by a study investigator (CR) and three pelvic radiologists, and were assigned to either an adenomyosis only, endometriosis only or combined endometriosis and adenomyosis sub-group. Subsequently, patient records of women with MRI-confirmed adenomyosis and/or endometriosis were assessed to identify women who underwent IVF or ICSI procedures in our centre. In the case of multiple MRIs, the one performed closest to IVF/ICSI treatment was assessed.

Women were excluded in case there was no MRI or IVF/ICSI data, if no embryo transfer took place, or if they objected to the use of their medical data.

Control group

For the control group, women between 18 and 42 years old who underwent their first, fresh IVF/ICSI cycle with embryo transfer between 2008 and 2020 due to confirmed male subfertility were included. Adenomyosis was assumed as not present if the patient had no reported uterine abnormalities and no reported history of symptoms associated with adenomyosis or endometriosis. Patients were excluded if no embryo transfer took place (e.g. freeze all, IVF cancellation), if there were signs of adenomyosis on TVUS or MRI (if available), or if they objected to use of their medical data.

Table 1
Patient Characteristics before Matching.

		Adenomyosis (N = 36)	Endometriosis (N = 61)	Combined (N = 93)	Control (N = 889)	P-value
BMI in kg/m^2 (Median, IQR)		23.59 IQR: 7.76	23.03 IQR: 6.52	23.94 IQR: 6.21	23.63 IQR: 5.61	0.284[2]
Infertility time in months* (Mean, SD)		37.00 IQR: 30	27.50 IQR: 28	31.00 IQR: 23	28.00 IQR: 22	0.236[2]
Age during IVF (Mean, SD)		33.75 (±3.61)	30.92 (±4.03)	31.23 (±4.11)	31.47 (±4.47)	0.012[1]
Cycle length (Median, IQR)		29.00 IQR: 3	28.00 IQR: 3	28.00 IQR: 2	28.00IQR: 2	0.260[2]
Age at MRI		37.71 (±4.32)	32.43 (±4.94)	34.04 (±5.71)	Not applicable	<0.0005
Type of subfertility*	Primary	18 (50.0 %) $_a$	46 (76.7 %) $_b$	65 (69.1 %) $_{a, b}$	616 (69.4%) $_{a, b}$	<0.0005[3]
	Secondary	15 (41.7 %) $_a$	13 (21.7 %) $_a$	23 (24.5 %) $_a$	272 (30.6%) $_a$	
	Unknown	3 (8.3%)	1 (1.7%)	6 (6.4%)	1	
Indication**	Male	11 (30.6 %) $_a$	9 (15.0%) $_a$	12 (12.8 %) $_a$	889 (100%) $_b$	<0.0005[3]
	Female	5 (13.9 %) $_a$	10 (16.7%) $_a$	9 (9.6%) $_a$	$_b$	
	* Ovulatory disorder	1 (3.0 %)	3 (5.0%)	6 (7.1%)		
	* Tubal factor	1 (3.0 %)	7 (11.7%)	7 (8.2%)		
	Combined Male and Female factor	4 (11.1 %) $_a$	21 (35.0 %) $_b$	24 (25.5%) $_{a, b}$	$_c$	
	Endometriosis	5 (15.2 %) $_a$	22 (36.7 %) $_b$	36 (38.3%) $_b$	$_c$	
	Idiopathic	7 (21.2%) $_a$	5 (8.3 %) $_b$	12 (12.8%) $_b$	$_c$	
Dysmenorrhoea	Yes	8 (22.2%) $_{a, b}$	37 (61.7%) $_c$	48(51.1%) $_{b, c}$	165 (18.6%) $_a$	<0.0005[3]
	No	15 (41.7%) $_{a, b}$	13 (21.7%) $_c$	25 (26.6%) $_{b, c}$	584 (65.7%) $_a$	
	Unknown	13 (36.1%)	10 (16.7%)	21 (22.3%)	140 (15.7%)	
Endometriosis Treatment prior to IVF/ICSI	No treatment	15 (45.5%)	20 (33.3%)	29 (34.1%)	0 (0)	
	Oral contraceptive pill	4 (12.1%)	12 (20.0%)	7 (8.2%)	0 (0)	
	Hormonal Intra-uterine device	0 (0.0%)	3 (5.0%)	1 (1.2%)	0 (0)	
	GnRH Antagonist	3 (9.1%)	9 (15.0%)	12 (14.1%)	0 (0)	
	Endometriosis surgery	9 (27.3%)	30 (50.0%)	38 (44.7%)	0 (0)	0.080[3]
Endometriosis Type***	Deep invasive Endometriosis	0 (0)	18 (30.0%)	23 (24.7%)	0 (0)	0.661[3]
	Endometriomas	0 (0)	32 (52.4%)	52 (55.9%)	0 (0)	0.364[3]
	Superficial Plaques	0 (0)	29 (47.5%)	50 (53.7%)	0 (0)	0.212[3]
Adenomyosis Type	Focal	16 (44.4%)	0 (0)	42 (45.1%)	0 (0)	0.162[3]
	Diffuse	5 (13.9%)	0 (0)	26 (27.9%)	0 (0)	
	Cystic	0 (0)	0 (0)	5 (5.5%)	0 (0)	
	Combined Focal + Cystic	5 (13.9%)	0(0)	12 (12.9%)	0 (0)	
	Combined Diffuse + Cystic	5 (13.9%)	0 (0)	5 (5.5%)	0 (0)	
	Unclear****	5 (13.9%)	0 (0)	3 (3.2%)	0(0)	

For normally distributed variables, values are depicted as Mean, standard deviation (SD) and for abnormally distributed variables as Median, Interquartile range (IQR).
[1] = One-Way ANOVA, [2] = Kruskal-Wallis Test, [3] = Chi-square Test. Subscript letters denote significant differences between groups with different letters
* Primary subfertility are women/couples who are nulliparous, and secondary subfertility involves women/couples who are multiparous.
** Percentages can add up to > 100% as patients could have multiple IVF/ICSI treatment indications simultaneously
*** Total number of patients is greater than the group size as patients could have presence of different types of endometriosis simultaneously (i.e. endometriomas and superficial plaques)
**** Unclear adenomyosis type was assigned in cases whereby the imaging quality was insufficient, or the uterus was too abnormal to be able to accurately assess adenomyosis subtype

Matching

Patients from the adenomyosis/endometriosis groups were automatically matched to the control group using SPSS Statistics to male subfertility controls. Matching was performed to account for various clinically significant confounders, namely: age during IVF, type of subfertility (i.e. primary or secondary) and number of embryos transferred (single or double embryo transfer). Since adenomyosis can be asymptomatic and often goes undiagnosed, total exclusion of adenomyosis from the control group could not be guaranteed. Therefore, study group patients were matched to control group patients in a 1:2 ratio to reduce this influence on the outcome. A preference was given for exact matches.

Table 2
IVF/ICSI Treatment Characteristics between Groups.

		Adenomyosis (n = 36)	Endometriosis (n = 61)	Combined (n = 93)	Control (n = 889)	P-value
Type of treatment	IVF	27 (75%) $_{a}$	46 (75.4%) $_{a}$	70 (75.3%) $_{a}$	177 (19.9%) $_{b}$	<0.0005[3]
	ICSI	9 (25%) $_{a}$	15 (24.6%) $_{a}$	23 (24.7%) $_{a}$	712 (80.1%) $_{b}$	
Ovarian stimulation product	Gonal-F	22 (61.1%) $_{a, b}$	34 (56.7%) $_{b, c}$	39 (41.5%) $_{c}$	710 (85.4%) $_{a}$	<0.005[3]
	Menopur	4 (11.1%) $_{a, b}$	19 (31.7%) $_{b}$	34 (36.2%) $_{b}$	56 (6.7%) $_{a}$	
	Fostimon	0 $_{a}$	2 (3.3%) $_{a}$	5 (5.3%) $_{a}$	42 (5.1%) $_{a}$	
	Other	0	1 (1.7%)	0	23 (2.8%)	
Baseline Endometrial Thickness (mm, Median, IQR)		5.0 (4.0) $_{a. b.}$	3.0 (1.8) $_{b}$	3.3 (1.0)	3.0 (2.0) $_{a}$	0.000[2]
Maximum Endometrial Thickness (mm, Median, IQR)		10.3 (±1.8)	10.2 (±2.2)	10.3 (±2.05)	10.7 (2.97)	0.794[1]
Number of viable oocytes (Mean, SD)		8.69 (±5.32)	9.44 (±5.08)	7.42(±4.35)	10.12 (±5.73)	<0.0005[1]
Number of viable embryos (Mean, SD)		4.56 (±3.36)	5.61 (±3.57)	4.30 (±2.99)	5.53 (±3.72)	0.009[1]
Fertilisation rate (Median, IQR)		0.56	0.64	0.60	0.56	0.215[2]
		IQR: 0.27	IQR: 0.32	IQR: 0.50	IQR: 0.33	
Embryos Transferred (N)	1	21 (58.3%)	47 (77%)	64 (70.3%)	570 (64.2%)	0.113[3]
	2	15 (41.7%)	14 (23%)	27 (29.7%)	318 (35.8%)	
Embryo quality 1*	Super	5 (14.7%)	14 (23.7%)	25 (27.8%)	298 (33.7%)	0.295[3]
	Good	6 (17.6%)	8 (13.6%)	12 (13.3%)	105 (11.9%)	
	Fair	15 (44.1%)	27 (45.8%)	36 (40%)	314 (35.6%)	
	Moderate	7 (20.6%)	10 (16.9%)	16 (17.8%)	133 (15.1%)	
	Poor	1 (2.9%)	0	1 (3%)	33 (3.7%)	
Embryo quality 2*	Super	2 (15.4%)	2 (16.7%)	0	34 (10.8%)	0.459[3]
	Good	2 (15.4%)	3 (25%)	5 (20%)	40 (12.7%)	
	Fair	8 (61.5%)	4 (5.3%)	14 (56%)	134 (42.7%)	
	Moderate	1 (7.7%)	3 (25%)	5 (20%)	83 (26.4%)	
	Poor	0	0	1 (4%)	23 (7.3%)	

For normally distributed variables, values are depicted as Mean, standard deviation (SD) and for abnormally distributed variables as Median, Interquartile range (IQR).
[1] = One-Way ANOVA, [2] = Kruskal-Wallis Test, [3] = Chi-square Test. Subscript letters denote significant differences between groups with different letters
* In some patients, 2 embryos are transferred. In those cases, embryo quality 2 indicates the quality of the second embryo according to alpha criteria .

Table 3
IVF/ICSI Outcome after Matching.

	Adenomyosis (N = 33)	*Control (N = 53)*	*P-value*
Biochemical pregnancy	*11 (33.3%)*	*19 (35.8%)*	*0.812*[1]
Ongoing pregnancy	*9 (28.1%)*	*15 (28.3%)*	*0.986*[1]
*Miscarriage rate**	*2 (5.2%)*	*4 (7.5%)*	*1.000*[1]
Live birth	*8 (25.0 %)*	*14 (26.9%)*	*1.000* [1]
	Endometriosis (N = 60)	*Control (N = 118)*	*P-value*
Biochemical pregnancy	*17 (28.8%)*	*47 (39.8%)*	*0.267* [1]
Ongoing pregnancy	*15 (25.4%)*	*35 (29.7%)*	*0.690* [1]
Miscarriage Rate	*2 (3.4%)*	*12 (10.1%)*	*0.145*
Live birth	*15 (25.0%)*	*29 (24.6%)*	*0.353* [1]
	Combined (N = 85)	*Control (N = 164)*	*P-value*
Biochemical pregnancy	*18 (21.2%)*	*63 (37.8%)*	*0.010* [1]
Ongoing pregnancy	*11 (12.9%)*	*54 (33.1%)*	*0.000* [1]
Miscarriage rate	*7 (8.3%)*	*8 (4.7%)*	*0.216*[1]
Live birth	*10 (11.9%)*	*48 (30.4%)*	*0.001* [1]

Comparisons of IVF/ICSI outcome after matching for all study subgroups compared to their matched controls. [1] = Chi-square test.
* The difference between biochemical and ongoing pregnancy

Outcomes

The primary study outcomes were: biochemical pregnancy (positive serum HCG 16 days after embryo transfer (ET), ongoing pregnancy (a viable pregnancy 11 weeks after ET, with presence of foetal heartbeat on ultrasound) and live birth (delivery of a live foetus > 24 weeks gestational age). Further patient characteristics collected included: age, BMI, indication for IVF/ICSI treatment, adenomyosis and/or endometriosis phenotypes, and IVF/ICSI treatment characteristics (type of subfertility (primary or secondary), infertility time (in months), treatment type (IVF or ICSI), fertilisation rate, embryo quality, number of transferred embryos). Full details and definitions of all outcomes can be found in Table A1 in Appendix A.

Data sources

Data regarding the IVF and ICSI cycles was taken from the Landelijk Specialistisch Fertiliteits Dossier (LSFD, Stichting Automatisering Fertiliteit (SAF), Utrecht, the Netherlands), the Dutch national electronic patient fertility database, and MRI data was taken from the local hospital patient records HiX (ChipSoft, Amsterdam, The Netherlands).

Statistical analysis

Data analysis was done using IBM SPSS Statistics Version 26. For normally distributed continuous variables, one-way ANOVA was used to evaluate differences between groups, the Kruskal-Wallis test was used in the case of abnormal distribution. A post-hoc test with Bonferroni correction was used to evaluate which groups showed significant differences. For categorical variables, differences between groups were evaluated using the Chi-square test using Bonferroni correction. Univariate and multivariate logistic regression (correcting for embryo quality) was carried out to calculate the odds ratio for primary outcomes for the study group(s) versus (matched) controls. A p-value < 0.05 was considered statistically significant.

Ethical approval

Ethical approval was granted by the local institutional review board and the regional medical ethical committee, with study number nWMO-2020.005/W20.045.

Results

Between the years of 2008 and 2020, 10.033 cycles of IVF/ICSI were performed at our institution. 2174 were fresh cycles carried out due to male subfertility in 938 patients. Forty-nine patients were excluded (see Appendix G for full details and reasoning), ultimately leaving 889 patients for the control group undergoing their first, fresh cycle of IVF/ICSI due to male subfertility. Simultaneously, 255 women undergoing their first, fresh cycle of IVF/ICSI received a pelvic MRI in our centre, 190 of which showed signs of adenomyosis and/or endometriosis, and thereby met inclusion criteria for the study group. Ultimately, this yielded 36 patients for the adenomyosis only group, 61 for the endometriosis only

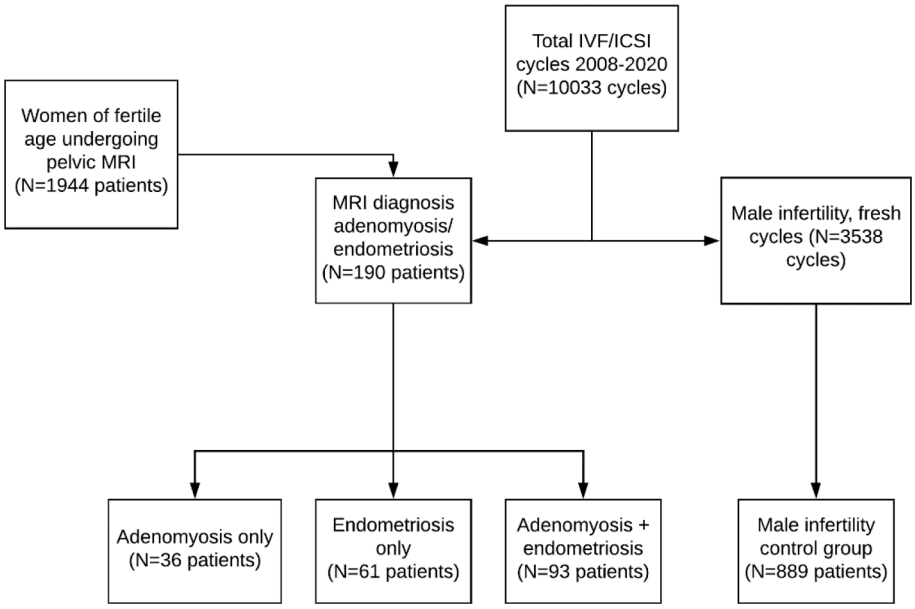

Fig. 1. Flowchart of patient selection. Patients were recruited and assigned to either an adenomyosis only, endometriosis only, combined adenomyosis and endometriosis based on MRI. or male subfertility control.

group and 93 for the combined group (see Fig. 1).

Patient characteristics before matching

Patient characteristics are summarised in Table 1. The adenomyosis group was on average 2.83 years older than the endometriosis group ($p = 0.013$), 2.52 years older than the combined group ($p = 0.021$) and 2.28 years older than the male subfertility controls ($p = 0.014$) at the time of IVF treatment.

Additionally, women with only endometriosis had more primary subfertility compared to women with adenomyosis ($p < 0.0005$). The age at the time of the MRI diagnosis was also different between the study subgroups, with the adenomyosis group having the highest mean age at MRI diagnosis (37.71 years, $p < 0.0005$). Other characteristics were comparable between groups. Adenomyosis and endometriosis subtypes also did not differ significantly between groups ($p > 0.05$). The number of patients receiving (hormonal or surgical) adenomyosis/endometriosis treatment prior to IVF was also not significant ($P > 0.05$)

IVF/ICSI characteristics between groups before matching

Subsequently, IVF/ICSI characteristics were compared between groups (see Table 2). The control group had more patients undergoing ICSI (vs. IVF) compared to the study groups ($p < 0.05$). Baseline endometrium thickness was higher in the adenomyosis only group compared to the other groups (5.0 vs. 3.0, $p = 0.000$). Maximum endometrium thickness was comparable however. A difference in number of viable oocytes was also seen; the control group had 2.70 more viable oocytes than the combined group ($p < 0.005$). The control group also had 1.23 more viable embryos than the combined group ($p < 0.005$). The fertilisation rate was comparable between groups however ($p = 0.215$). Embryo quality of the transferred embryos was not significantly different between groups ($p = 0.295$ and $p = 0.459$), nor was the number of embryos transferred ($p = 0.113$).

Matching

Matching of the study group(s) based on age during IVF/ICSI, number of embryos transferred and type of subfertility (primary or secondary) was performed separately for each study subgroup. This resulted in 33 adenomyosis patients matched to 53 controls, with three unmatched patients in the adenomyosis group and one patient with only one match. For the endometriosis only group, 60 patients were matched to 118 controls, with one unmatched patient. In the combined group, 85 patients were matched to 164 controls, with eight unmatched patients. In total, 178 adenomyosis/endometriosis patients were matched to 354 male infertility controls. The resulting separate control groups had comparable characteristics, allowing for differences across the matching variables (see Appendix C). Matching based on embryo quality was not possible, due to the low number of exact matches (55 unmatched subjects).

IVF/ICSI outcomes after matching

IVF/ICSI outcomes after matching were compared between the different adenomyosis/endometriosis subgroups and the control group (see Table 3). Compared to their matched controls, the biochemical pregnancy rate was 33.3% for the adenomyosis group, 28.8% for the endometriosis group and 21.2% for the combined group. The ongoing pregnancy rate was 28.1% in the adenomyosis group, 25.4% in the endometriosis group and 12.9% in the combined group. Miscarriage rate (as the difference between biochemical and ongoing pregnancy, see Table 3) was not significantly different between groups. The live birth rate was 25% for both the adenomyosis and endometriosis group and was 11.9% in the combined group. Only the outcomes of the combined group differed significantly from their matched controls ($p < 0.01$).

Logistic regression after matching

After matching, the ORs were calculated using multivariate logistic regression (see Appendix D) and corrected for embryo quality (for full patient and IVF/ICSI characteristics after matching per study group, see Appendix C). ORs were not corrected for endometriosis surgery before IVF/ICSI, dysmenorrhoea or type of treatment (IVF or ICSI) since this did not have a significant effect on the outcome in the regression analysis ($p > 0.05$). The aOR for biochemical pregnancy after matching was 0.895 for the adenomyosis group (95% CI (0.538; 2.236), 0.677 for the endometriosis group (95% CI (0.340; 1.348)) and 0.453 for the combined group (95% CI (0.241; 0.850) (see Fig. 2). For ongoing pregnancy, the aOR for the adenomyosis group was 0.991 (95% CI (0.347; 2.629),

for the endometriosis only group it was 0.945 (95% CI (0.455; 1.963)) and for the combined group 0.302 (95% CI (0.145; 0.628)). Similar results were found for live birth: the aOR was 0.905 for the adenomyosis group (95% CI (0.330; 2.479)), 0.843 for the endometriosis group (95% CI (0.398; 1.787)) and 0.309 for the combined group (95% CI (0.144; 0.662)) respectively.

Discussion

Overall, infertile women with combined endometriosis and adenomyosis on MRI undergoing their first IVF/ICSI fresh embryo transfer had significantly worse fertility outcomes than matched male subfertility controls. These women had a 55% decreased chance of biochemical pregnancy (OR 0.453), a 70% decreased chance of ongoing pregnancy (OR 0.302) and a 69% decreased chance of a live birth (OR 0.309). Women with only adenomyosis or endometriosis did not appear to have significantly reduced chance of achieving pregnancy compared to male subfertility controls. This effect persisted after matching for age, parity and number of transferred embryos, and correcting for embryo quality.

Our results are largely in line with current literature. Sharma et al. looked at similar patient groups as this study, (albeit with a diagnosis based on TVUS). They reported a significantly reduced clinical pregnancy rate after IVF of 34.55% for the adenomyosis group, 36.62% in the endometriosis group and 22.72% for the combined group versus tubal factor controls. This is in accordance with our results, showing that a combined presence of adenomyosis and endometriosis results in the lowest clinical pregnancy rate in IVF/ICSI patients [19]. Similarly, a study by Ballester et al. in colorectal endometriosis patients reported that an added presence of adenomyosis lead to significantly reduced cumulative clinical pregnancy rates (19% vs. 82.4%) [20]. Not all studies have reported significant associations between the presence of adenomyosis in endometriosis patients and IVF/ICSI outcome however, with the topic still being contentious [6,21]. It has been recently been suggested that the age-associated nature of adenomyosis forms an important confounder for worse fertility outcomes in this population [6]. For this reason, we chose to match for maternal age during IVF, with our results still reaching statistical significance.

Based on our results therefore, we do suggest that patients with combined adenomyosis and endometriosis have a more severe form of the disease thus more impaired fertility compared to women with only one of the two disorders. The current data also seems to show that this is the case regardless of the individual adenomyosis or endometriosis phenotype. It is noteworthy also that the combined group constitute the largest proportion of infertile women undergoing IVF/ICSI treatment in our study: it suggests that these women having more severely impaired fertility and thereby seek treatment in the first place. It is possible this is due to an added uterine or implantation factor in these women, as matching and correcting embryo quality did not diminish this effect.

In general clinical practice, when undergoing IVF/ICSI, arguably little attention is paid to whether a patient has adenomyosis, due to inconsistent diagnostic criteria and a lack of symptoms in many women. As a result, few clinical guidelines exist to tailor fertility treatments to women with adenomyosis (or endometriosis for that matter), and in many cases they simply follow the locally established IVF/ICSI protocols. The results presented here suggest that screening for adenomyosis in (infertile) endometriosis patients (on MRI) is clinically useful in an IVF/ICSI setting. Furthermore, due to the suspected severity of disease in the combined group, these patients represent a potential target group for additional hormonal therapy or surgery before undergoing IVF/ICSI, resulting in disease attenuation/regression [22].

Investigating this patient group separately, as done in this study, thus constitutes one of its strengths: it was possible to investigate the independent influence of adenomyosis and endometriosis on fertility. A further strength of this study is that only women with adenomyosis based on MRI were included, a more reliable method of diagnosing adenomyosis, as opposed to TVUS [18]. Moreover, the extensive re-evaluation of the MRIs by three experienced pelvic radiologists in the context of this study also reduces the risk of bias that inevitably accompanies a retrospectively designed study. To the best of our knowledge, this is the first study which investigates fertility outcomes of adenomyosis and endometriosis separately and combined, based on MRI diagnosis.

This study does however have several limitations. First, the control group as a rule were healthy women, with no indication for MRI. This means no definitive assessment of adenomyosis presence in these women could be carried out. Hence, it is possible that some of these women had undiagnosed adenomyosis. To account for this eventuality, we chose to match the control group 1:2 with the study group. Second, although our study group was larger than many previously executed studies investigating the relationship between adenomyosis and infertility, the sample size was still relatively small, which reduces the power of the results. This was reflected in the broad reported confidence intervals. Third, while the endometriosis and adenomyosis diagnosis was based on the MRI closest to the IVF/ICSI start date, in many cases the adenomyosis diagnosis was made after IVF/ICSI (see Table 1). Therefore, it is not known whether the adenomyosis was already present (to a similar extent) at the time of IVF/ICSI. However, when conducting a sensitivity analysis for only patients receiving an MRI prior to IVF, our results did not significantly differ. We believe this reflects the theory that adenomyosis is a disease which develops gradually over a life-time rather than representing a de novo diagnosis [23]. Finally, there are some women ($n = 5$, see Table 1) in the adenomyosis group that underwent assumed complete surgery for endometriosis before undergoing IVF, as the pelvic MRI showed no signs of endometriosis. Therefore, these patients were assigned to the adenomyosis only group, whilst they did show a history of endometriosis. Finally, several IVF/ICSI treatment parameters are not reported in our study population as part of standard treatment procedures, and thus could not be assessed for their potential confounding effect (e.g. baseline follicle count, AMH levels, (peak) serum oestradiol).

Overall, it can be said that adenomyosis negatively affect fertility outcomes, especially in conjunction with endometriosis. It is suspected that in IVF/ICSI patients with combined adenomyosis and endometriosis, the disease is more severe than in patients with only adenomyosis or endometriosis and thus has a greater impact on fertility. Accurate diagnosis of adenomyosis and endometriosis before undergoing IVF/ICSI is crucial. Therefore, making a pelvic MRI to diagnose or eliminate the presence of adenomyosis/endometriosis is recommended. More research is needed to further identify the relationship between adenomyosis and endometriosis and infertility. Especially large-scale studies with patient subdivision into adenomyosis only, endometriosis only and combined adenomyosis and endometriosis groups is valuable so as to tailor (pre) treatment per patient sub-type.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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outcome data. Furthermore we would like to thank Catharina Hospital statistician Dr. Saskia Houterman for her support in analysis.

Appendix

Appendix A:. Baseline characteristics definitions

Table A1
Baseline Characteristics

Age during IVF/ICSI	in years
BMI	in kg/m^2
Length of menstrual cycle	in days
Type of subfertility	Primary or secondary. Primary subfertility included women with no previous pregnancy (nulliparity) and secondary subfertility includes women with a previous pregnancy (multiparity).
IVF/ICSI Indication	Either a male factor, combined (both male and female factor), unknown infertility, endometriosis, tubal factor, ovulation disorder, cervical factor, uterine factor
Dysmenorrhoea	Reported presence of menstrual cramps
Age at MRI	In years, at the time the MRI was performed upon which the adenomyosis/endometriosis diagnosis was based
Infertility time	Number of months for which patients had a child wish prior to starting IVF/ICSI
Type of treatment	IVF or ICSI. In IVF/ICSI, ovulation is first stimulated to retrieve viable oocytes (during follicle aspiration, which are then fertilized in the laboratory to form embryos. These embryos (often 1, sometimes 2) are then transferred into the uterus. While in IVF, the oocyte and spermatozoa are simply placed together in a petri dish, in ICSI the spermatozoa is injected directly into the cytoplasm of the oocytes.
Ovarian stimulation product	E.g. Gonal-F (Merck-Serono Darmstadt, Germany), Menopur (Ferring, Hoofddorp, The Netherlands), Fostimon (IBSA Farmaceutici, Italy) or other
Oocytes	Number of oocytes retrieved after follicle aspiration
Embryos	Number of viable embryos remaining after fertilisation of oocytes
Fertilisation rate	Number of embryos divided by the number of oocytes (expressed as a ratio)
Embryos transferred	Single embryo transfer (1 embryo) or double embryo transfer (2 embryos)
Embryo quality	Quality for all transferred embryos. Assessed on a 5-point scale according to the alpha criteria and local protocol; either super, good, fair, moderate or poor [24]. Criteria for assessment include the number of cells in the embryo, division equality of those cells and the extent of fragmentation. An embryo with 8 equally divided cells and a fragmentation of 0–10% was considered super (see appendix 6 for further details).
Endometriosis surgery before IVF	Indicates whether women underwent surgery before IVF/ICSI treatment for endometriosis removal.

Appendix B:. IVF/ICSI outcomes before matching

Table B1

Table B1
IVF/ICSI outcome before matching.

	Adenomyosis (n = 36)	Endometriosis (n = 61)	Combined (n = 93)	Control (n = 889)	Total (n = 1079)	P-value
Biochemical pregnancy	11 (30.6%)	17 (27.9%)	**20 (21.5%)**	**323 (36.3%)**	371 (34.4%)	0.021[1]
Ongoing pregnancy (of total population)	9 (25.7%)	15 (24.6%)	**11 (25.6%)**	**261 (29.4%)**	296 (27.5%)	0.004[1]
Ongoing pregnancy (of pregnant women)	9 (81.8 %)	15 (88.2%)	**11 (55%)**	**261 (80.8%)**	296 (79.8%)	0.035 [1] OR 0.049 [2]
Live birth	8 (22.9%)	15 (25%)	**10 (10.8%)**	**233 (26.8%)**	266 (25.2%)	0.009[1]

The ongoing pregnancy rate was both evaluated for the entire study group and for the women who had a biochemical pregnancy. [1] = Chi-square test, [2] = Fisher's Exact test. Bold + underlined values indicate significant differences.

Appendix C:. Matching details

(See Table C1 and C2, C3)

Table C1
Patient and IVF/ICSI characteristics after matching between the adenomyosis and control group. For normally distributed variables, values are depicted as Mean, standard deviation (SD) and for abnormally distributed variables as Median, Interquartile range (IQR). *Infertility time is defined as the period in months between having a child wish and starting the first round of IVF. [1] = One-Way ANOVA, [2] = Kruskal-Wallis Test, [3] = Chi-square Test.

		Adenomyosis (N = 33)	Control (N = 53)	P-value
BMI in kg/m^2 (Median, IQR)		24.84 IQR: 7.63	24.22 IQR: 6.25	0.622[2]
Infertility time in months* (Median, IQR)		37.00 IQR: 30	33.00 IQR: 25	0.391[2]
Cycle length (Mean, SD)		29.95 (±3.471)	28.63 (±3.080)	0.118[1]
Indication	Male	11 (11.1 %)	53 (100%)	<0.0005[3]
	Female	3 (15.2 %)		
	Combined	4 (12.1 %)		
	Endometriosis	3 (9.1 %)		
	Unknown	10 (30.3 %)		
Dysmenorrhoea	Yes	8 (34.8%)	7 (15.9%)	0.121[3]
Type of treatment	IVF	27 (75.8%)	18 (34%)	0.000[3]
	ICSI	8 (24.2%)	35 (66%)	
Ovarian stimulation product	Gonal-F	22 (84.6%)	43 (89.6%)	0.017[3]
	Menopur	4 (15.4%)	0	
	Fostimon	0	4 (8.3%)	
Number of viable oocytes (Mean, SD)		8.67 (±5.55)	8.98 (±5.08)	0.788[1]
Number of viable embryos		4.45 (±3.46)	4.55 (±2.92)	0.894[1]
Fertilisation rate		0.56 (±0.26)	0.53 (±0.23)	0.620[1]
Subfertility type	Primary	18 (54.5%)	13 (58.5%)	0.824[3]
	Secondary	15 (45.5%)	22 (42.5%)	
Embryos transferred	1	19 (57.6%)	28 (52.8%)	0.824[3]
	2	13 (42.4%)	25 (47.2%)	
Age at IVF (Mean, SD)		33.82 (±3.64)	33.7 (±3.87)	0.881[1]
Embryo quality 1	Super	3 (9.7%)	15 (28.2%)	0.347[3]
	Good	6 (19.4%)	6 (11.3%)	
	Fair	14 (45.2%)	20 (37.7%)	
	Moderate	7 (22.6%)	10 (18.9%)	
	Poor	1 (3.2%)	2 (3.8%)	
Embryo quality 2	Super	1 (8.3%)	3 (12%)	0.383[3]
	Good	2 (16.7%)	4 (16%)	
	Fair	8 (66.7%)	9 (36%)	
	Moderate	1 (8.3%)	7 (28%)	
	Poor	1 (3.2%)	2 (8%)	

Table C2

Patient characteristics after matching between the endometriosis and control group. For normally distributed variables, values are depicted as Mean, standard deviation (SD) and for abnormally distributed variables as Median, Interquartile range (IQR). *Infertility time is defined as the period in months between having a child wish and starting the first round of IVF. [1] = One-Way ANOVA, [2] = Kruskal-Wallis Test, [3] = Chi-square Test.

		Endometriosis (N = 60)	Control (N = 118)	P-value
BMI in kg/m^2 (Median, IQR)		23.26 IQR: 5.06	23.8 IQR: 6.05	0.239[2]
Infertility time in months* (Median, IQR)		27.50 IQR: 28	26.00 IQR: 19	0.391[2]
Cycle length (Mean, IQR)		28.00 IQR: 3	28.00 IQR: 2	0.682[2]
Indication	Male	9 (15.0 %)	118 (100%)	<0.0005[3]
	Female	3 (3.3 %)		
	Combined	22 (36.7 %)		
	Endometriosis	22 (36.7%)		
	Unknown	5 (8.3 %)		
Dysmenorrhoea	Yes	37 (72.5%) $_a$	15 (15.0%) $_b$	0.000[3]
Type of treatment	IVF	45 (75%)	25 (21.2%)	0.000[3]
	ICSI	(25%)	93 (78.8%)	
Ovarian stimulation product	Gonal-F	35 (62.5%)	101 (89.4%)	0.000[3]
	Menopur	18 (32.1%)	4 (3.5%)	
	Fostimon	2 (3.6%)	6 (5.3%)	
Number of viable oocytes (Mean, SD)		9.50 (±5.10)	10.00 (±5.10)	0.527[1]
Number of viable embryos		5.62 (±3.60)	5.22 (±3.30)	0.464[1]
Fertilisation rate		0.61 (±0.26)	0.53 (±0.21)	0.390[1]
Subfertility type	Primary	47 (78.3%)	93 (78.8%)	0.946[3]
	Secondary	13 (34.2%)	25 (21.2%)	
Embryos transferred	1	46 (76.7%)	91 (77.1%)	0.824[3]
	2	14 (23.3%)	27 (22.9%)	
Age at IVF (Mean, SD)		30.90 (±4.06)	30.81 (±4.05)	0.893[1]
Embryo quality 1	Super	14 (24.1%)	51 (43.6%)	0.008[3]
	Good	8 (13.8%)	19 (16.2%)	
	Fair	27 (46.6%)	29 (24.8%)	
	Moderate	9 (15.5%)	12 (10.3%)	
	Poor	0	6 (5.1%)	
Embryo quality 2	Super	2 (16.7%)	2 (7.4%)	0.560[3]
	Good	3 (25%)	4 (14.8%)	
	Fair	4 (33.3%)	10 (37%)	
	Moderate	3 (25%)	7 (25.9%)	
	Poor	0	4 (14.8%)	

Table C3

Patient characteristics after matching between the combined and control group. For normally distributed variables, values are depicted as Mean, standard deviation (SD) and for abnormally distributed variables as Median, Interquartile range (IQR). *Infertility time is defined as the period in months between having a child wish and starting the first round of IVF. [1], [2],

		Combined (N = 85)	Control (N = 164)	P-value
BMI in kg/m^2 (Median, IQR)		23.88 IQR: 5.59	23.39 IQR: 6.22	0.637[2]
Infertility time in months* (Median, IQR)		31.00 IQR: 23	27.00 IQR: 21	0.165[2]
Cycle length (Mean, IQR)		28.00 IQR: 2	28.00 IQR: 3	0.771[2]
Indication	Male	12 (14.3 %)	164 (100%)	<0.0005[3]
	Female	9 (10.7 %)		
	Combined	21 (25 %)		
	Endometriosis	33 (39.2%)		
	Unknown	9 (10.7 %)		
Dysmenorrhoea	Yes	44 (65.7%)	31 (22.8%)	0.000[3]
Type of treatment	IVF	63 (74.1%)	43 (26.2%)	0.000[3]
	ICSI	22 (25.9%)	121 (73.8%)	
Ovarian stimulation product	Gonal-F	37 (51.4%)	142 (92.2%)	0.000[3]
	Menopur	30 (41.7%)	7 (4.5%)	
	Fostimon	5 (6.9%)	4 (2.6%)	
Number of viable oocytes (Median, IQR)		7.00 IQR: 6	8.00 IQR: 7	0.001[2]
Number of viable embryos		4.11 (±2.80)	4.97 (±3.37)	0.044[1]
Fertilisation rate		0.62 (±0.28)	0.54 (±0.24)	0.026[1]
Subfertility type	Primary	63 (74.1%)	122 (68.9%)	0.934[3]
	Secondary	22 (25.9%)	42 (25.6%)	
Embryos transferred	1	59 (69.4%)	113 (68.9%)	0.934[3]
	2	26 (30.6%)	51 (31.1%)	
Age at IVF (Mean, SD)		31.32 (±3.92)	31.32 (±3.85)	0.999[1]
Embryo quality 1	Super	21 (25.6%)	49 (30.1%)	0.081[3]
	Good	11 (13.4%)	24 (14.7%)	
	Fair	33 (40.2%)	46 (28.2%)	
	Moderate	16 (19.5%)	29 (17.8%)	
	Poor	1 (1.2%)	15 (9.2%)	
Embryo quality 2	Super	0	6 (12%)	0.150[3]
	Good	5 (20.8%)	6 (12%)	
	Fair	14 (58.3%)	19 (38%)	
	Moderate	4 (16.7%)	16 (32%)	
	Poor	1 (4.2%)	3 (6%)	

Appendix D:. Multivariate regression after matching

(See Table D1)

Table D1
Multivariate logistic regression after matching. Biochemical and ongoing pregnancy and live birth after correcting for embryo quality following matching. ORs for the adenomyosis only group are not corrected for embryo quality, since it did not have a significant effect on the outcome.

		OR (vs Control)	95% CI	
Biochemical pregnancy	Adenomyosis	0.895	0.385	2.236
	Endometriosis	0.677	0.340	1.348
	Combined	0.453	0.241	0.850
	Full study group	0.557	0.396	0.839
Ongoing pregnancy	Adenomyosis	0.991	0.347	2.629
	Endometriosis	0.945	0.455	1.963
	Combined	0.302	0.145	0.628
	Full study group	0.551	0.351	0.866
Live birth	Adenomyosis	0.905	0.330	2.479
	Endometriosis	0.843	0.398	1.787
	Combined	0.309	0.144	0.662
	Full study group	0.587	0.364	0.919

Appendix E:. Local protocol for embryo quality assessment

(Table E1)
Criteria for choice of Fresh ET Embryo:

- For ET, the embryo's of the highest available quality are chosen.
- Super > Good > Fair > Moderate > Poor
- When multiple embryo's of equal final quality are available, the choice depends on how the embryo(s) were on day 2,. Whereby: 4 cell > 2 cell > 3 cell
- IN the case of continued division from day 2 to day 3, priority is given to the embryo that is dividing 'on schedule'.
- In the case of fragmentation, concentrated pockets of fragmentation are preferred to diffuse fragmentation
- If there are no embryo dividing 'on schedule' preference is given to embryos with higher uniformity
- $2pn^a > 2pn^b > 0pn > 1pn$
- Embryos > 24 h behind the expected stage of development are not eligible for ET.

In the case of stagnation between days 2 and 3 (**without** deterioration in quality), ET is potentially possible

Appendix F:. Local requirements for IVF/ICSI treatment.

In- and Exclusion criteria for fertility treatment in general
Eligibility:

- Subfertility for > 1 year

Exclusion criteria:

- No sustainable or monogamous relationship
- If one of the partners is < 18 years of age.
- If the women wishing to undergo fertlity treatment is > 42 years of age, unless she wishes to undergo oocyte donation for which the maximum age is 45 years.
- If the woman's BMI is < 18 kg/m2 or > 38 kg/m2; if the BMI is < 38 kg/m2 the ovaries should at least be visible on transvaginal ultrasound
- If one of the two partners refuses to sign the informed consent forms
- If one of the two partners refuses to undergo necessary testing needed to obtain a diagnosis or start the treatment
- If the partner/husband does not attend the consultation of the physician

Table E1
Local protocol of embryo quality assessment, Embryo quality is based on the appearance of the embryos on day 1, 2 and 3. A final embryo quality assessment is given on day 3.

Day	Criterion	Super	Good	Fair	Moderate	Poor
1	Type pn*	$2pn^a$ $2pn^b$ /0pn →	$2pn^a$ $2pn^b$/0pn →	$2pn^a$	$2pn^a$ / $2pn^b$ / 0pn/ 1pn with IVF	$2pn^a$ / $2pn^b$ / 0pn / 1pn
		No vacuoles	Some small vacuoles	Some small vacuoles	N.a.	N.a.
2	Number of Cells	4 Cells	4/5 Cells	2–5 Cells	≥2 Cells	≥ 2 Cells
	Fragmentation	≤20% (score 1 + 2*)	≤20% (score1 + 2)	≤50% (score 1 + 2 + 3)	≤50% (score 1 + 2 + 3)	N.a.
	Blastomere Uniformity	Uniform	Uniform/Somewhat uneven	N.a.	N.a.	N.a.
	Mulitnuclear blastomeres (MNB)	None	None	None	MNB's ≤ 25 %	N.a.
	Vacuoles/Irregularities	None	None	Some vacuoles	N.a.	N.a.
	Clarity	Clear	Clear	N.a.	N.a.	N.a.
3	Number of Cells	8/9 Cells	7–10 cells / starting. Morula	6–10 cells / starting Morula	≥ 4 cells	≥ 4 cells
	Fragmentation	≤20% (score1 + 2)	≤20% (score 1 + 2)	≤20% (score 1 + 2)	≤50% (score 1 + 2 + 3)	N.a.
	Blastomere Uniformity	Uniform/Somewhat uneven	Uniform/Somewhat uneven	N.a.	N.a.	N.a.
	Mulitnuclear blastomeres	None	None	Some vacuoles	N.a.	N.a.
	Vacuoles/Irregularities	Clear	Clear	N.a.	N.a.	N.a.

$2pn^b$ → If the embryo has a lower 2pn score (a instead of b), the overall quality will decrease by one level. There should be progression between days 2 and 3, or there should be at least 2 blastomeres present for an embryo to have a quality score of 'II'. If this is not the case, the embryo is automatically scored as having a quality of III.
* score 1= < 10% fragmentation; score 2 = 10–20% fragmentation; score 3 = 20–50% fragmentation ; score 4= >50% fragmentaton

- If there is a medical contra-indication for pregnancy
- If there are (or have been) severe psychosocial issues, including but not limited to:
  - Reported history of child abuse or neglect
  - History of volatile psychiatric issues
  - Must permit the professional evaluation of fitness for parenthood
- If one of the partners refuses proper registration of the treatment costs

In- and exclusion criteria for IVF/ICSI treatment
IVF/ICSI Treatment will not be initiated if:

- The patient is a 'Bad responder': 'Bad responders' are patients who produce < 3 follicles with standard treatment twice in a row. zijn patiënten die eerder bij het standaardschema voor IVF tot 2 maal toe < 3 follikels produceerden. Patients who initiate treatment with maximal dosage and still produce < 3 follicles will also not continue with IVF/ICSI procedures.
- Medical risk factors are present:
  - HIV seropositivity of the male or female partner
  - Hepatitis B (only if undergoing ICSI)
  - Increased risk of a severe congenital disorder or other medical risk factors
- Female Weight:
  - BMI < 18 or > 38
- If the male VCM < 1 million
- Previous total fertilisation failure during IVF/ICSI

Inclusion criteria for IVF/ICSI

Medical indications for IVF/ICSI:

- Confirmed tubal factor infertility
- If both fallopian tubes are proven to be obstruction IVF/ICSI can be started immediately
- Reduced tubal function without complete obstruction, and six failed intra-uterine insemination (IUI) attempts, OR, 1–2 years after tubal surgery
- If the women is 36 or older this period is reduced to one year
- Endometriosis
- In the case of minimal/mild endometriosis the protocol for 'unexplained subfertility' is followed (see below)
- Severe endometriosis is treated as tubal factor
- Male subfertility
  - If sperm analysis shows only IVF/ICSI are realistic for fertilisation to occur
- Hormonal imbalance
  - IVF/ICSI only initiated if ovulation induction (OI) and IUI are unsuccessful
- Unexplained subfertility
  - IVF/ICSI only offered after at least 6 unsuccessful IUI attempts if the woman is < 38 years of age
  - If the woman is > 38 years of age IVF/ICSI can be started immediately
- Therapy-resistant cervical hostility
- IVF/ICSI possible after 6 unsuccessful IUI attempts

Requirements for ICSI treatment:

- The couple should undergo standard virus screening
- The couple should be informed about the risks of ICSI treatment, such as the potential for carrying over of genetic disorders, and a higher chance of infertility in ICSI-children.
- Because the higher risk of genetic disorder:
- Preconceptional chromosomal examinations will take place for the male partner in the case of azoospermia. In the case of an abnormal result the couple will bes een by a clinical geneticist.
- A family history will be taken from both partners. In the case of the (potential) presence of genetic disorders, further genetic testing may follow.
- The results of genetic testing will be discussed with the couple, after which it will be decided if they are eligible for ICSI treatment.

Indications for ICSI Treatment

- <1 million total motile spermatozoa in ejaculate
- Absence of fertilisation (total fertilisation failure) after routine IVF procedures
- <5% fertilisation in 2 subsequent IVF cycles.

Exclusion criteria for ICSI treatment

- Same as for IVF

Local IVF/ICSI Treatment Protocol:

- Standard dose for patients undergoing their first IVF/ICSI cycle receiving gonadotrophins is 150 IE/mL. As all included patients were undergoing their first IVF cycle this was the standard dosage also applied to our patient population. Several exceptions applied:
- Age > 39 years: standard starting dosage is 225
- If patients are diagnosed with PCOS or have a high AFC: lower dosage (e.g. 100 IE/mL)
- Maximum dosage: 225

The following treatment protocol was applied, as briefly described in the materials and methods section:

- Start OAC on cycle day 3 prior to IVF
- Start Decapeptyl 7 days prior to stop OAC
- Continue Decapeptyl until the day of Pregnyl (HCG)
- Baseline ultrasound on cycle day 1, 2 weeks after initiation of decapeptyl treatment
- Start GnRH treatment if follicle count is low (this becomes CD 1)
- Continue GnRH treatment in any case until cycle day 8 when an ultrasound for follicle count is made to determine timing of follicle aspiration. "

Appendix G:. Details of patient inclusion and exclusion:

(See Fig. G1)

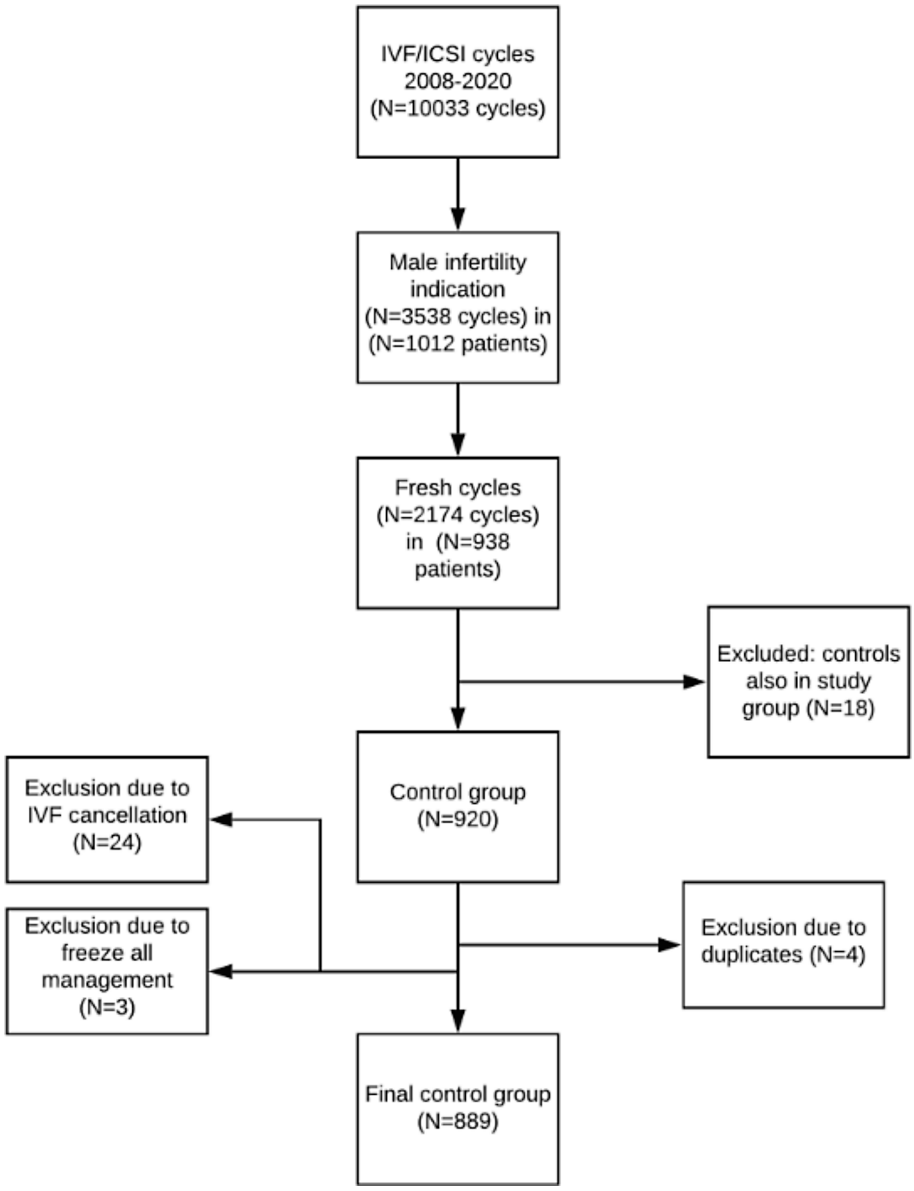

Fig. G1. Flowchart of patient recruitment for the control group.

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