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Assisted reproductive technology and the risk of gestational diabetes mellitus: a systematic review and meta-analysis

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Abstract

Background: The use of assisted reproductive technology (ART) is increasing worldwide, and observational studies have indicated that women who conceived by ART have an increased risk of pregnancy complications including gestational diabetes mellitus (GDM). We aimed to determine the risk of GDM among women who conceived with ART by systematic review and meta-analysis.

Main text: A systematic literature search was conducted in ISI Web of Knowledge, MEDLINE, Scopus, and Embase through May 2017 for English-language articles using a list of keywords. All studies comparing GDM in women conceived by ART and those who conceived spontaneously were included. Data extraction was performed by two authors independently and discrepancies were resolved by discussion. In total, 48 studies with 91,487 pregnancies conceived through ART and 2,525,234 spontaneously conceived met the inclusion criteria. There was evidence of substantial heterogeneity among these studies ($P < 0.001$, $I^2 = 98.6\%$). Random effects meta-analysis showed a significant increase in GDM among those who conceived by ART compared with those who conceived spontaneously (pooled relative risk = 1.51, 95% confidence interval = 1.18–1.93). Visual inspection of the funnel plot did not reveal any publication bias, which was supported by Egger's test and Begg's test.

Conclusion: The findings of this systematic review indicate that the use of ART treatment is associated with a 1.51-fold increase in GDM. Women need to be counselled carefully before undergoing ART treatment about the possibility and risk of GDM.

Keywords: Assisted reproductive technology, Gestational diabetes mellitus, Infertility, Meta-analysis, Systematic review

Background

Assisted reproductive technology (ART) is a group of medical methods for treating the infertile human in which both male and female gametes are used outside the body to achieve pregnancy [1]. To date, approximately 5 million babies are born worldwide via ART [2]. Although ART may help infertile couples, its use has increased concerns associated with pregnancy-related complications and adverse consequences [3]. It has been suggested that obstetric outcomes in gestation after ART are poor when compared with those pregnancies spontaneously conceived [4]. Moreover, evidence from meta-analyses [4–8] has revealed that singleton pregnancies after ART are at higher risk of adverse consequences than those conceived naturally. One of the outcomes followed by ART is gestational diabetes mellitus (GDM) and is known as one of the most common complications in pregnancy [9, 10]. GDM is defined as "carbohydrate intolerance of variable severity with onset or first recognition during pregnancy" [11]. GDM is a worldwide public health problem and complicates about 7% of all pregnancies [12, 13]. The cause and pathogenesis of GDM is both multifunctional and complex [14]. GDM is prone to causing a woman and her baby a wide range of complications during pregnancy and in later life [15, 16]. women with GDM are more

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likely to develop metabolic syndrome in the future, including type 2 diabetes [17]. Therefore, it is important to realize the risk factors of GDM such as family history of diabetes, obesity, high parity, advanced maternal age, previous adverse pregnancy, non-white race, history of a baby with birth weight > 3800 g, and hypothyroidism [12, 18].

In addition, studies have indicated that ART pregnancies are related to an increased risk of GDM [19–22]. Another study in Australia reported those who underwent ART are more prone to experience GDM compared to those who conceived spontaneously [23]. However, it was shown in another study that the rate of GDM was lower in women who conceived under intracytoplasmic sperm injection (ICSI) compared to those of spontaneously, in vitro fertilization (IVF) or simple ART [24]. Finally, we conducted a meta-analysis to provide an up-to-date survey of pregnancies resulting from ART and the increased risk of GDM between 1997 and 2017. We aimed to investigate the higher risk of GDM in pregnancies following ART and compare them to those of spontaneous conceptions.

Material and methods

Search strategy

This systematic review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist [25]. We searched the electronic databases ISI Web of Knowledge, MEDLINE/PubMed, Scopus, and Embase through May 2017, for studies investigating the relationship between ART and GDM. The search terms used were presented in Table 1. Reference lists from all identified studies were also searched for any relevant articles. Two authors (MM and AA) evaluated the studies, and discrepancies were resolved by discussion.

Table 1 Search strategy for MEDLINE (MeSH, Medical Subject Headings)

	Word or term
1	Gestational Diabetes Mellitus [Text word])
2	"Gestational Diabetes Mellitus" [Text word])
3	Diabetes, Gestational [Text Word])
4	"Diabetes, Gestational" [Text Word])
5	"Diabetes, Gestational" [Mesh]
6	1 OR 2 OR 3 OR 4 OR 5
7	Reproductive techniques, assisted [Text word]
8	Reproductive techniques, assisted [MeSH terms]
9	7 OR 8
10	Cohort studies [Text word]
11	Cohort studies [MeSH terms]
12	Retrospective studies [Text word]
13	Retrospective studies [MeSH terms]
14	Prospective studies [Text word]
15	Prospective studies [MeSH terms]
16	Case-control studies [Text word]
17	Case-control studies [MeSH terms]
18	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
19	6 AND 9 AND 18

Inclusion and exclusion criteria

We included published studies that examined the relationship between the use of ART and the risk of GDM. No restriction criteria were imposed with regard to the size or type of the studied population, nor to the type of ART treatment. The following study types were excluded from the analyses: (a) non-English articles; (b) animal studies; (c) repeated or overlapping studies; (d) reviews, meta-analyses, case reports, editorials, and letters-to-the-editor articles; and (e) unpublished studies.

Outcome and exposure

The exposure variable was all types of ART treatment. Our outcome was GDM, defined as "carbohydrate intolerance of variable severity with onset or first recognition during pregnancy" [11].

Data extraction and quality assessment

Two reviewers (MM and AA) independently abstracted the following data from all eligible articles: first author's name; year of publication; location; study period; design; sample size; type of ART; and study findings. Discrepancies were resolved by discussion between two reviewers.

Quality assessment of included studies was performed independently by two reviewers using the Newcastle–Ottawa Scale (NOS) [26]. The NOS assesses the methodological quality of the observational studies according to three domains: (a) selection of study groups; (b) comparability of groups; and (c) ascertainment of exposure and outcomes. Total scores range from 0 (lowest quality) to 9 (highest quality).

Statistical analysis

Data were analyzed using STATA version 13.0 (Stata Corp, College Station, TX, USA). The pooled relative risk (RR) was calculated with its 95% confidence interval (CI) to assess the strength of the association between the use of ART and GDM risk. To assess between study heterogeneity, both the Cochran Q test and the I^2 statistic (the percentage of total variation across studies attributable to heterogeneity beyond chance) were calculated [27]. I^2 values of 25, 50, and 75% were used as evidence of low, moderate, and high heterogeneity, respectively [27]. Subgroup analysis was performed to detect factors

that may explain heterogeneity in outcome between each study. Publication bias was assessed using visual inspection of a funnel plot, Egger's test, and Begg's test [28, 29]. In all statistical tests, results with $P < 0.05$ were deemed statistically significant, except for the Cochran Q test where $P < 0.10$ was used.

Results

Study selection

The steps of the study selection are displayed in Fig. 1. A total of 950 related published articles were retrieved by using a search strategy in four international databases (638 from Scopus, 91 from PubMed, 62 from ISI Web of Knowledge, and 159 from Embase) and also seven records were identified from Google Scholar and reference lists of final included papers in the meta-analysis. In this study, 829 papers remained after removing duplicate papers using EndNote software. After title and abstract screening, 278 relevant articles were recognized as eligible and they were considered for additional full-text screening. After excluding 230 non-eligible studies, finally, 48 studies (four case-control studies, three cross-sectional studies, and 41 cohort studies) were included in this meta-analysis.

Study characteristics

The study characteristics of the included studies are summarized in Table 2. In total, we included 48 studies published from 1987 to 2017. Observational studies (i.e., cross-sectional, case control and cohort studies) were included in the meta-analysis, whereas non-English studies and studies without relevant data or partial data were excluded. Sample size in the ART group ranged from 31 to 21,615 cases and in the non-ART group it ranged from 20 to 595,168 cases. Of the 48 studies, 19 were conducted in Asia, 17 in Europe, and 12 in America. Fourteen studies were published before 2011 and 34 studies were published from 2011 to 2017.

Quantitative data synthesis

In the present study, 91,487 ART cases (with 6819 cases of GDM) and 2,525,234 non-ART cases (with 113,505 cases of GDM) were included in the analysis. RRs and their 95% CIs were calculated using the Mantel–Haenszel method and, because of significant heterogeneity

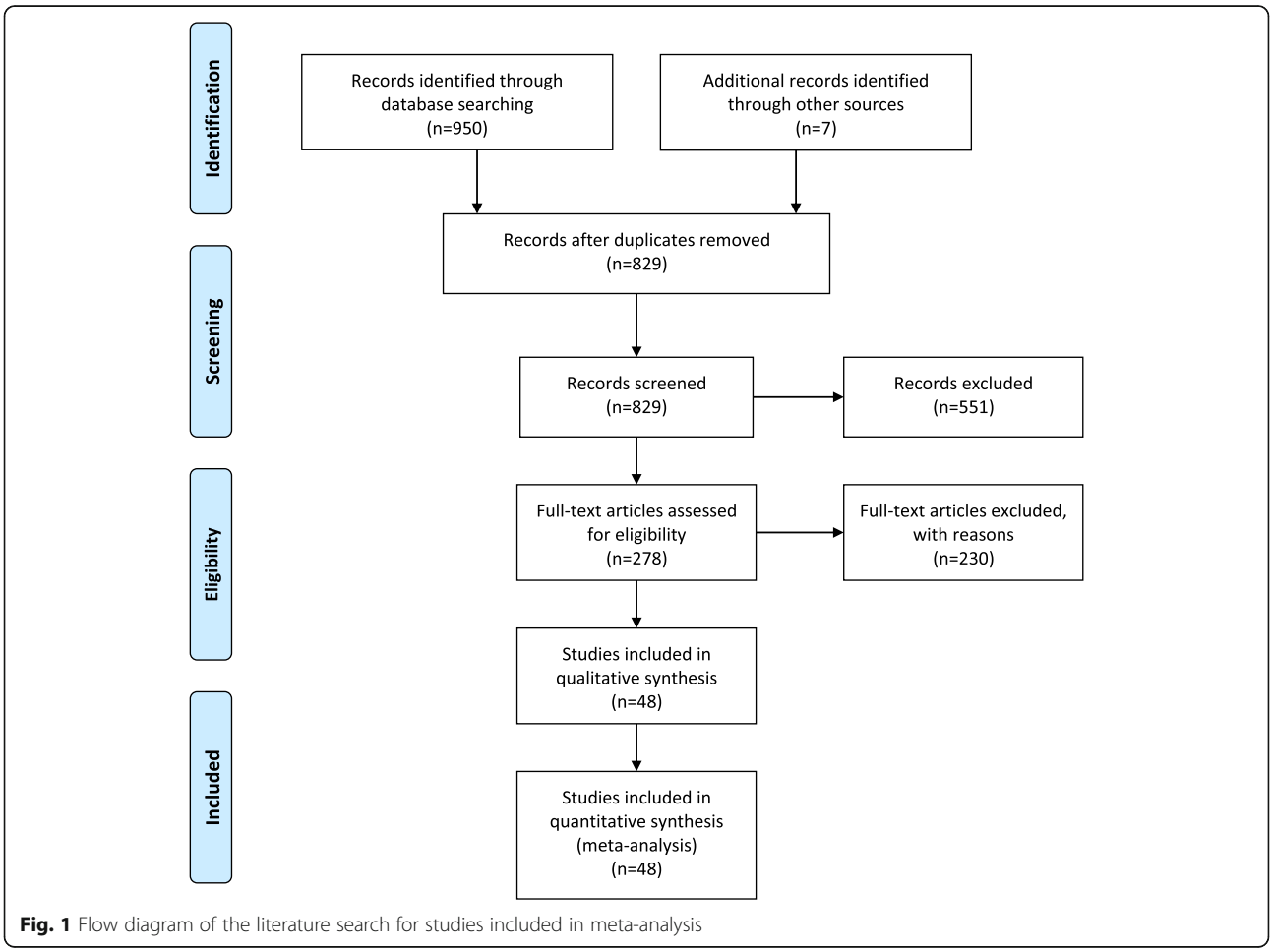

Fig. 1 Flow diagram of the literature search for studies included in meta-analysis

Table 2 Characteristics of the primary studies included in the meta-analysis

First author	DOP	Country	Period	Design	Mean of age		Type of ART	# of GDM in ART group		# of GDM in non-ART group	
					ART	Non-ART		*n* (GDM)	*N* (Total)	*n* (GDM)	*N* (Total)
Varma TR [30]	1987	UK	1983–1985	Cohort	NA	NA	NA	7	362	67	7284
Vollenhoven B [31]	2000	Australia	1990–1997	Case–Control	NA	NA	OI	22	60	10	60
Bjercke S [32]	2002	Norway	1993–1998	Cohort	31.32	32.7	IVF	4	52	2	355
Koivurova S [33]	2002	Finland	1990–1995	Cohort	31.8	31.8	IVF	12	225	21	671
Nassar AH [34]	2003	USA	1995–2000	Cohort	35	36	IVF	3	56	6	112
Pinborg A [35]	2004	Denmark	1997	Cohort	33.1	30.5	IVF/ICSI	13	236	16	566
Shevell T [36]	2005	USA	1999–2002	Cohort	33.19	29.9	IVF/OI	92	1776	1166	34,286
Saygan-Karamürsel B [21]	2006	Turkey	1999–2003	Case–Control	31.45	28.94	ICSI	22	274	10	348
Buckett WM [37]	2007	Canada	1998–2003	Cohort	34.375	34	IVF/ICSI/IVM	39	344	25	344
Adler-Levy Y [22]	2007	Israel	1988–2002	Case–Control	30.27	29.4	IVF/OI	96	1036	153	3694
Eskandar M [38]	2007	Saudi Arabia	2004–2006	Cohort	28.29	26.44	ICSI	3	35	7	73
Krieg SA [39]	2008	USA	2001–2005	Cohort	42.7	41.3	IVF	10	71	9	108
Vasario E [40]	2010	Italy	2004–2008	Cohort	31.5	33.5	IVF	10	84	13	139
Suzuki S [41]	2010	Japan	2000–2007	Cohort	37.8	37.9	IVF	1	64	1	87
Tepper NK [42]	2011	USA	1997–2004	Cohort	36	30	NA	112	6256	4434	595,168
Montoya JB [43]	2012	Mexico	2005–2009	Cohort	32.5	31.6	NA	7	57	7	57
Moini A [44]	2012	Iran	2008–2010	Cohort	30.6	27.3	IVF/ICSI	21	230	15	170
Bamberg C [45]	2012	Germany	1998–2008	Cohort	32.5	30.1	IVF/ICSI	19	426	26	813
Le Ray C [46]	2012	France	2008–2010	Cohort	>43	>43	IVF/OD	11	144	12	236
Werder E [47]	2013	USA	2002–2008	Cohort	NA	NA	IVF	155	2233	30	299
Wang Y [48]	2013	Australia	2007–2009	Cross–Sectional	NA	NA	NA	1044	13,732	19,333	386,660
Farhi A [49]	2013	Israel	2006–2008	Cohort			IVF/ICSI	61	561	59	600
Toshimitsu M [50]	2014	Japan	2006–2010	Cohort	NA	NA	IVF/ICSI	0	116	6	664
Castera D [51]	2014	Italy	2007–2011	Cohort	38.5	33.5	IVF/ICSI	14	138	6	207
Ashrafi M [52]	2014	Iran	2011–2012	Cross–Sectional	30	26.4	IVF	174	468	17	234
Ashrafi M [53]	2014	Iran	2011–2012	Cross–Sectional	30.35	26.6	ICSI/IVF/IUI	13	54	4	20
Silberstein T [54]	2014	Israel	1988–2006	Cohort	30.9	28.49	IVF/OI	492	3268	11,319	171,513
Yang X [55]	2014	China	2011	Cohort	NA	NA	ART	172	1139	5179	111,264
Domingues A [56]	2014	Portugal	1996–2011	Cohort	NA	NA	IVF/ICSI	15	180	31	698
Stern JE [57]	2015	USA	2004–2008	Cohort	NA	NA	NA	81	3689	3363	302,085
Jie Z [58]	2015	China	2010–2013	Cohort	32.53	29.87		48	428	190	2788
Nunes F [59]	2015	NA	NA	Case–Control	34.3	31.4	NA	11	77	23	208
Barua S [60]	2016	Australia	2007–2010	Cohort	32.1	29.2	ART	224	1727	3270	48,654
Zhu L [61]	2016	China	2006–2014	Cohort	31.84	31.73	IVF/ICSI	309	2641	342	5282
Martin AS [62]	2016	USA	2008–2012	Cohort	NA	NA	ART	397	14,761	22,925	100,857
Luke B [63]	2016	USA	2004–2010	Cohort	36.65	30.1	ART	93	1338	2951	56,755
Bashmakova NV [64]	2016	Russia	NA	Cohort	NA	NA	ART	12	37	6	96
Rosato E [65]	2016	Italy	2010–2011	Cohort	44.2	44.1	ART	6	72	6	80
Valenzuela-Icaraz B [66]	2016	Spain	2004–2010	Cohort	33.46	31	IVF/ICSI/OI	17	488	4	200
Marton V [67]	2016	Sweden	1994–2014	Cohort	35.25	33.275	IVF/ICSI	54	312	44	912
Beyer DA [68]	2016	German	NA	Cohort	39	39	IVF/ICSI	4	467	161	6417
Pourali L [69]	2016	Iran	2009–2014	Cohort	28.9	27.1	ART	8	31	8	96

Table 2 Characteristics of the primary studies included in the meta-analysis *(Continued)*

First author	DOP	Country	Period	Design	Mean of age		Type of ART	# of GDM in ART group		# of GDM in non-ART group	
					ART	Non-ART		*n* (GDM)	*N* (Total)	*n* (GDM)	*N* (Total)
Ben-Yaakov RD [70]	2016	Israel	1988–2012	Cohort	30.9	28.7	IVF/OI	585	4153	5895	95,138
Qin J [71]	2016	China	2013–2016	Cohort	31.3	29.26	IVF	165	1260	823	4379
Wang YPA [72]	2016	Australia	2007–2011	Cohort	NA	NA	NA	1736	21,615	30,869	574,905
Korosec S [73]	2016	Slovenia	2004–2011	Cohort	33.42	33.42	IVF/ET/FET	43	1127	129	3381
Morency AM [74]	2016	Canada	2000–2013	Cohort	33	31.4	ART	4	49	19	181
Luke B [75]	2017	USA	2004–2010	Cohort	35.3	30.4	IVF	378	3538	493	6090

DOP date of publication, *GDM* gestational diabetes mellitus, *ART* assisted reproductive technology, *Non-ART* non-assisted reproductive technology, *NA* not available

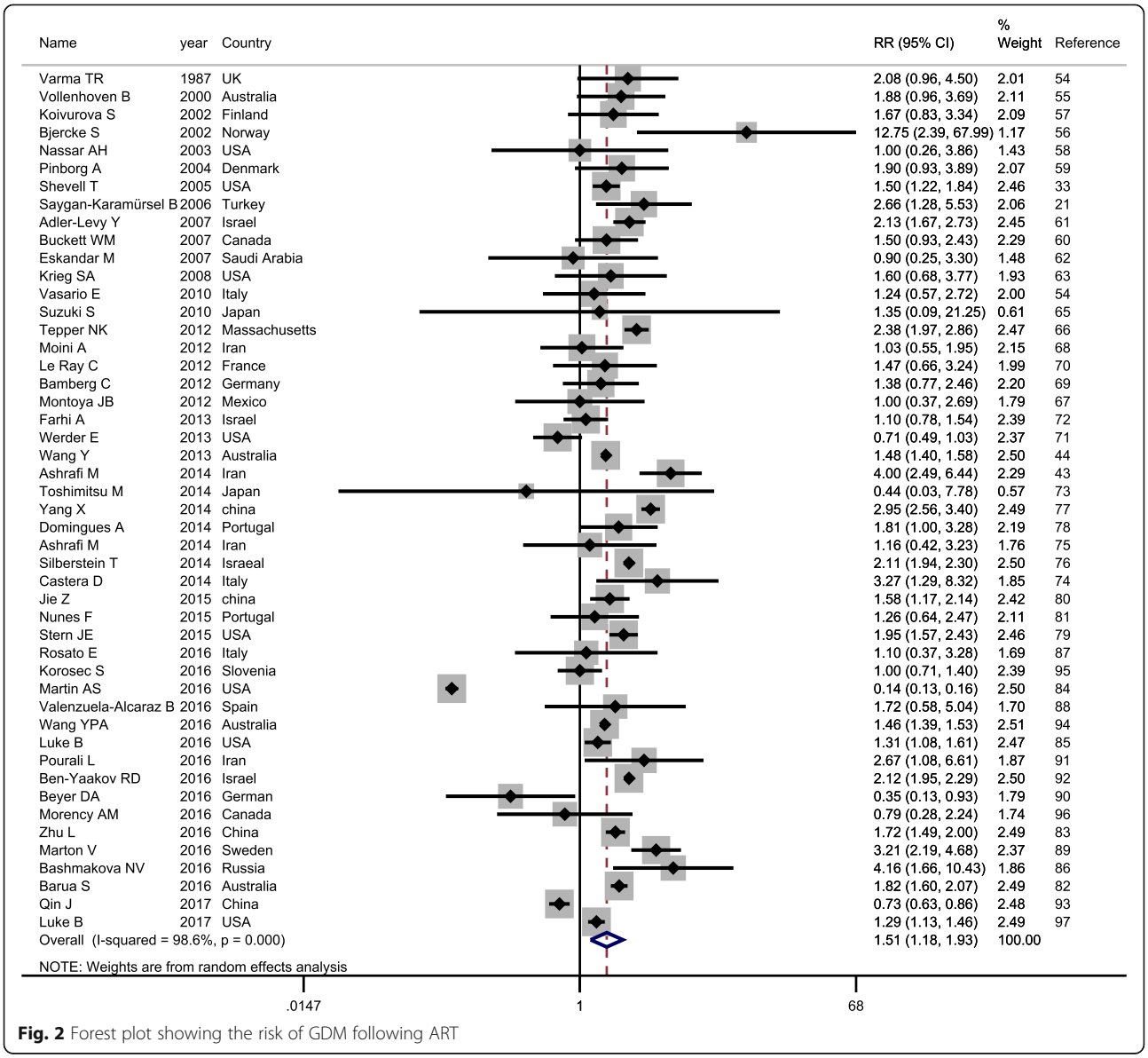

Fig. 2 Forest plot showing the risk of GDM following ART

between studies, random effect models were also used. The relationship of ART and the risk of GDM was estimated using 48 included primary studies. The summary estimate of RR in this meta-analysis suggested that ART significantly was associated with higher risk of GDM (pooled RR = 1.51, 95% CI = 1.18–1.93, P = 0.001); that is, the risk of GDM in the ART group is 1.51 times compared to that in the non-ART group (Fig. 2 and Table 3).

Heterogeneity analysis

To check the heterogeneity between studies, chi-square test, I-squared, and Tau-squared were conducted. Chi-square analysis revealed that there was a significant heterogeneity between primary studies (P < 0.001, I^2 = 98.6%); consequently, to pool the effect sizes in this study, a random effect model was used. To find the source of heterogeneity between studies, subgroup analyses were performed on the basis of study design, study region, and study period (Table 3). Even after the aforementioned subgroup analyses, heterogeneity across the studies did not diminish successfully in all subgroups; for that reason, some estimations of pooled RR were measured by the random effects model and only pooled RR for case control studies and the papers that were published between 1987 and 2010 were estimated by a mixed-effect model (Figs. 3, 4 and 5).

Risk of publication bias

Graphical (funnel plot) and statistical tools (Begg's and Egger's test) were done to test the existence of publication bias in the studies. The results of the symmetrical funnel plot (Fig. 6), Egger's test (P = 0.331), and Begg's test (P = 0.810) suggested that there was no significant publication bias in this study.

Discussion

The current study aimed to assess the impact of ART on GDM using a systematic review of related articles. This meta-analysis included 344,021 cases, in which 91,487 cases used ART to achieve pregnancy. Statistical approaches were determined based on the heterogeneity of the included studies and publication bias was checked. Several subgroups were defined based on the study design, time period, and region.

The results from this meta-analysis revealed that GDM is strongly affected by the use of ART. The relative risk of GDM was significant regarding the use of ART. Regarding the magnitude of the RR, the results from different study designs were in accordance. However, the included cross-sectional studies did not report a significant pooled RR in contrast to cohort and case-control studies and this might be due to the lower number of cross-sectional studies. Moreover, the impact of ART on GDM did not differ in two distinct periods of time (2010 as the cut-off point). In contrast to America, consistent results were found in two regions of Asia and Europe. The pooled RR resulting from American studies showed a higher risk of GDM among those in the non-ART group.

The ART has been defined as treatments including in vitro handling of oocytes and sperm, and embryos, in which establishing pregnancy is the goal [76]. There have been many debates on the efficacy and safety of using ART regarding its increasing trend of use across most countries [77, 78]. It has been shown that ART is responsible for a high number of adverse pregnancy-related complications and obstetric outcomes such as polyhydramnios, low and very low infant birth weight, pregnancy-induced hypertension, pre-eclampsia, perinatal mortality, preterm and very preterm birth, placenta

Table 3 Summary of meta-analysis results and subgroups analysis

Groups	# of studies	Test of association			Heterogeneity	
		RR (95% CI)	P	Model	P	I square
Total studies	48	1.51 (1.18–1.93)	0.001	Random	< 0.001	98.9%
Study design						
Cohort	41	1.44 (1.07–1.95)	0.021	Random	< 0.001	98.8%
Case control	4	2.04 (1.65–2.51)	0.001	Fixed	0.445	0
Cross-sectional	3	1.99 (0.93–4.26)	0.095	Random	< 0.001	88.1%
Time period						
1987–2010	14	1.75 (1.50–2.05)	< 0.001	Fixed	0.343	10.1%
2011-2017	34	1.42 (1.05–1.90)	0.022	Random	< 0.001	99.0%
Region						
Europe	16	1.75 (1.31–2.34)	< 0.001	Random	< 0.001	65.3%
Asia	19	1.70 (1.45–1.98)	< 0.001	Random	< 0.001	94.2%
America	12	1.07 (0.46–2.52)	< 0.001	Random	< .001	99.4%

RR relative risk, *CI* confidence interval

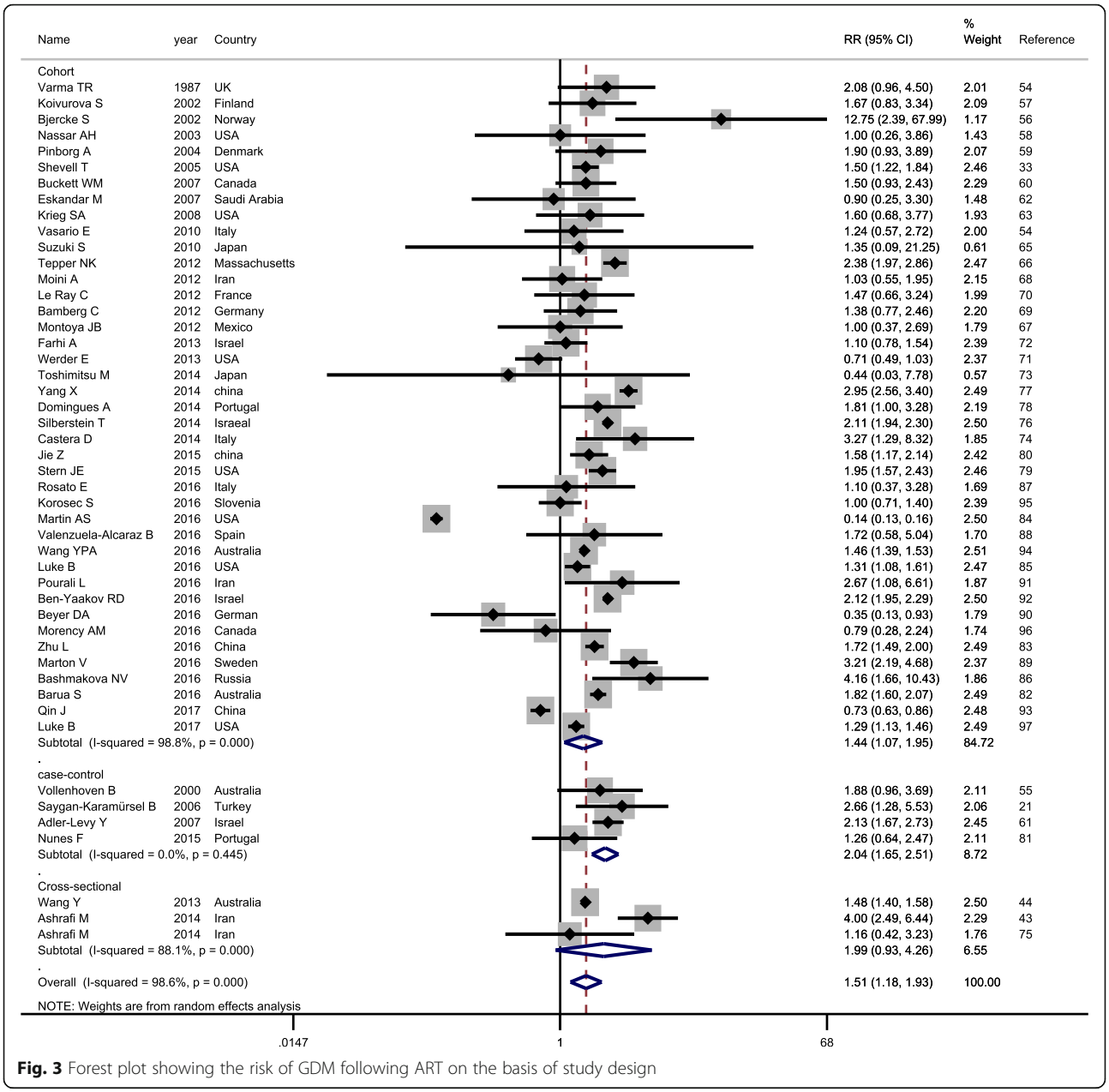

Fig. 3 Forest plot showing the risk of GDM following ART on the basis of study design

previa, antepartum hemorrhage, multiple pregnancy congenital malformation, higher risk of ectopic pregnancy, lower odds of vaginal delivery, postpartum hemorrhage, oligohydramnios, small for gestational age, and placental abruption [36, 79–83]. As mentioned, using ART was associated with GDM, which is diabetes diagnosed during pregnancy. Pregnancy may cause insulin resistance and hyperinsulinemia and can be followed by diabetes. GDM is defined as glucose intolerance with the first recognition during pregnancy and usually progresses in the second trimester [84]. GDM is associated with a large number of risk factors, such as elevated pre-pregnancy body mass index, older maternal age, history of GDM, diabetes among family members, polycystic ovary syndrome (PCOS), pre-existing hypertension, weight gain during pregnancy, smoking, ART, and higher parity [85–87]. The adverse effect of ART on GDM is discussed by several studies; however, the mechanism has not been well clarified [48, 52]. Several hypotheses are introduced in which GDM is influenced by the use of ART, including the etiology of infertility, the drugs used in the treatment procedure, the hormonal levels, and metabolic and vascular factors [19, 52]. However, it has been revealed that maternal age is the most effective factor on GDM [88]. Wang et al. have discussed the association between GDM and ART through

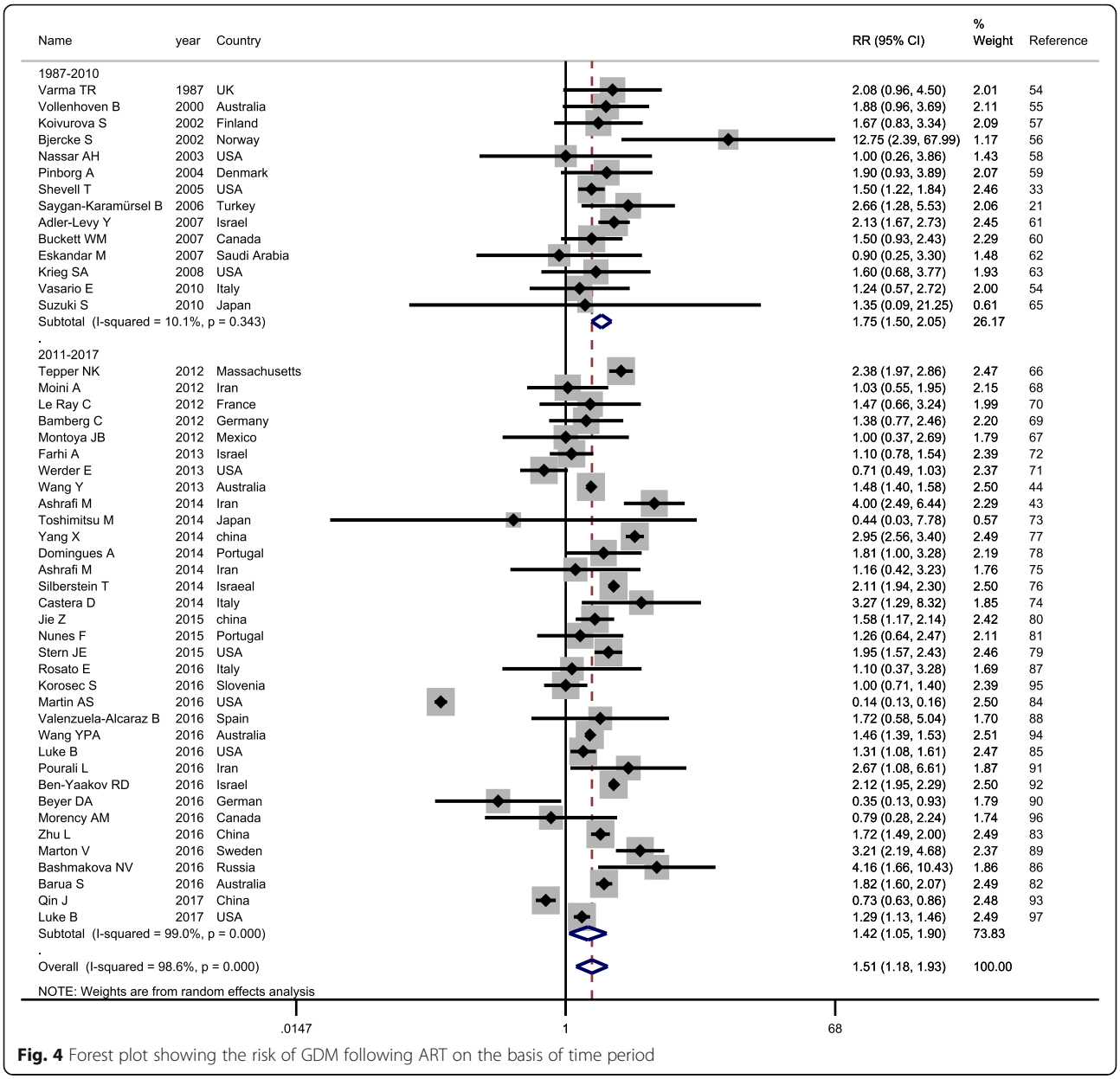

Fig. 4 Forest plot showing the risk of GDM following ART on the basis of time period

impaired glucose tolerance in comparison to those of spontaneous conceptions. Moreover, they have exposed that for singleton mothers, GDM was more common among cases that underwent ART. However, the risk increases for singleton mothers younger than 40 [48]. Double embryo transfer has been introduced as a significant factor for multiple gestational pregnancy, which is followed by an elevated risk of GDM [89, 90]. Vitthala et al. assessed the risk of monozygotic twins after ART using a systematic review and they revealed that in comparison to cleavage embryo transfer, GDM is more affected by blastocyst transfer [91]. Hammoud et al. addressed the scientific question of whether it is important to diagnose GDM by screening or symptoms. They showed that GDM is strongly related to large-for-gestational-age births [92] and Sazonova et al. showed that babies after embryo transfer have a higher large for gestational age compared to fresh embryo transfer [93]. Pre-existing hypertension is associated with GDM [87] and this might be due to higher rates of ART mothers being of high maternal age [94]. Sibai and Ross assessed the pathophysiology and long-term consequences of hypertension in GDM. They demonstrated that mothers of twins are at a higher risk of GDM in contrast to those of singletons [90]. Risk of GDM among women with PCOS was assessed by Toulis et al. in a systematic review. They showed an increased likelihood of

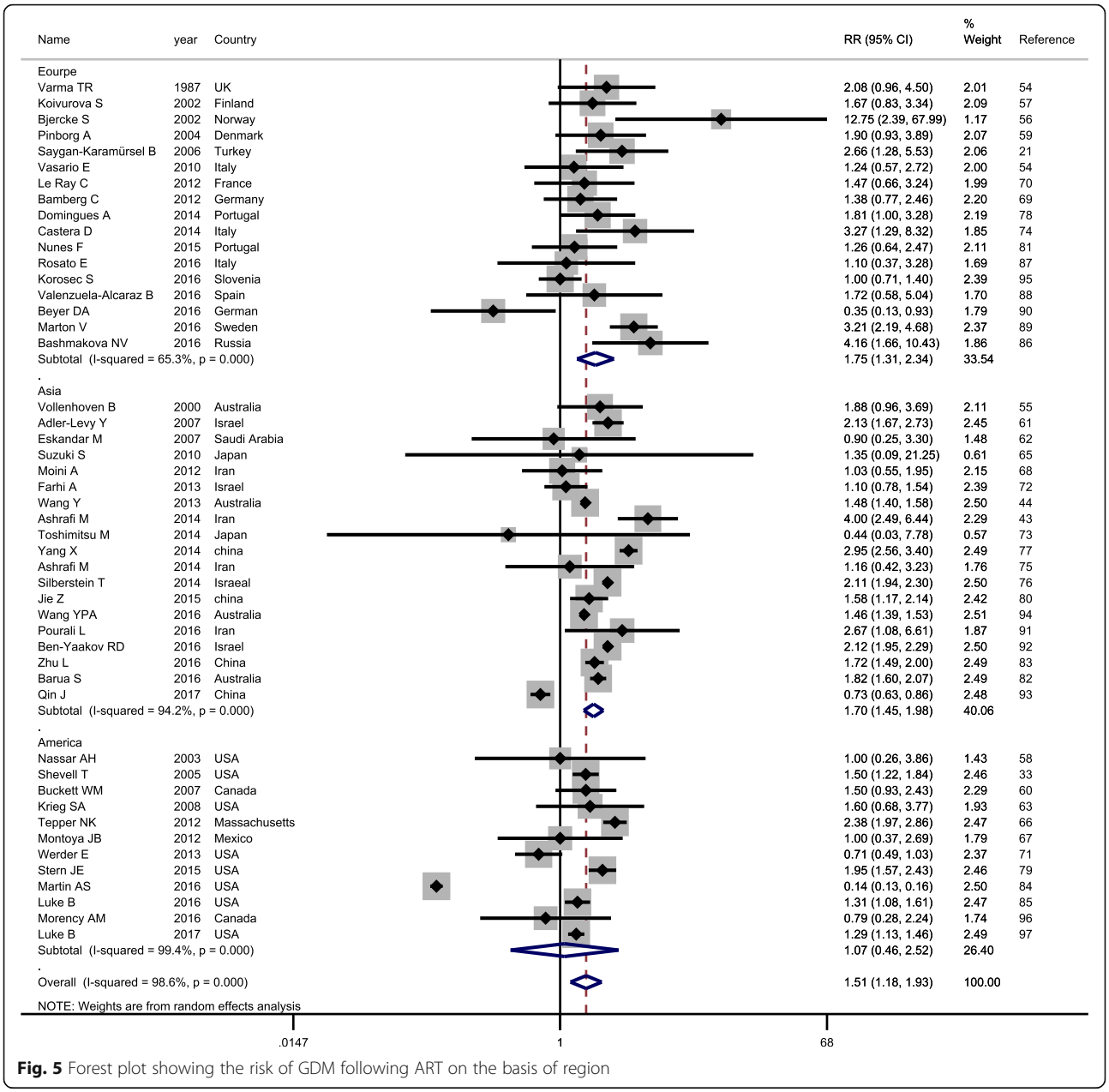

Fig. 5 Forest plot showing the risk of GDM following ART on the basis of region

developing GDM among women with PCOS compared with general cases [95].

The current meta-analysis revealed a significant heterogeneity among the pooled studies, the cohort and cross-sectional studies, the studies conducted during 2011–2017, and the three regions of Asia, Europe, and America. Several statistical tools are available to check the heterogeneity of included studies in a meta-analysis and its selection mechanism depends on several factors such as sample size, the frequency of included studies, etc. The two common tests for heterogeneity (chi-square and the I^2 value) can result in controversial conclusions regarding the number of included studies and the magnitude of the relative risks [96]. There might be many reasons for the presence of heterogeneity in the results, such as different cultural and ethnic conditions and diversity in the amount of regions' development.

The present systematic review has several limitations that should be noted. First, the most important limitation for this study as for other meta-analysis studies is the lack of data for subgroup analysis based on type of pregnancy (singleton versus twin pregnancy), type of ART, or for data analysis controlling for known confounders. Second, there were no data on the relationship between ART and GDM for large regions such as Africa and Latin America, thus the generalizability of the

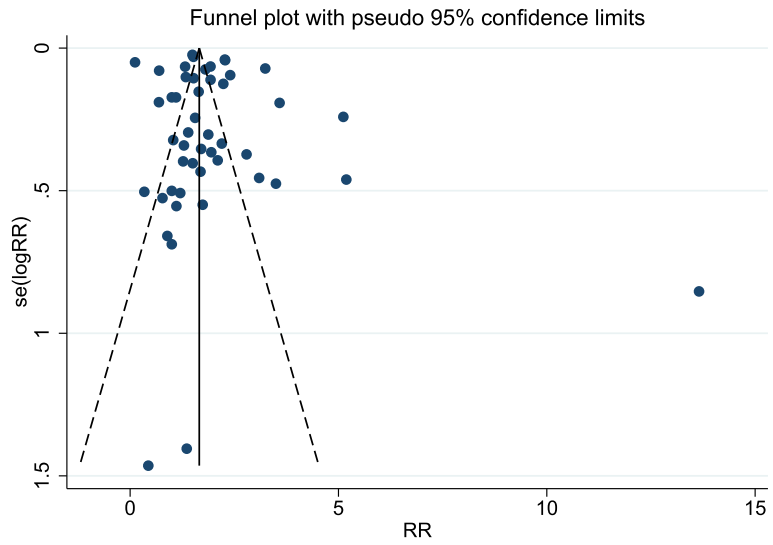

Fig. 6 Funnel plot to assess the presences of publication bias

results may be limited. Third, this study included only English papers.

In sum, the findings of the present systematic review and meta-analysis indicate that the use of ART is associated with a 1.51-fold increase in GDM. Women need to be counselled carefully before undergoing ART treatment about the possibility and risk of GDM.

Abbreviations

ART: Assisted reproductive technology; CI: Confidence interval; GDM: Gestational diabetes mellitus; NOS: Newcastle–Ottawa Scale; PCOS: Polycystic ovary syndrome; RR: Relative risk

Acknowledgments

Not applicable.

Authors' contributions

AA, MM, ROS, SM, and AAH conceived the study. MM, PA, BN, SM, EKM, and AA collected the data. AAH and SM analyzed the data. All authors contributed equally to draft the manuscript. All authors revised the manuscript and approved the final version.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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