Relation between Traditional Semen Parameters, Sperm DNA Fragmentation, and Unexplained Recurrent Miscarriage: A Systematic Review and Meta-analysis

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Abstract

Background: Several studies have explored the relation between traditional semen parameters, sperm DNA fragmentation (SDF), and unexplained recurrent miscarriage (RM), but these findings remain controversial. Hence, we conducted this meta-analysis to explore the relation between traditional semen parameters, SDF, and unexplained RM.

Methods: Multiple databases including PubMed, Google Scholar, MEDLINE, EMBASE, Cochrane Library, Web of Science databases, and China National Knowledge Infrastructure (CNKI) were searched to identify relevant publications. From the eligible publications, data were extracted independently by two researchers. The heterogeneity between publications was calculated using the I^2 statistics and Cochran's Q test. Statistical analyses were conducted using Stata/SE 12.0 (StataCorp, College Station, Texas, USA). Based on heterogeneity assessment, random- or fixed-effects models were selected to calculate the weighted mean differences (WMDs) and their corresponding 95% confidence intervals (CIs). To estimate the stability of the pooled results, a sensitivity analysis was conducted by excluding each study. To estimate the possible publication bias, Egger's regression test and Begg's funnel plot were used.

Results: A total of 280 publications were produced using the search strategy. According to the inclusion/exclusion criteria, 19 publications were eligible. A total of 1182 couples with unexplained RM and 1231 couples without RM were included in this meta-analysis to assess the relation between traditional semen parameters, SDF, and unexplained RM. Our results showed that couples with unexplained RM had significantly increased levels of SDF (WMD=8.77, 95% CI=4.03 to 13.51, $P<0.001$) and significantly decreased levels of progressive motility (WMD=-4.75, 95% CI=-8.35 to -1.15, $P<0.05$) and total motility (WMD=-10.30, 95% CI=-15.03 to -5.57, $P<0.05$) than those of couples without RM, but not significantly different in volume (WMD=-0.12, 95% CI=-0.32 to 0.08, $P>0.05$), sperm concentration (WMD=-2.28, 95% CI=-4.58 to 0.02, $P>0.05$) and total sperm count (WMD=-10.73, 95% CI=-22.11 to 0.66, $P>0.05$) between couples with and without RM.

Conclusion: Couples with unexplained RM had significantly increased levels of SDF and significantly decreased levels of progressive motility and total motility than those of couples without RM. SDF assay may be considered as part of the evaluation of couples with unexplained RM.

Introduction

There is no uniform definition of recurrent miscarriage (RM). The American Society for Reproductive Medicine (ASRM) defines RM as two or more consecutive miscarriages [1]. The Royal College of Obstetricians and Gynecologists (RCOG) defines RM as three or more consecutive miscarriages before 24 gestational weeks [2]. The Chinese Society of Obstetrics and Gynecology defines RM as three or more consecutive miscarriages before 28 gestational weeks [3]. The European Society of Human Reproduction and Embryology (ESHRE) guideline defines RM as three or more consecutive miscarriages before 20 gestational weeks [4]. It affects about 1% of couples of childbearing age [5]. In almost half of the cases of RM, the etiology of affected couples remains unclear [1]. Research has mainly focused on female factors for RM, but the role of male factors in RM has recently gained attention [6–8].

Semen quality is usually assessed by volume, sperm concentration, total sperm count, progressive motility, and total motility. Implications of these parameters on RM are debatable. But traditional semen parameters do not assess the integrity of sperm chromatin. Sperm DNA fragmentation (SDF) is used to assess the integrity of sperm chromatin and it is increasingly recognized as being crucial for its diagnostic capabilities of male fertility potential and pregnancy outcomes. The main methods are as follows: sperm chromatin dispersion (SCD) technique [9–13], terminal deoxyuridine nick end labeling (TUNEL) assay [14–18], acridine orange test (AOT) [19], sperm chromatin structure assay (SCSA) [17, 20–25], aniline blue (AB) staining [26].

This systematic review and meta-analysis aimed to assess the relation between traditional semen parameters, SDF, and unexplained RM.

Materials And Methods

Literature search

The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. Multiple databases including PubMed, Google Scholar, Cochrane Library, EMBASE, Web of Science databases, MEDLINE, and China National Knowledge Infrastructure (CNKI) were searched to identify relevant articles. We searched the literature

using the following terms: “recurrent pregnancy loss”, “repeated pregnancy loss”, “recurrent abortions”, “recurrent spontaneous abortion”, “recurrent miscarriage”, “sperm DNA fragmentation”, “sperm DNA integrity”, “sperm DNA damage”, “SDF”, “DFI”, “traditional semen parameters”, and “conventional semen parameters”.

selection criteria

Studies that met the following criteria were included in this study: (1) original research; (2) the topic is unexplained RM; (3) the data for traditional semen parameters and SDF are expressed as the means with standard deviations (SDs). The exclusion criteria were the following: (1) reviews, letters, editorials, and abstracts; (2) inaccessible full articles; (3) case-only studies; (4) duplicate publications.

Selection of publications

Based on the predefined inclusion/exclusion criteria, all publications were independently selected for eligibility by two authors (Y.D. and J.L.). After removing the duplicates, articles were selected by reviewing the titles and abstracts. The remaining publications were retrieved for full-text assessment if appropriateness could not be determined. Any discrepancy was resolved through discussion with the third reviewer (E.Y.).

Data extraction

From the eligible publications, data were extracted independently by two authors (Y.D. and J.L.). Any discrepancy between the two authors (Y.D. and J.L.) was resolved by discussing with the third reviewer (E.Y.). The following information was collected for each eligible publications: name of the first author, publication year, country of origin, ethnicity group, type of study design, sample size, and methods to evaluate SDF.

Quality assessment of the included publications

Quality assessment were performed using the Newcastle-Ottawa Scale (NOS) [28]. A NOS score of ≥ 6 was considered as high quality [29].

Statistical analysis

All analyses were performed using Stata/SE 12.0 (StataCorp, College Station, Texas, USA). The heterogeneity between publications was calculated using the I^2 statistics and Cochran’s Q test. If the $P>0.10$ and/or $I^2<50\%$, the heterogeneity was considered significant. Based on heterogeneity assessment, random- or fixed-effects models were selected to calculate the weighted mean differences (WMDs) and their corresponding 95% confidence intervals (CIs). To explore the potential sources of heterogeneity, the subgroup analyses were performed. To estimate the stability of the pooled results, a sensitivity analysis was conducted by excluding each publication. To estimate the possible publication bias, Egger’s regression test and Begg’s funnel plot were used. Statistical significance was set at $P< 0.05$.

Results

Selection of publications

Figure 1 shows the selection process of eligible publications. Based on our search strategy, 280 publications were initially identified through databases searching. A total of 249 titles and abstracts of publications were reviewed after removing 31 duplicates. After screening the titles and abstracts of publications, 26 potentially relevant publications were found. The remaining publications were retrieved for full-text assessment After full-text assessment of the remaining publications, 7 publications were excluded for various reasons. A total of 19 publications were finally included in the meta-analysis, which involved 2413 subjects (1182 couples with unexplained RM and 1231 couples without RM).

Characteristics of eligible publications

Table I presents the main characteristics of the eligible publications. All included articles, published between 2003 and 2019, were of relatively high quality.

Table I
The maincharacteristics of the included studies in the meta-analysis.

Author (year)	Country	Ethnicity	Study design	Cases	Controls	Sample size Cases/controls	Samples for DFI	Assay	Quality score
Absalan et al. (2012)	Iran	Asian	Prospective	RPL≥ 3 times	Fertile	30/30	Fresh semen	SCD	7
Bareh et al. (2016)	USA	Caucasian	Prospective	RPL≥ 2times	≥1 live birth	26/31	Fresh semen	TUNEL	7
Bhattacharya et al. (2008)	India	Asian	Prospective	RPL≥ 2times	≥1 live birth	74/65	Fresh semen	AOT	7
Brahem et al. (2011)	Tunisia	African	Prospective	RPL≥ 2times	Fertile	31/20	Frozen semen	TUNEL	7
Carlini et al. (2017)	Italy	Caucasian	Prospective	RPL≥ 2times	≥1 live birth	112/114	Fresh semen	TUNEL	8
Carrell et al. (2003)	USA	Caucasian	Prospective	RPL≥ 3 times	≥1 live birth	21/26	Frozen semen	TUNEL	7
Coughlan et al. (2015)	UK	Caucasian	Prospective	RPL≥ 3 times	≥1 live birth	16/7	Fresh semen	SCD	8
Eisenberg et al. (2017)	USA	Caucasian	Prospective	RPL≥ 2times	Currently pregnant	14/246	Frozen semen	SCSA	9
Gil-villa et al. (2010)	USA	Caucasian	Prospective	RPL≥ 2times	≥1 live birth	23/11	Frozen semen	SCSA	7
Imam et al. (2011)	India	Asian	Retrospective	RPL≥ 3 times	≥1 live birth	20/20	Frozen semen	SCSA	8
Kamkar et al. (2018)	Iran	Asian	Retrospective	RPL≥ 2times	≥1 live birth	42/42	Frozen semen	SCSA and TUNEL	7
Khadem et al. (2014)	Iran	Asian	Prospective	RPL≥ 3 times	Currently pregnant	30/30	Fresh semen	SCD	8
Kumar et al. (2012)	India	Asian	Prospective	RPL≥ 3 times	≥1 live birth	45/20	Frozen semen	SCSA	7
Ribas-Maynou et al. (2012)	Spain	Caucasian	Prospective	RPL≥ 2times	≥1 live birth	20/25	Frozen semen	SCD	8
Ruixue et al. (2013)	China	Asian	Prospective	RPL≥ 3 times	Currently pregnant	68/63	Fresh semen	AB staining	7
Venkatesh et al. (2011)	India	Asian	Prospective	RPL≥ 3times	≥1 live birth	16/20	Frozen semen	SCSA	7
Zhang et al. (2012)	China	Asian	Prospective	RPL≥ 2times	≥1 live birth	111/30	Fresh semen	SCD	7
Zhu et al. (2019)	China	Asian	Retrospective	RPL≥ 2times	Fertile	461/411	Fresh semen	SCSA	8
Zidi-Jrah et al. (2016)	Tunisia	African	Prospective	RPL≥ 2times	≥1 live birth	22/20	Frozen semen	TUNEL	7

Sperm chromatin structure assay (SCSA), sperm chromatin dispersion (SCD), terminal TdT-mediated dUTP-nick-end labelling (TUNEL), acridine orange test (AOT). AB staining, aniline blue staining.

The relation between traditional semen parameters and unexplained RM

Sixteen studies explored the relation between traditional semen parameters and unexplained RM. The pooled results showed that there were no relations between unexplained RM and volume (WMD=-0.12, 95% CI=-0.32 to 0.08, $P > 0.05$), sperm concentration (WMD=-2.28, 95% CI=-4.58 to 0.02, $P > 0.05$), and total sperm count (WMD=-10.73, 95% CI=-22.11 to 0.66, $P > 0.05$) (Fig. 2). However, the pooled results showed that there were significant relations between unexplained RM and progressive motility (WMD=-4.75, 95% CI=-8.35 to -1.15, $P < 0.05$) and total motility (WMD=-10.30, 95% CI=-15.03 to -5.57, $P < 0.05$) (Fig. 2).

The relation between SDF and unexplained RM

Seventeen studies explored the relations between SDF and unexplained RM. The pooled results showed that couples with unexplained RM had significantly increased levels of SDF compared with those of couples without RM (WMD = 8.77, 95% CI = 4.03 to 13.51, $P < 0.001$) (Table II and Fig. 3). However, there was marked between-study heterogeneity that could not be ignored ($I^2 = 99.0\%$, $P < 0.001$) (Table II and Fig. 3). Therefore, subgroup analyses by assay, the definition of RM, sperm preparation, ethnicity were performed to explore the source of heterogeneity. The subgroup analysis by SDF assay showed that couples with unexplained RM had significantly increased levels of SDF compared with those of couples without RM for the SCD assay (WMD = 3.24, 95% CI = 1.49 to 4.98, $P < 0.001$), SCSA assay (WMD = 5.30, 95% CI = 1.42 to 9.17, $P < 0.001$) and TUNEL assay (WMD = 15.68, 95% CI = 6.49 to 24.87, $P = 0.001$) (Table II and Fig. 3A). The pooled WMDs were highest for the TUNEL assay compared with WMDs for SCD and SCSA assays. In the subgroup analysis of the definition of RM, couples with a history of RM ≥ 3 times did not have significantly increased levels of SDF compared with those of couples without RM (WMD = 8.97, 95% CI=-0.34 to 18.28, $P = 0.059$), but couples with RM ≥ 2 times had significantly increased levels of SDF than those of couples without RM (WMD = 8.67, 95% CI = 2.74 to 14.60, $P = 0.004$) (Table II and Fig. 3B). The subgroup analysis by the semen preparation used indicated that couples with unexplained RM had significantly increased levels of SDF compared with those of couples without RM in the fresh semen subgroup (WMD = 8.45, 95% CI = 1.48 to 15.42, $P = 0.018$) and the frozen semen subgroup (WMD = 9.02, 95% CI = 2.11 to 15.92, $P = 0.010$) (Table II and Fig. 3C). Similarly, the subgroup analysis by ethnicity showed that couples with unexplained RM had significantly increased levels of SDF compared with those of coupels without RM in the Caucasian population (WMD = 10.14, 95% CI = 0.35 to 19.93, $P = 0.042$) and Asian population (WMD = 6.23, 95% CI = 3.60 to 8.86, P 0.001), but did not have significantly increased levels of SDF in African population (WMD = 11.63, 95% CI=-0.37 to 23.62, $P = 0.057$) (Table II and Fig. 3D).

Table II
Meta-analysis results of age, height, weight and body mass index (BMI).

Outcomes	*N*	Model used	Heterogeneity		Pooled WMD		Begg's test *P*
			I^2 (%)	*P* value	WMD (95 CI)	*P* value	
Sperm DNA fragmentation							
SCD	4	Random-effects	67.9	0.025	3.24 (1.49 to 4.98)	0.001	
TUNEL	6	Random-effects	99.2	0.001	15.68 (6.49 to 24.87)	0.001	
AOT	1	NA	NA	NA	NA	NA	
SCSA	6	Random-effects	88.7	0.001	5.30 (1.42 to 9.17)	0.007	
AB staining	1	NA	NA	NA	NA	NA	
Overall	18	Random-effects	99.0	0.001	8.77 (4.03 to 13.51)	0.001	0.880
Definition of RPL							
RPL≥3 times	6	Random-effects	99.4	0.001	8.97 (-0.34 to 18.28)	0.059	
RPL≥2 times	12	Random-effects	98.7	0.001	8.67 (2.74 to 14.60)	0.004	
Overall	18	Random-effects	99.0	0.001	8.77 (4.03 to 13.51)	0.001	0.880
Sperm preparation							
Fresh semen	8	Random-effects	99.4	0.001	8.45 (1.48 to 15.42)	0.018	
Frozen semen	10	Random-effects	98.1	0.001	9.02 (2.11 to 15.92)	0.010	
Overall	18	Random-effects	99.0	0.001	8.77 (4.03 to 13.51)	0.001	0.880
Ethnicity							
Asian	8	Random-effects	93.3	0.001	6.23 (3.60 to 8.86)	0.001	
Caucasian	7	Random-effects	99.2	0.001	10.14 (0.35 to 19.93)	0.042	
African	3	Random-effects	97.3	0.001	11.63 (-0.37 to 23.62)	0.057	
Overall	18	Random-effects	99.0	0.001	8.77 (4.03 to 13.51)	0.001	0.880

Sensitivity analyses

The sensitivity analysis showed that the pooled results were stable and reliable (Fig. 4).

Publication bias

As shown in and Table II and Fig. 5, our results showed that there was no publication bias for SDF ($P = 0.880$).

Discussion

Some studies have reported that men couples with unexplained RM had significantly decreased levels of volume[16] and progressive motility [9, 17, 21, 24, 25] than those of couples without RM, but not significantly different in sperm concentration [9–11, 13–21, 23, 25, 26, 30], total sperm count [13, 14, 16, 17, 19, 20] and total motility [10, 11, 14, 26] between the two groups. Some studies reported that couples with unexplained RM had significantly increased levels of sperm concentration [24] and total motility [15, 17–19] compared with those of couples without RM, but there were no significant differences in volume [11, 13, 15, 17, 18, 20–25] and progressive motility [13, 16, 19] between the two groups. The combined results of this meta-analysis showed that couples with unexplained RM had significantly decreased levels of progressive motility and total motility than those of couples without RM, but there were no significant differences in volume, total sperm count and sperm concentration between the two groups.

Some studies [9, 10, 12, 14–19, 22, 23, 25, 26, 30] have reported that couples with unexplained RM had significantly increased levels of SDF compared with those of couples without RM. However, some studies [13, 20, 21] have reported no significant differences in SDF between couples with and without RM. The combined results of this meta-analysis demonstrated that couples with unexplained RM had significantly increased levels of SDF compared with those of couples without RM.

However, there was marked between-study heterogeneity that could not be ignored. Several factors may account for the measured heterogeneity. First, there are several methods used to assess SDF. Second, there are two definitions of unexplained RM. Third, SDF was assess used fresh or cryopreserved semen samples. Fourth, the subjects included in the studies were of diverse ethnical backgrounds. All the factors mentioned above may have significantly affected the between-study heterogeneity. However, the heterogeneity still existed although subgroup analyses by SDF assay, the definition of RM, sperm preparation, ethnicity were performed.

There were four strengths of this meta-analysis. First, more reliable results can be obtained as result of the larger sample size was relatively large to draw. Second, we also assess the relation between traditional semen parameters and unexplained RM. Third, the subgroup analyses by SDF assay, the definition of unexplained recurrent pregnancy loss, ethnicity and sperm preparation were also conducted in this study. Fourth, no publication bias was found in this meta-analysis.

This meta-analysis has two limitations. First, the between-study heterogeneity was also found despite using strict inclusion/exclusion criteria. Second, the number of the included publications was small in some subgroups.

In conclusion, couples with unexplained RM had significantly increased levels of SDF than those of couples without RM but had significantly decreased progressive motility and total motility. SDF assay may be considered as part of the evaluation of couples with unexplained RM.

Abbreviations

CNKI: China National Knowledge Infrastructure; RM: recurrent miscarriage; SDF: sperm DNA fragmentation; WMDs: weighted mean differences; CIs: confidence intervals; ASRM: the American Society for Reproductive Medicine; RCOG: the Royal College of Obstetricians and Gynecologists; ESHRE: the European Society of Human Reproduction and Embryology; PRISMA: the Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SCD: sperm chromatin dispersion; TUNEL: terminal deoxyuridine nick end labeling; AOT: acridine orange test; SCSA: sperm chromatin structure assay; AB; aniline blue.

Declarations

Ethics approval and consent to participate

Not applicable.

Cosent for publication

Not applicable.

Availability of data and materials

Data can be obtained from relevant published articles.

Competing interests

There is no confilict of interest to declare.

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Authors' contributions

YD and JL participated in drafting this manuscript and study design; EY and YS searched and selected the relevant articles. LZ contributed to statistical analysis. All authors gave final approval for publications.

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Figures

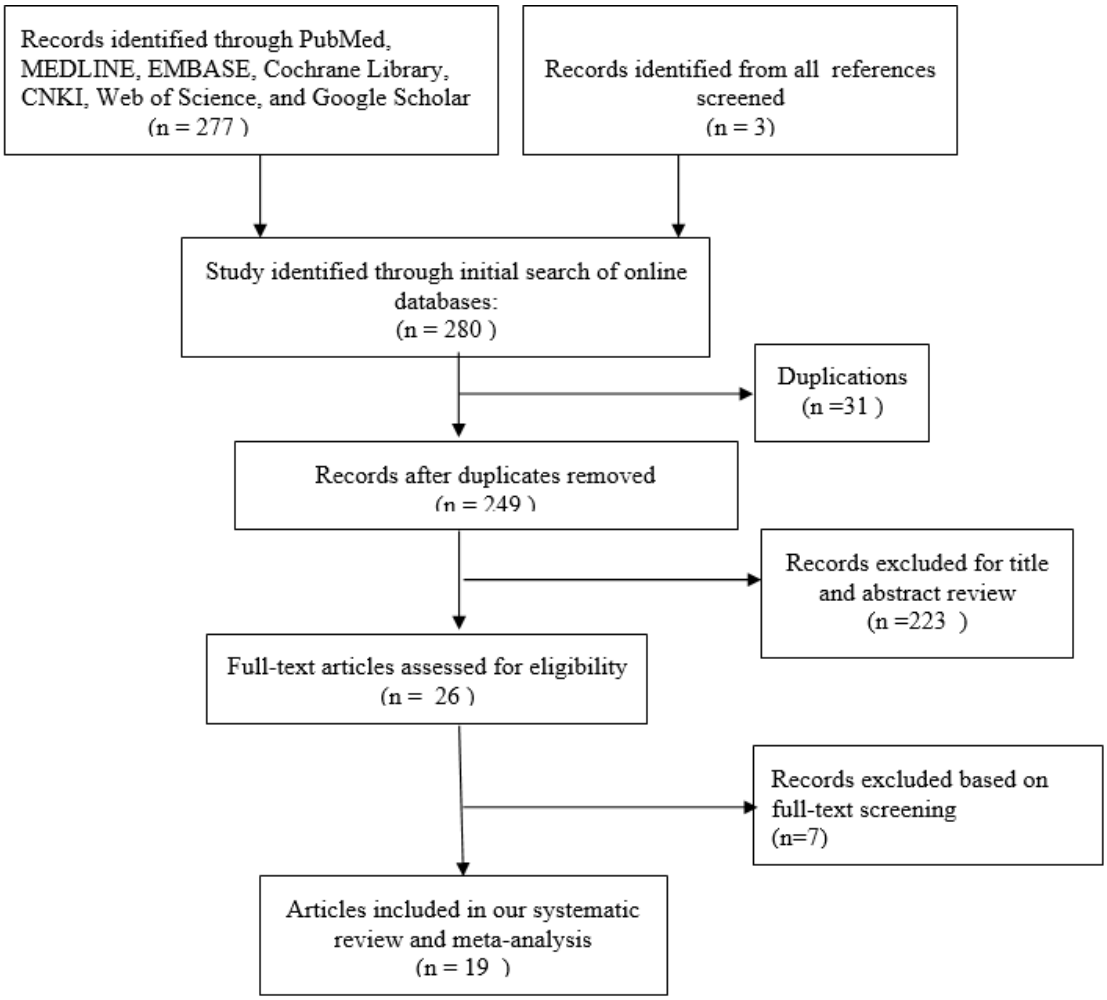

Figure 1

The selection process of eligible publications.

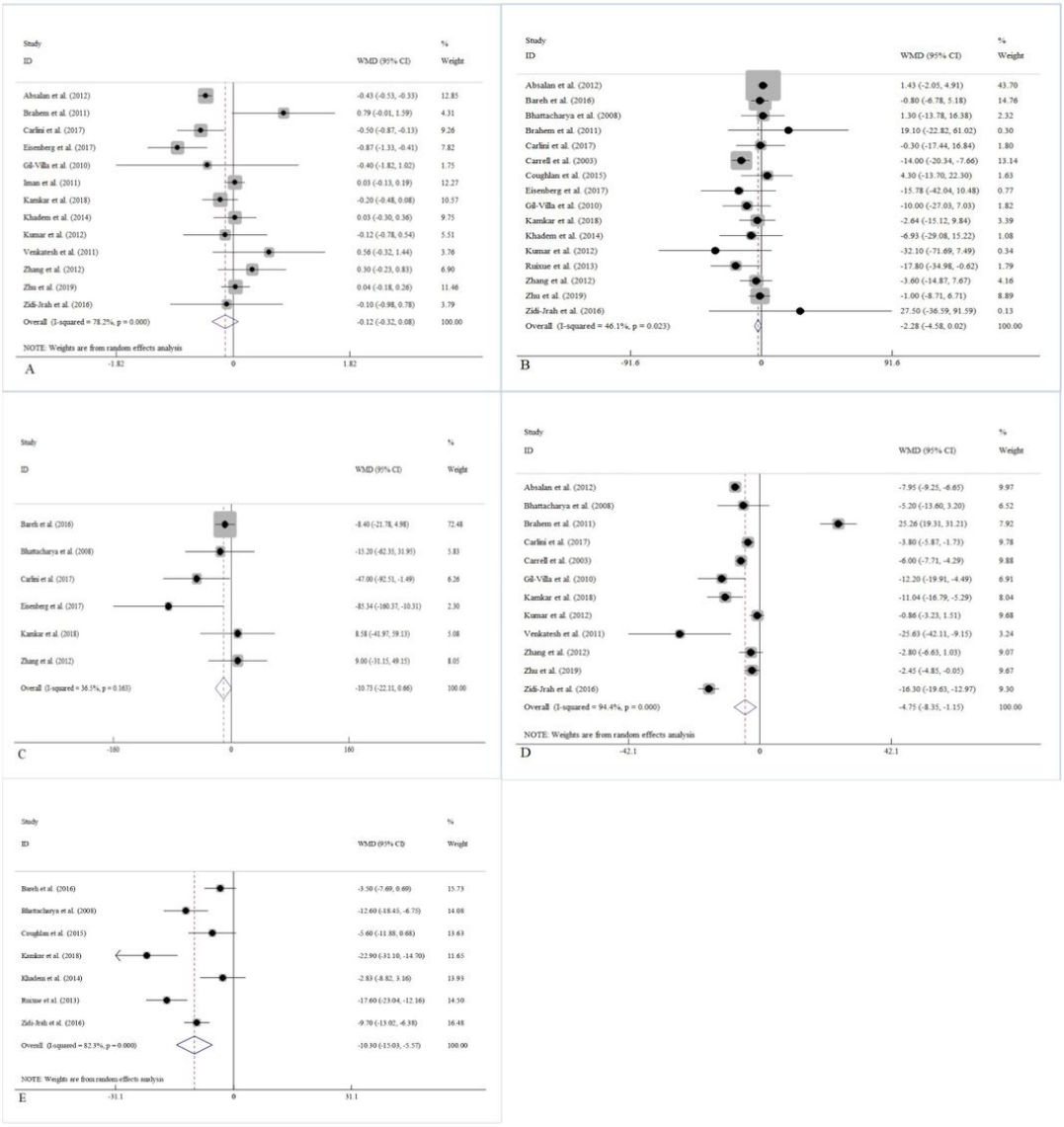

Figure 2

Meta-analysis of the relations between traditional semen parameters and unexplained recurrent miscarriage. (A) The relation between volume and unexplained recurrent miscarriage; (B) the relation between sperm concentration and unexplained recurrent miscarriage; (C) the relation between total sperm count and unexplained recurrent miscarriage; (D) the relation between progressive motility and unexplained recurrent miscarriage; (E) the relation between total motility and unexplained recurrent miscarriage.

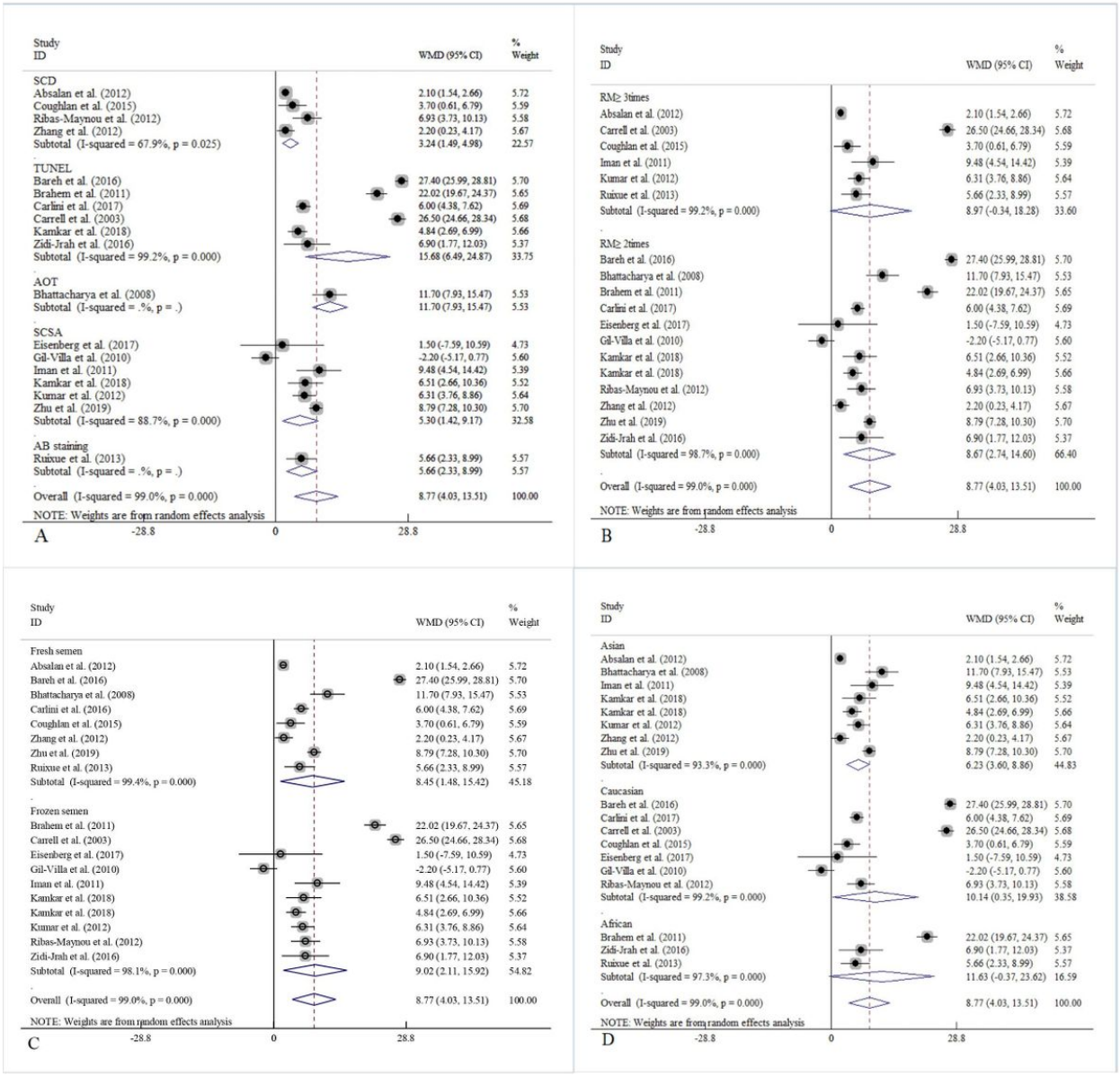

Figure 3

Subgroup analyses by sperm DNA fragmentation assay (A), the definition of recurrent miscarriage (B), sperm preparation (C) and ethnicity (D).

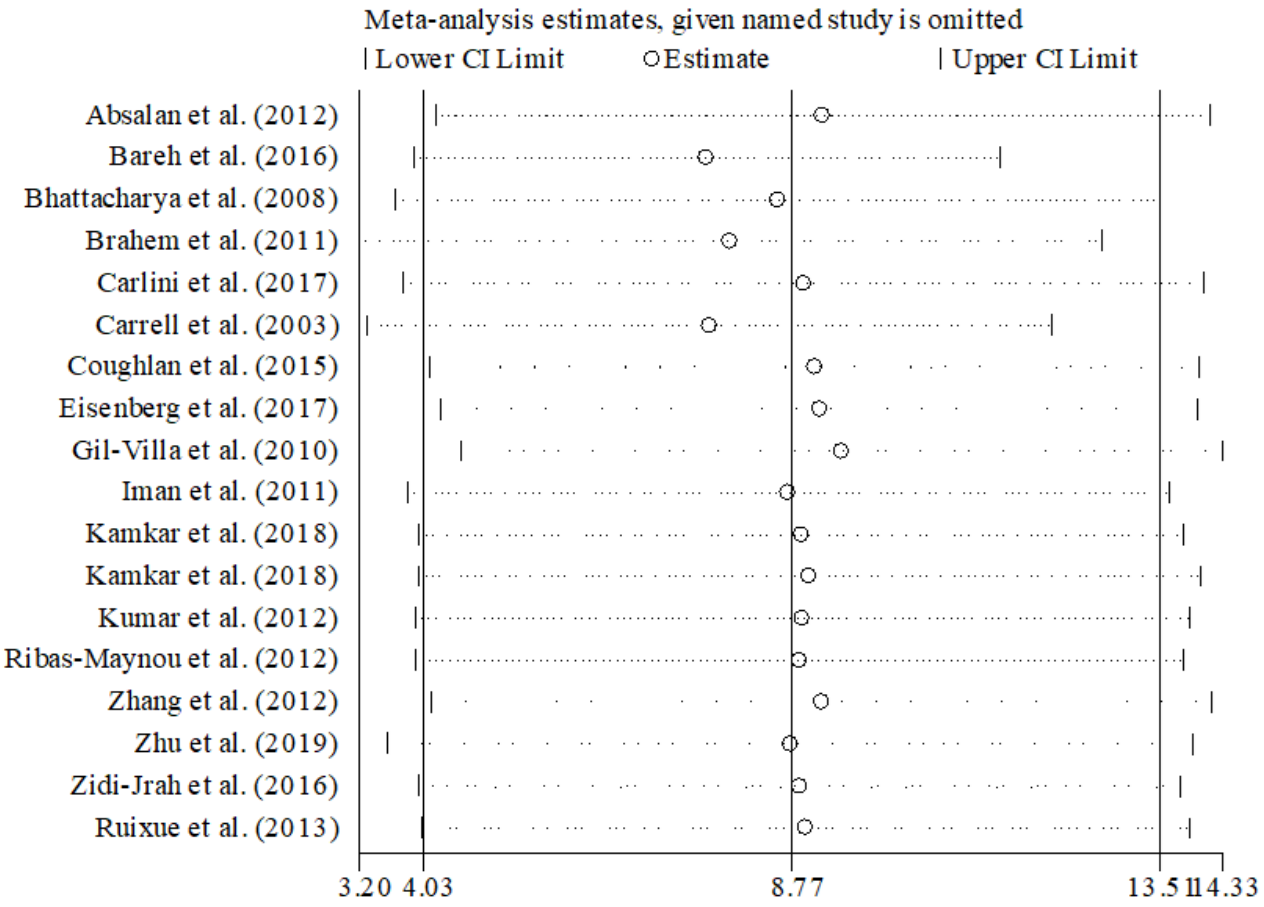

Figure 4

Begg's funnel plot of the relation between sperm DNA fragmentation and unexplained recurrent miscarriage.

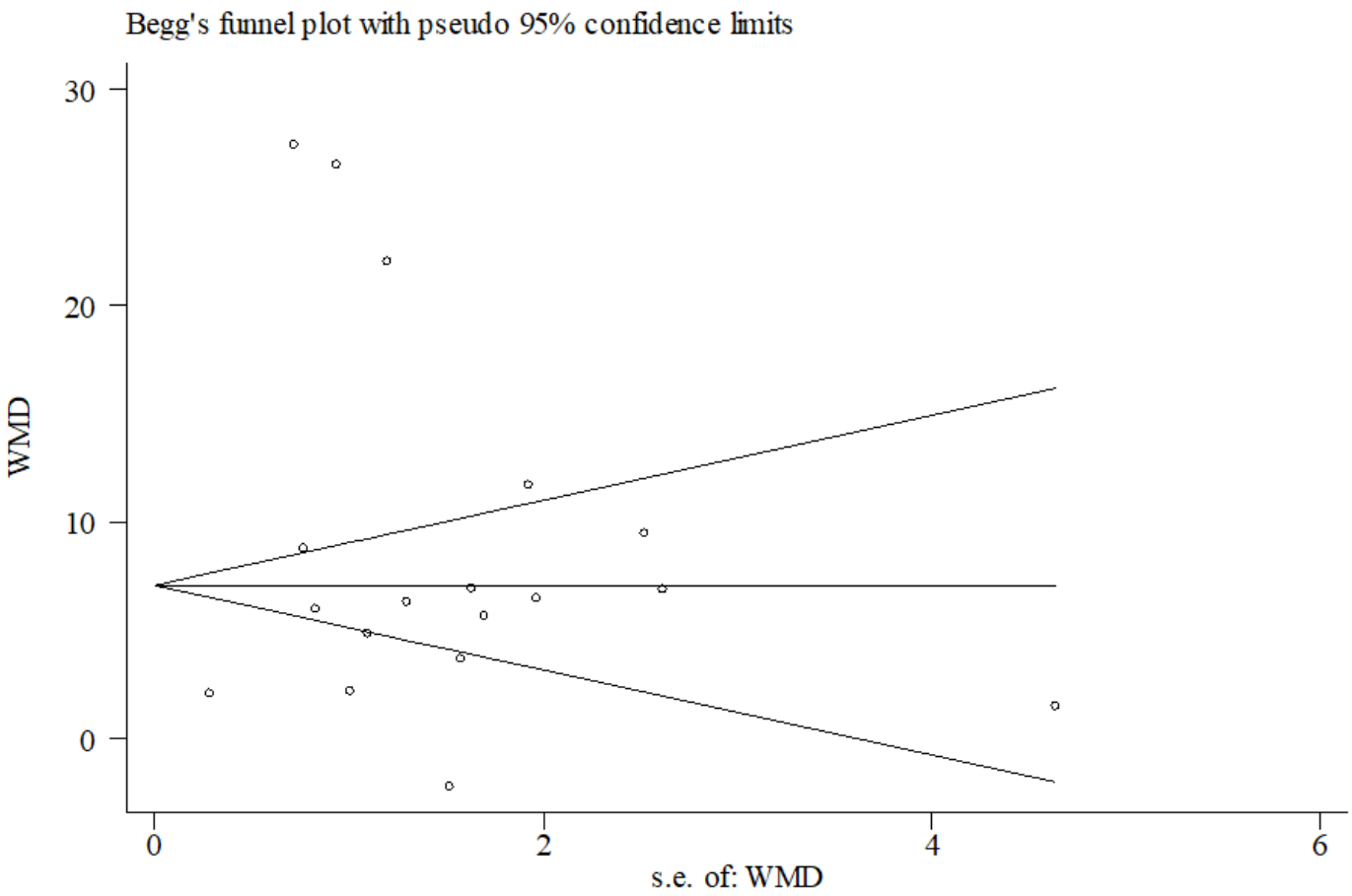

Figure 5

Sensitivity analysis of the relation between sperm DNA fragmentation and unexplained recurrent miscarriage.