

## Supplemental Online Content

Paffoni A, Casalechi M, De Ziegler D, et al. Live birth after oocyte donation in vitro fertilization cycles in women with endometriosis: a systematic review and meta-analysis. *JAMA Netw Open*. 2024;7(2):e2354249. doi:10.1001/jamanetworkopen.2023.54249

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This supplemental material has been provided by the authors to give readers additional information about their work.

## **eAppendix. Supplemental Methods**

### **Information Sources, Search, and Eligibility Criteria**

We conducted a comprehensive search of electronic databases, including Scenedirect, Pubmed, Scopus, Embase, the Cochrane library, Clinicaltrials.gov, EU Clinical Trials Register, and World Health Organization International Clinical Trials Registry, until August 31, 2023, without date restrictions. Two authors (A.V., M.C.) independently assessed the electronic search and study eligibility. Our search terms included endometriosis, endometrioma, donor IVF, oocyte donation, oocyte recipient, and heterologous IVF. After removing duplicates, we screened citations based on titles and abstracts. Additionally, we manually searched the references of included studies to ensure we did not miss any relevant research. Any disagreements were resolved through consensus, and selected items were thoroughly evaluated for eligibility in full-text.

### **Study selection and Data Collection Process**

The inclusion of studies was based on the following criteria: oocyte donation cycles with donors under 35 years of age unaffected by endometriosis; comparison between women with endometriosis versus without endometriosis; reported frequencies of women achieving clinical pregnancy rate or live birth in the two groups; studies reported in the English language; full-text studies. The following exclusion criteria were applied: case reports, case series, non-controlled studies; non-original or duplicated data.

The data extraction process was conducted by two authors (A.V., M.C.) who collected information on study characteristics, populations (number of patients and inclusion criteria), embryo transfer cycle (protocol for endometrial preparation, luteal phase support), and study outcomes. Outcome data were obtained from the text and/or tables of the original studies. If outcome data were not explicitly mentioned, they were calculated based on other available outcome data (e.g., miscarriage rate calculated as the difference between clinical and ongoing pregnancies). In case of missing data, the authors of the original studies were contacted to obtain additional information relevant to the outcomes of our study. One author (P.V.) reviewed the entire data extraction process.

### **Assessment of the risk of bias**

Two reviewers (A.V., M.C.) independently judged the methodological quality of studies included in the meta-analysis using a modified version of the “Newcastle-Ottawa Scale”. Quality of the studies was evaluated in five different domains: “*sample representativeness*”, “*sampling technique*”, “*ascertainment of endometriosis diagnosis*”, “*quality of description of the population*”, “*incomplete outcome data*”. According to the total number of points assigned, each study was judged to be at low risk of bias ( $\geq 3$  points) or high risk of bias ( $< 3$  points). Any discrepancies concerning Author’s judgements were referred to a third reviewer (P.V.) and resolved by consensus.

### **Grading of evidence**

The body of evidence was assessed by two Authors (A.V., A.P.) using the GRADE (Grading of Recommendations Assessment Development and Evaluation working group) methodology. The final score was obtained by evaluating the following domains: *study design, risk of bias, indirectness, inconsistency, imprecision, large effect size, plausible confounding and publication bias*. *Dose response gradient* was not evaluated since the intervention was dichotomous.

**eTable 1: Modified Newcastle-Ottawa Scoring Items.**

**(1) Sample representativeness:**

1 point: Sample size was greater than or equal to 100 participants per group.

0 points: Sample size was less than 100 participants per group.

**(2) Sampling technique:**

1 point: Patients recruited consecutively or randomly, with or without matching techniques.

0 points: Potential convenience sampling or unspecified sampling technique.

**(3) Ascertainment of endometriosis diagnosis:**

1 point: The criteria for the diagnosis of endometriosis were clearly described and included the use of one or more of the following techniques, including transvaginal ultrasound, magnetic resonance imaging, and laparoscopy.

0 points: The diagnosis was based on other unvalidated approaches (e.g., chronic pelvic pain), or the diagnostic methods were not described.

**(4) Quality of population description:**

1 point: The study reported a clear description of the population (e.g. age, BMI, duration of infertility) with proper measures of dispersion (e.g., mean, standard deviation) and ovarian stimulation-embryo transfer protocol.

0 points: The study did not report a clear description of the population or ovarian stimulation-embryo transfer protocol, incompletely reported descriptive statistics, or did not report measures of dispersion.

**(5) Incomplete outcome data:**

1 point: The study reported complete data about the primary outcome of the review (live birth rate).

0 points: Selective data reporting could not be excluded.

**Legend:** The individual components listed above are summed to generate a total modified Newcastle-Ottawa risk of bias score for each study. Total scores range from 0 to 5.

For the total score grouping, studies were judged to be of low risk of bias ( $\geq 3$  points) or high risk of bias ( $< 3$  points).

eTable 2: Results From Assessment of the Risk of Study Bias

STUDY ID	SAMPLE REPRESENTATIVENESS	SAMPLING TECHNIQUE	ASCERTAIN-MENT OF ENDOMETRIOSIS DIAGNOSIS	QUALITY OF DESCRIPTION OF THE POPULATION	INCOMPLETE OUTCOME DATA	TOTAL SCORE	RISK OF BIAS
<i>Diaz et al, 2010</i>	-	-	★	★	★	★★★	LOW
<i>Kamath et al, 2022</i>	★	★	-	-	★	★★★	LOW
<i>Prapas et al, 2012</i>	★	-	★	★	★	★★★★	LOW
<i>Sung et al, 1997</i>	-	★	★	-	-	★★	HIGH

**eTable 3: Results From Assessment of the Quality of Evidence**

<b>Endometriosis compared to Controls in oocyte donation cycles</b>						
Patient or population: oocyte donation cycles						
Intervention: Endometriosis						
Comparison: Controls						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Controls	Risk with Endometriosis				
Live birth rate (LBR)	311 per 1,000	<b>255 per 1,000</b> (190 to 333)	<b>OR 0.76</b> (0.52 to 1.11)	6973 (3 observational studies)	⊕⊕○○ Low <sup>a</sup>	
Clinical Pregnancy Rate (CPR)	409 per 1,000	<b>327 per 1,000</b> (250 to 417)	<b>OR 0.70</b> (0.48 to 1.03)	537 (3 observational studies)	⊕○○○ Very low <sup>a,c</sup>	
Implantation Rate (IR)	189 per 1,000	<b>152 per 1,000</b> (121 to 189)	<b>OR 0.77</b> (0.59 to 1.00)	1679 (3 observational studies)	⊕○○○ Very low <sup>a,c</sup>	
Miscarriage Rate (MR)	153 per 1,000	<b>191 per 1,000</b> (90 to 361)	<b>OR 1.31</b> (0.55 to 3.13)	149 (2 observational studies)	⊕○○○ Very low <sup>a</sup>	

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

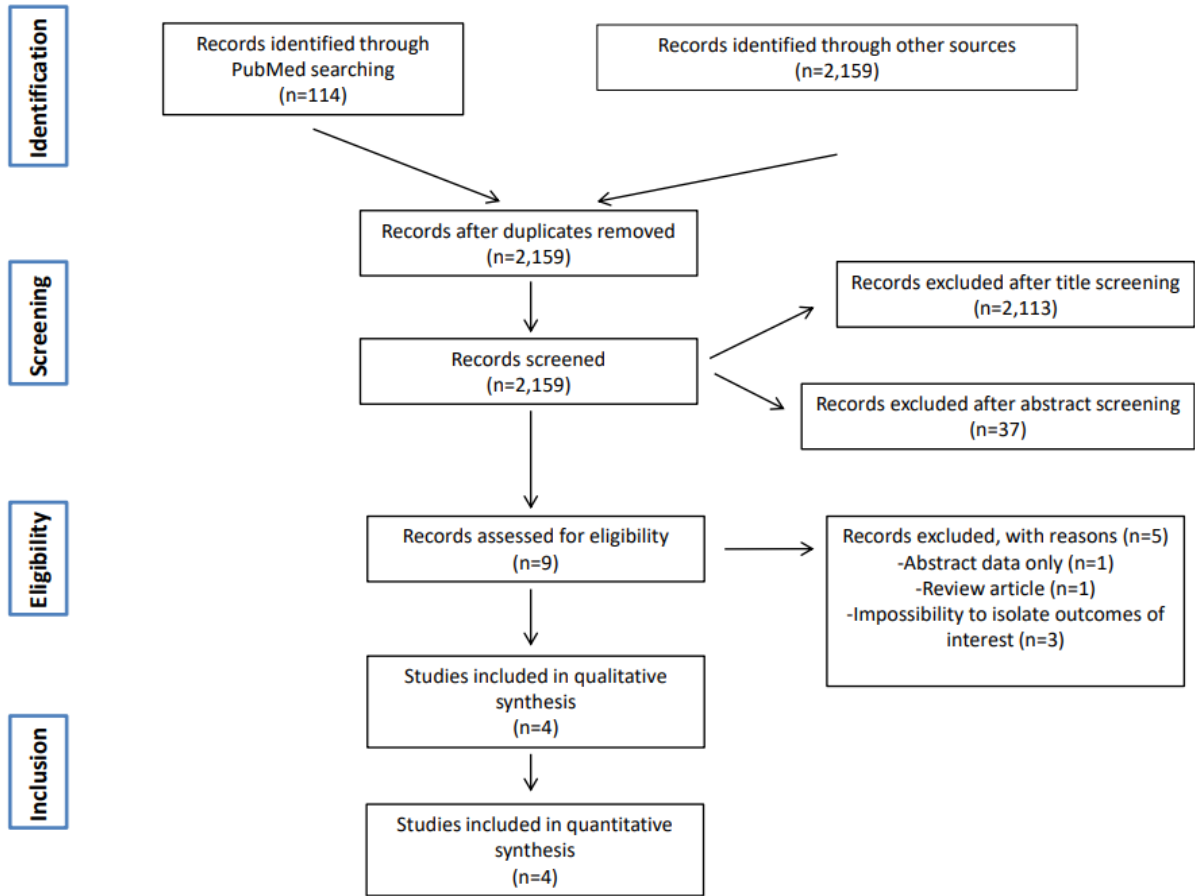
CI: confidence interval; OR: odds ratio

**GRADE Working Group grades of evidence**  
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.  
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.  
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.  
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

**Explanations**

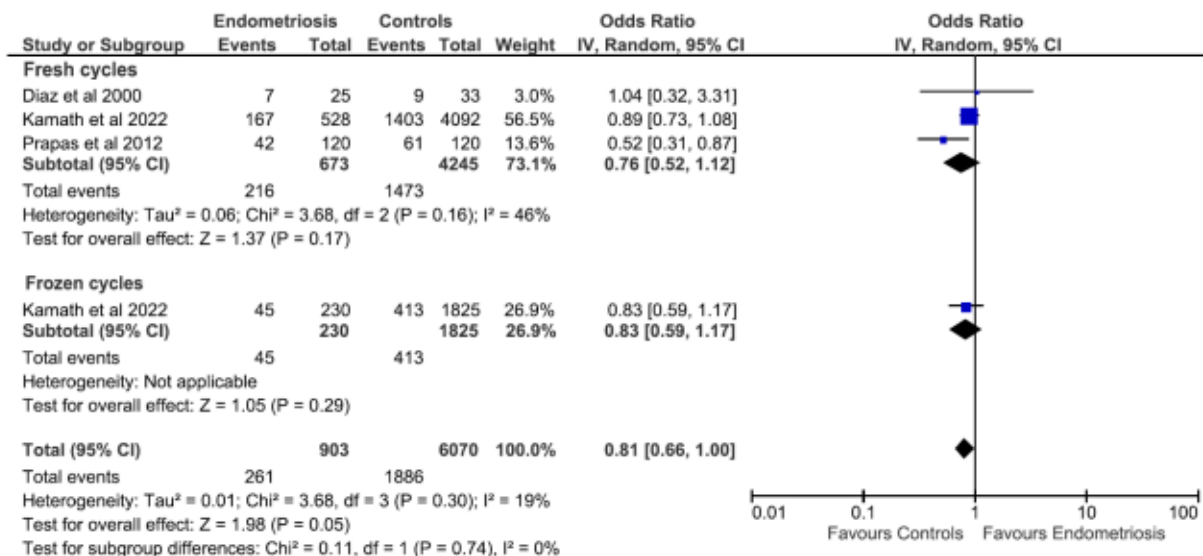
- a. Higgins I<sup>2</sup> value between 30% and 60% indicating moderate statistical heterogeneity in the study results.
- b. Low number of patients and events. Two studies included in the analysis utilized an older clinical and laboratory standard (studies published in 1997 and 2000).
- c. All the studies performed multiple embryo transfers at the cleavage stage (ranging from 2 to 4 embryos per single transfer).
- d. Low number of events and pregnancies. High risk of twin pregnancies due to multiple embryo transfers. Significant age differences between patients with endometriosis and those without endometriosis (women with endometriosis older on average).

eFig.1 PRISMA Flow-Diagram

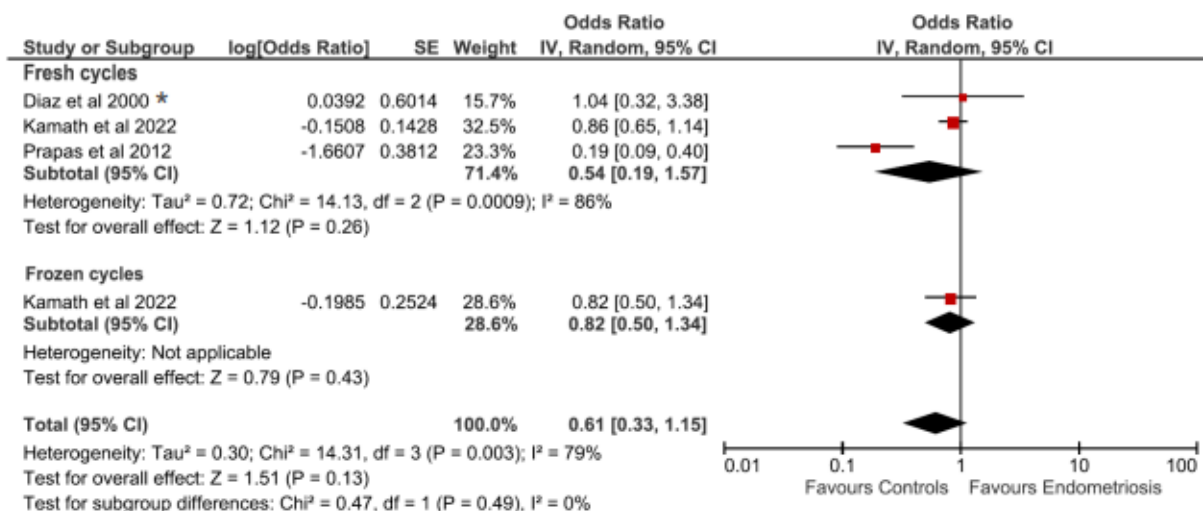


eFigure 1. PRISMA Flow Diagram

**A**



**B**



**Figure 2.** Forest plots for live birth rate for the unadjusted (A) and mixed models (B) subgroup analysis based on the type of oocyte donation cycles (fresh vs. frozen). The asterisk refers to non-adjusted data. Blue squares refer to dichotomous variables presented in A. Red squares indicate the inclusion of log odds ratio and the standard error of the log odds ratio in the meta-analysis shown in B. Size of the squares depends on the weight assigned to each study in the analysis.



eTable 4: Comparison of Main Characteristics of Women With and Without Endometriosis Included in the HFEA Register.

	Endometriosis, Total=931		Controls, Total=23969		<i>p</i>
	n	%	n	%	
Patient age					0.001
Patient age (18-34 years)	145	15.6%	4419	18.4%	
Patient age (35-37 years)	157	16.9%	2685	11.2%	
Patient age (38-39 years)	118	12.7%	2328	9.7%	
Patient age (40-42 years)	248	26.6%	4709	19.6%	
Patient age (43-44 years)	131	14.1%	3779	15.8%	
Patient age (45-50 years)	132	14.2%	6049	25.2%	
Egg donor age					0.001
Egg donor age (<21 years)	17	1.8%	597	2.5%	
Egg donor age (21-25 years)	194	20.8%	4058	16.9%	
Egg donor age (26-30 years)	333	35.8%	8119	33.9%	
Egg donor age (31-35 years)	376	40.4%	10481	43.7%	
Egg donor age (>35 years)	11	1.2%	714	3.0%	
Patients with previous ART live births	123/893*	13.8%	3310/22292*	14.8%	0.38
Presence of a male factor	204	21.9%	4875	20.3%	0.24
N° embryos transferred					0.74
1	556	59.7%	14344	59.8%	
2	375	40.3%	9610	40.1%	
3	0	0.0%	15	0.1%	
Year of treatment					0.93
2010-2014	425	45.6%	10979	45.8%	
2015-2018	506	54.4%	12990	54.2%	
Type of cycle					0.96
Fresh oocytes	516	55.4%	13337	55.6%	
Frozen oocytes	64	6.9%	1588	6.6%	
Thawed embryos	351	6.9%	9044	37.7%	
Double donation	49	5.3%	5018	20.9%	0.001

\* Missing information in 38 cases and 1677 controls. ART: Assisted Reproductive Technologies

Table 5. Live birth rates and implantation rates in women with and without endometriosis undergoing donor egg cycles across various age categories based on the HFEA dataset

Patients' age, n	Outcome	2010-2014		2015-2018		Total	
		Endometriosis	Controls	Endometriosis	Controls	Endometriosis	Controls
18-34 years, n=4564	Live birth occurrence	n 18 % 23,7%	667 35,0%	28 40,6%	950 37,8%	46 31,7%	1617 36,6%
	Number of foetal sacs	0 50	1161	23 771		73 1932	
	with pulsation	1 21	601	30 969		51 1570	
		2 5	145	5 123		10 268	
		3 0	1	0 1		0 2	
	Embryos transferred	1 36	979	44 1889		80 2868	
		2 40	926	25 622		65 1548	
		3 0	3	0 0		0 3	
	Crude Implantation	26,7%	31,5%	42,6%	38,9%	33,8%	35,4%
	35-37 years, n=2842	Live birth occurrence	n 27 % 38,6%	437 35,6%	27 31,0%	536 36,7%	54 34,4%
Number of foetal sacs		0 41	747	34 468		75 1215	
with pulsation		1 22	386	28 573		50 959	
		2 7	93	3 47		10 140	
		3 0	0	0 2		0 2	
Embryos transferred		1 33	566	54 1083		87 1649	
		2 37	660	33 375		70 1035	
		3 0	0	0 1		0 1	
Crude Implantation		33,6%	30,3%	28,3%	36,7%	30,8%	33,4%
38-39 years, n=2446		Live birth occurrence	n 17 % 32,1%	406 36,2%	25 38,5%	456 37,8%	42 35,6%
	Number of foetal sacs	0 34	669	24 384		58 1053	
	with pulsation	1 16	349	29 476		45 825	
		2 3	102	3 44		6 146	
		3 0	2	0 1		0 3	
	Embryos transferred	1 22	459	45 865		67 1324	
		2 31	662	20 341		51 1003	
		3 0	1	0 0		0 1	
	Crude Implantation	26,2%	31,3%	41,2%	36,7%	33,7%	33,8%
	40-42 years, n=4957	Live birth occurrence	n 39 % 33,3%	831 36,3%	44 33,6%	928 36,3%	83 33,5%
Number of foetal sacs		0 74	1345	39 831		113 2176	
with pulsation		1 37	748	51 951		88 1699	
		2 6	193	3 118		9 311	
		3 0	1	0 3		0 4	
Embryos transferred		1 57	931	106 1709		163 2640	
		2 60	1354	25 711		85 2065	
		3 0	3	0 1		0 4	
Crude Implantation		27,7%	31,2%	36,5%	36,2%	31,8%	34,4%
43-44 years, n=3910		Live birth occurrence	n 17 % 37,8%	652 37,6%	32 37,2%	781 38,2%	49 37,4%
	Number of foetal sacs	0 28	998	37 712		65 1710	
	with pulsation	1 13	576	28 793		41 1369	
		2 4	158	7 95		11 253	
		3 0	3	0 1		0 4	
	Embryos transferred	1 23	729	58 1477		81 2206	
		2 22	1006	28 566		50 1572	
		3 0	0	0 1		0 1	
	Crude Implantation	31,3%	32,9%	36,8%	37,7%	34,8%	35,3%
	45-50 years, n=6181	Live birth occurrence	n 22 % 34,4%	882 32,7%	22 32,4%	1120 33,4%	44 33,3%
Number of foetal sacs		0 39	1680	20 1239		59 2919	
with pulsation		1 16	828	28 1172		44 2000	
		2 9	189	1 156		10 345	
		3 0	3	0 2		0 5	
		>3 0	0	0 1		0 1	
Embryos transferred		1 29	1218	49 2439		78 3657	
		2 35	1479	19 908		54 2387	
		3 0	3	0 2		0 5	
Crude Implantation		34,3%	29,0%	34,5%	35,0%	34,4%	32,1%
Overall	Live birth occurrence	n 140 % 32,9%	3875 35,3%	178 35,2%	4771 36,7%	318 34,2%	8646 36,1%
	Crude Implantation	29,7%	30,9%	36,3%	37,1%	33,0%	34,0%