Seminal significance: the forgotten father in recurrent pregnancy loss

Fossé, N.A. du

CHAPTER 3

Paternal smoking is associated with an increased risk of pregnancy loss in a dose-dependent manner: a systematic review and meta-analysis

N.A. du Fossé
M.L.P. van der Hoorn
N.H. Buisman
J.M.M. van Lith
S. le Cessie
E.E.L.O. Lashley

F&S Reviews 2021;2(3):227-238

ABSTRACT

Objective

To study the association between paternal lifestyle factors in the preconception period and the risk of pregnancy loss.

Evidence Review

The Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines for systematic reviews and meta-analysis were followed. PubMed and Embase databases were searched up to August 2020. Original articles in English language addressing the relation between paternal exposure status in the preconception period and pregnancy loss were included. Paternal lifestyle factors examined were: smoking, alcohol consumption and body mass index (BMI). Studies that only examined exposure status during pregnancy (and not in the preconception period) and those that solely focused on pregnancy outcome after artificial reproductive technology (ART) were excluded. The qualitative risk of bias assessments were performed. Meta-analysis using a random-effects model was performed if sufficient data were available, with the risk of pregnancy loss as the primary outcome.

Results

The systematic search included 3386 articles of which 11 articles met the inclusion criteria. In a meta-analysis of 8 studies, paternal smoking of >10 cigarettes per day in the preconception period was found to be associated with an increased risk of pregnancy loss, after adjustment for maternal smoking status (1-10 cigarettes per day: 1.01; 95% confidence interval [CI] 0.97-1.06; 11-19 cigarettes per day: 1.12; 95% CI 1.08-1.16; ≥20 cigarettes per day: 1.23; 95% CI 1.17-1.29). No clear association was found between paternal alcohol consumption and pregnancy loss, based on 5 available studies. No studies were identified evaluating the association between paternal BMI and spontaneous pregnancy loss.

Conclusion

Awareness of the association between paternal smoking in the preconception period and the risk of pregnancy loss should be raised. More well-designed studies are needed to further investigate the effects of other paternal lifestyle factors on the risk of pregnancy loss.

INTRODUCTION

Although cigarette smoking, alcohol consumption and obesity are generally known health hazards with a significant impact on general health and well-being, they remain highly prevalent. There is substantial evidence that these modifiable lifestyle risk factors also affect reproductive health, including the risk of pregnancy loss. Pregnancy loss comprises spontaneous demise of the pregnancy before the fetus reaches viability and is a common complication of pregnancy occurring in 15% of clinically recognized pregnancies and 30% of all pregnancies.(1, 2) Active maternal smoking, maternal obesity and alcohol consumption have been consistently associated with an increased risk of pregnancy loss.(3-5)

While maternal risk factors for pregnancy loss are well-established, studies on potentially contributing paternal factors remain sparse. Recently, a significant association was found between advanced paternal age and pregnancy loss, persisting after adjustment for maternal age.(6) In another systematic review and meta-analysis paternal smoking was related to birth defects including congenital heart defects and orofacial clefts.(7) As knowledge on the impact of paternal lifestyle risk factors on the risk of pregnancy loss is still limited, it is essential to gain more insights into this. Biological evidence indicates that male lifestyle behaviors in the preconception period exert their effects on spermatozoa and may, thereby, influence pregnancy outcome. Cigarette smoking, excessive alcohol consumption and obesity have all been linked with systemic oxidative stress, which may result in sperm oxidative DNA damage and eventually lead to both short-term pregnancy complications and long-term outcomes in the offspring.(8, 9)

This systematic review aimed to provide a detailed analysis of the existing literature on the association between paternal lifestyle factors during the preconception period and the risk of pregnancy loss. The paternal factors that were evaluated included cigarette smoking, alcohol consumption and body mass index (BMI).

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted following the Preferred Reporting Item for Systematic Reviews and Meta-analysis Statement and registered in the international prospective register of systematic reviews PROSPERO (ID CRD42020206057).(10)

Search and Selection Strategy

A systematic search of PubMed and Embase electronic databases was performed on August 23, 2020. The following free text and MeSH terms were used: pregnancy loss, abortion, spontaneous miscarriage, male, paternal, father, body mass index, BMI, obesity, smoking, alcohol, drinking behavior, lifestyle. The full search strategy for PubMed is shown in the Supplemental Material (available online). Additional searches in Google Scholar were conducted and reference lists of identified articles were manually searched for additional references.

The literature search was performed by two researchers (N.A.dF. and N.H.B.) and a librarian. The screening was performed by two researchers (N.A.dF. and N.H.B.). In the first stage, titles and abstracts were screened, and in the second stage, full manuscripts of the identified articles were read in detail. Any discordance on selection of studies and assessing risk of bias (described in the following) was resolved by consensus. If no agreement was obtained, the opinion of a third observer (E.E.L.O.L) was sought to gain consensus.

Eligibility Criteria

The inclusion criteria were original articles in English language addressing the relation between pregnancy loss and one or more of the following paternal exposure factors during the preconception period: smoking behavior, alcohol consumption and BMI. Pregnancy loss is generally defined as the spontaneous loss of conception before 20 or 24 weeks of gestation, including both biochemical and ultrasonically or histologically confirmed losses.(11-13) However, several studies used diverse definitions. We did not use a specific definition for pregnancy loss as a strict inclusion criterion, but we described the exact definitions used in all of the included studies. The preconception period in men has previously been described as around 10 weeks prior to conception, in line with the spermatogenic cycle.(14) We did not use a specific definition for the preconception period, but we described the exact definitions used in all of the included studies. Studies that only examined exposure status during pregnancy (and not in the preconception period) were excluded. To be included, a risk estimate for the relation between exposure and outcome had to be provided in the article. As we were interested in the relation between paternal lifestyle factors and pregnancy loss in the general population, studies

that solely focused on pregnancy outcomes after artificial reproductive technology were excluded.

Data Extraction

Two researchers (NF and NB) extracted data from all selected articles on: publication year, country, study period, study design, population characteristics, inclusion and exclusion criteria, exposure and outcome definitions, exposure and outcome ascertainment, sample size, type of effect measures, adjusted effect estimates with 95% confidence intervals (CI) and variables adjusted for in the analyses.

Risk of Bias Assessment

As stated by Dekkers et al.(15) in the Conducting Systematic Reviews and Meta-analyses of Observational Studies of Etiology guideline, it is not recommended to use a standard tool for assessing quality of observational epidemiologic studies. Because of the large heterogeneity in observational research, it is considered more appropriate to develop a tailored set of criteria for each observational systematic review to assess risk of bias in a qualitative matter.

For the current research question, we distinguished 3 relevant domains for risk of bias: bias due to confounding, information bias, and selection bias (including bias due to missing data or loss-to-follow-up). Risk of bias was assessed by 2 reviewers (N.A.dF. and N.H.B.). For each individual study, the risk of bias assessment is shown in the Supplemental Material.

Statistical analysis

The outcomes of the included studies were reported as adjusted odds ratios (AORs) or adjusted hazard ratios (AHRs) with 95% CIs. For meta-analysis, these effect measures were treated equally as risk measures. Standard errors were calculated from 95% CIs. Meta-analysis was only performed for the association between paternal smoking and pregnancy loss because insufficient data were available for paternal alcohol consumption and paternal BMI (as further explained in the Results section).

The meta-analysis for paternal smoking was stratified in four categories: 1-10 cigarettes per day, 11-19 cigarettes per day, ≥20 cigarettes per day and “any smoking” (regardless of the quantity of smoking). To prevent bias due to confounding by maternal smoking behavior, only studies that provided risk estimates adjusted for maternal smoking or studies that were conducted in nonsmoking women were included in the meta-analysis. One study reported AORs for different combinations of maternal and paternal smoking status.(16) The AOR for nonsmoking women with smoking male partners were used for meta-analysis.

If a study reported additional subcategories (e.g., 1-5 cigarettes per day and 5-10 cigarettes per day), the risk estimates of these categories were pooled using a within-study fixed-effect meta-analysis and included as such in the final meta-analysis. If a study used a broader category (e.g., 1-20 cigarettes per day), we used the same estimates for the subcategories (e.g., 1-10 cigarettes per day and 10-20 cigarettes per day) and standard errors were adjusted, assuming equal sample sizes in both subcategories. Some studies reported a risk estimate for smoking in general, that is, without specifying the quantity of smoking. These risk estimates were included in the meta-analysis in the category "any smoking". For studies that did not report a risk estimate for smoking in general, the risk estimates of the different subcategories for smoking used in that particular study were pooled using a within-study fixed-effect meta-analysis and this pooled risk estimate was used for "any smoking" in the final meta-analysis. One study included the average amount of cigarettes per day as a continuous variable in a multivariable model. (17) The AHR with 95% CI that was presented in the article was used to calculate risk estimates with 95% CIs for the subcategories 1-10, 11-19 and ≥20 cigarettes per day.

Evidence of publication bias was assessed through qualitative inspection of a funnel plot. Considering heterogeneity of study populations and study designs, random-effects meta-analyses with DerSimonian and Laird estimation were used (command metan in Stata 14: StataCorp LLC, TX).

RESULTS

Study selection

An overview of the study selection process is shown in the Preferred Reporting Items for Systematic Reviews and Meta-analysis Flow Diagram (Fig. 1). The systematic search retrieved a total of 3,386 original articles. After first-stage screening by reviewing titles and abstracts, 3,365 studies were excluded and 21 articles were identified to assess the full text for eligibility. After the assessment of full manuscripts, 10 articles were excluded for several reasons shown in Figure 1. Finally, 11 studies met all the inclusion criteria. Six studies evaluated the association between preconceptional paternal smoking behaviour and pregnancy loss, 2 studies studies focussed on paternal alcohol consumption and pregnancy loss and 3 studies adressed both exposures. No studies were retrieved that investigated the relation between paternal BMI and pregnancy loss.

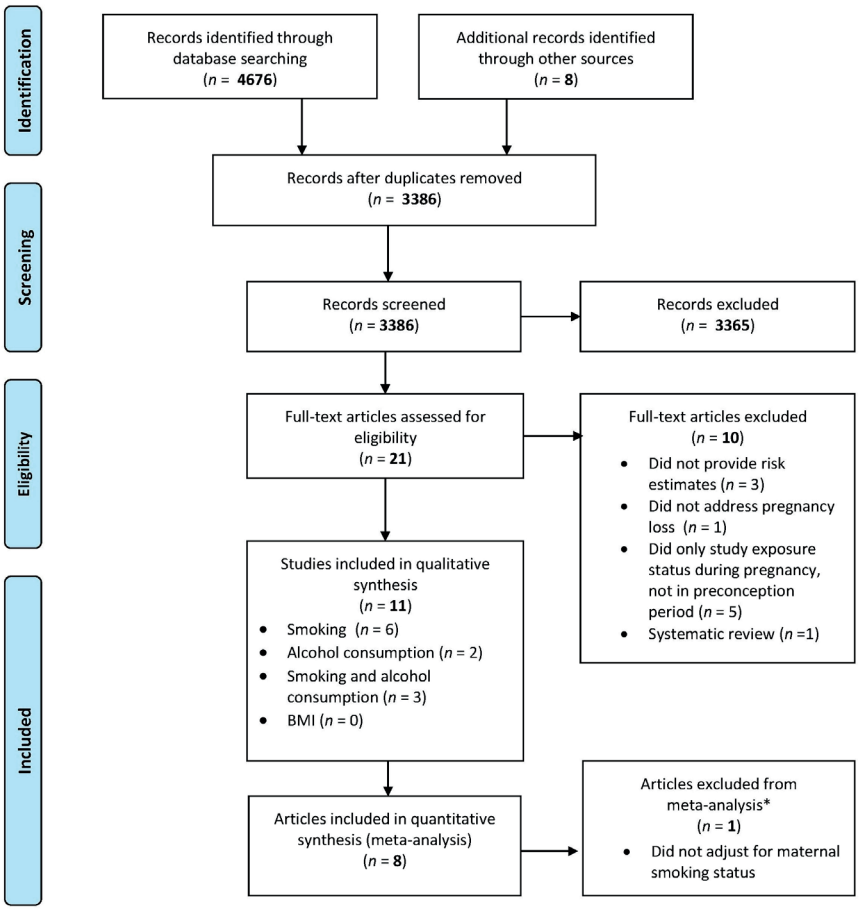

Figure 1. Flow diagram of study selection process

*Meta-analysis is only performed for the association between paternal smoking behavior and pregnancy loss, as explained in the Results section.

Characteristics of included studies

Six studies(16, 18-22) were case-control studies, 4 studies were prospective cohort studies, and 1 study was a retrospective cohort study.(16-26) Sample sizes varied from 107 participants in a case-control study to nearly 6 million pregnancies in the largest cohort study.(16, 26) Five studies were conducted in the USA, 2 in China, and 1 each in Italy, Denmark, Mexico and the United Kingdom.(16-26) The key characteristics of all included studies are summarized in Table 1.

Definition of outcome

In the studies included in this systematic review, pregnancy loss was mostly defined as a loss of conception before 20 weeks of gestation.(16, 21-23, 25) Three studies used <28 or <22 weeks of gestation and 3 studies focused on first trimester pregnancy loss, with gestational age <13 or <12 weeks.(17-20, 24, 26)

Risk of bias

Risk of bias was assessed for all of the included studies. The results of this assessment are shown in the Supplemental Material.

Bias due to confounding

When evaluating paternal lifestyle factors on pregnancy outcome, maternal lifestyle behaviors are important confounding factors. Of 11 included studies, 7 were adjusted for maternal smoking behavior and alcohol consumption.(17-19, 21, 22, 24) Three studies were restricted either to nonsmoking or non-alcohol-consuming women (depending on the studied paternal exposure).(23, 25, 26) One study provided a risk estimate for a subgroup of couples all consisting of smoking men and nonsmoking women.(16) One study that reported ORs for both paternal smoking and alcohol consumption did not adjust for the equivalent maternal factors and was, therefore, not included in the meta-analysis.(20) All studies adjusted for maternal age, being a well-established major risk factor for pregnancy loss. However, it is equivocal to what extent age is related to lifestyle factors and, thus, whether it should be considered as a confounding factor. Five studies controlled for 1 or more potentially confounding paternal factors, including lifestyle factors and exposure to toxins.(16, 17, 21, 23, 26)

Information bias

In 6 of the included studies, data on preconception paternal exposure status were collected during the preconception period or during early pregnancy.(16, 17, 23-26) In 5 studies, these data were collected in retrospect; that is, after outcome of the pregnancy. In these same 5 retrospective studies plus 1 prospective study, information on paternal exposure status was acquired from the female partners.(18-22, 25) In all other (prospective) studies, paternal exposure status was directly reported by the male

partners.(16, 17, 23, 24, 26) Regarding ascertainment of pregnancy outcome, 5 studies only included cases with hospital-confirmed pregnancy loss.(18, 19, 21, 22, 25) In 2 studies early pregnancy loss was detected by daily urine hCG assays and losses beyond 6 weeks were clinically confirmed.(17, 23) One study used daily hCG assays during early pregnancy, whereas later pregnancy outcomes were gained from questionnaires.(24) Two studies completely relied on self-reports of pregnancy outcomes, and 1 study did not state the ascertainment of pregnancy outcomes.(16, 20, 26)

Selection bias

Four studies were hospital-based, and 7 studies were population-based. All of the hospital-based studies were restricted to women that underwent a medical procedure for their miscarriage.

Loss to follow-up was low for all studies, except for the study of Blanco-Muñoz et al.(16), who reported an attrition rate of 28% after confirmation of pregnancies. Missing data were low for all studies that reported missing data. Two studies did not report missing data.(19, 24)

Narrative synthesis

Paternal smoking

Windham et al.(21) conducted a case-control study in the United States to assess the relation between cigarette smoking and the risk of pregnancy loss. The AORs for all categories of paternal smoking (1-10, 11-20, and >20 cigarettes per day) approximated unity. Information on paternal smoking during the 3 months before pregnancy was based on maternal reporting. In a small subsample, male partners were also interviewed to validate maternal reporting. Maternal reporting of paternal smoking status showed good agreement, whereas the quantity of smoking tended to correspond less well. Seven years later, the same authors performed a second study within a prospective cohort only including nonsmoking women.(25) Similar to their previous study, no association between paternal smoking and pregnancy loss was found.

The Italian hospital-based case-control study by Chatenoud et al.(18) examined the association between paternal smoking status and loss <12 weeks of gestation. They did not find any significant relationship between paternal smoking habits before conception and the risk of pregnancy loss (AOR for >10 cigarettes per day 0.9; 95% CI 0.7-1.1). Data on paternal smoking habits were acquired from the female partner.

Table 1. Characteristics of included studies

Author, year, country	Studied factor(s)	Study period	Study design	Study setting	No. of pregnancies or no. of cases and controls	Definition and ascertainment of pregnancy loss
Windham et al. (1992), United States	Paternal smoking	1986-1987	Case-control	Hospital-based	Cases: *n* = 626 Controls: *n* = 1,300 (live birth)	<20-wk gestation Pathology specimen submitted to the hospital laboratory
Chatenoud et al. (1998), Italy	Paternal smoking	1993-1998	Case-control	Hospital-based	Cases: *n* = 782 Controls: *n* = 1,543 (live birth >37 wk)	<12-wk gestation Uterine curettage and pathological examination
Windham et al. (1999), USA	Paternal smoking	1990-1991	Prospective cohort	Population-based (recruited from a large prepaid health plan)	4,196 pregnancies	<20-wk gestation Medical records
Venners et al. (2004), USA	Paternal smoking	1996-1998	Prospective cohort	Reproductive health study in China	526 women	<20-wk gestation Early pregnancy loss (<6 wk) detected by daily urinary hCG assay; later pregnancy losses clinically confirmed
Blanco-Muñoz et al. (2009), Mexico	Paternal smoking	2001-2004	Nested case-control	Recruited during the state's obligatory prenuptial marriage counselling in four municipalities in Mexico	Cases: *n* = 23 Controls: *n* = 84 (ongoing pregnancy >20 wk)	<20-wk gestation Ascertainment of pregnancy loss not stated
Wang et al. (2018), China	Paternal smoking	2010-2016	Retrospective cohort	Population-based (National Free Pre-Pregnancy Checkups Project)	5,770,691 pregnancies	<28-wk gestation Self-reports (recontacted within 1 year after confirmation of pregnancy)

Definition and ascertainment of exposure		Adjusted risk estimates	Risk factors adjusted for
Average amount smoked in 3 mo before pregnancy	Cigarettes/day in three months before pregnancy	AOR (95% CI)	Maternal age, race, caffeine, alcohol, bottled water, tobacco consumption, prior fetal loss, marital status, insurance coverage
Indirectly by the female partner; a small subsample of men (n = 94) was interviewed for validation	None	1 (reference)	
	1-10	0.9 (0.6-1.3)	Paternal age, race, education, alcohol consumption
	11-20	1.1 (0.7-1.5)	
	>20	1.0 (0.6-1.5)	
	Any smoking	1.1 (0.9-1.4)	
Average amount smoked before conception	Smoking status	AOR (95% CI)	Centre, age, education, marital status, maternal family history of spontaneous abortion, history of miscarriages, nausea, maternal alcohol and coffee intake and smoking in the first trimester
	Never	1 (reference)	
Indirectly reported by the female partner	Former	0.8 (0.6-1.1)	
	Current	0.8 (0.7-1.0)	
	Cigarettes/day before conception		
	≤10	0.8 (0.6-1.0)	
	>10	0.9 (0.7-1.1)	
Average amount smoked in 3 mo before pregnancy	Cigarettes/day during three months before pregnancy	AOR (95% CI)	Maternal age, prior fetal loss, alcohol and caffeine consumption, gestational age at interview
Indirectly reported by the female partner	None	1 (reference)	
	1-20	0.98 (0.73-1.3)	*Only non-smoking women were included*
	>20	0.97 (0.41-2.3)	
Average amount smoked before the date of stopping use of contraceptive methods	Smoking status	AOR (95% CI)	Maternal age, education, perceived life stress, exposures to dust and noise, BMI, tea drinking
	Non-smoker	1 (reference)	
	<20 cigarettes/day	1.01 (0.68-1.50)	
Directly reported by the male partner	≥20 cigarettes/day	1.45 (0.82-2.56)	Paternal age, alcohol consumption, previous smoking, exposure to toxins
			Only non-smoking women and non-alcohol consuming women were included
Average amount smoked at the prenuptial marriage counselling	Smoking status	AOR (95% CI)	Maternal age, occupation, intake of coffee
	Man non-smoker	1 (reference)	
Directly reported by the male partner	Man smoker	2.89 (0.99-8.45)	Paternal occupation
	M-F+	1 (reference)	
	M-F+	1.96 (0.40, 10.1)	
	M+F-	3.60 (0.80, 16.3)	
	M+F+	4.61 (1.04, 20.5)	
Average amount smoked at preconception health examination	Cigarettes/day before conception	AOR (95% CI)	Maternal age, last menstrual period, maternal higher education, Han ethnicity, preconception BMI, alcohol drinking, passive smoking, region of provinces
	No	1	
	Yes	1.11 (1.08-1.14)	
Directly reported by the male partner	1-4	1.03 (0.96-1.11)	Paternal age, paternal passive smoking
	5-9	1.02 (0.97-1.08)	
	10-14	1.11 (1.06-1.16)	*Only non-smoking women were included*
	15-19	1.21 (1.09-1.33)	
	≥20	1.23 (1.17-1.30)	

Table 1. Continued.

Author, year, country	Studied factor(s)	Study period	Study design	Study setting	No. of pregnancies or no. of cases and controls	Definition and ascertainment of pregnancy loss
Maconochie et al. (2007), UK	Paternal smoking and alcohol consumption	1980-2000	Case-control	Population-based (National Women's Health Study)	Cases: *n* = 603 Controls: *n* = 6,116 (ongoing pregnancy >12 weeks)	<13-wk gestation Self-reports (questionnaire)
Xu et al. (2014), China	Paternal smoking and alcohol consumption	2009-2012	Matched case-control	Hospital-based	Cases: *n* = 620 Controls: *n* = 1,240 (ongoing pregnancy >12 weeks)	<13-wk gestation Clinically confirmed
Buck Louis et al. (2016), USA	Paternal smoking, alcohol consumption and BMI	2005-2009	Prospective cohort	Population-based (16 counties in Michigan and Texas)	344 pregnancies	<22-wk gestation Conversion to negative hCG test or clinical confirmation
Windham et al. (1992), USA	Paternal alcohol consumption	1986-1987	Case-control	Hospital-based	Cases: *n* = 626 Controls: *n* = 1,300 (live birth)	<20-wk gestation Pathology specimen submitted to the hospital laboratory
Henriksen et al. (2004), Denmark	Paternal alcohol consumption	1992-1994	Prospective cohort	Population-based (members of four trade unions in Denmark)	186 pregnancies	<28-wk gestation Early pregnancy loss detected by daily urinary hCG assay; outcomes of clinically recognized pregnancies collected by questionnaires (self-reports)

AHR = adjusted hazard ratio; AOR = adjusted odds ratio; BMI = body mass index; CI = confidence interval; F = female; hCG = human chorionic gonadotropin; M = male

	Definition and ascertainment of exposure		Adjusted risk estimates	Risk factors adjusted for
	Average amount of cigarettes per day and alcohol per week) in 3 mo before pregnancy Indirectly reported by the female partner	Cigarettes/day No Yes <5 5-10 11-20 >20 Alcohol/week (standard UK units) No drinking <1 1-10 10-21 21-35 >35	AOR (95% CI) 1 (reference) 1.04 (0.87-1.25) 0.68 (0.43-1.07) 1.03 (0.71-1.50) 1.13 (0.88-1.44) 1.19 (0.86-1.66) 1 (reference) 0.77 (0.48-1.26) 0.73 (0.49-1.07) 0.87 (0.58-1.29) 0.95 (0.61-1.50) 0.84 (0.51-1.40)	Year of conception, maternal age, previous miscarriage, previous live birth
	Average amount of cigarettes per day and alcohol per week in 3 mo before pregnancy Indirectly reported by the female partner	Cigarettes/day No smoking 1-10 11-20 >20 Amount of alcohol per week (mL) No drinking or <200 200-500 >500	AOR (95% CI) 1 (reference) 1.05 (0.81-1.27) 1.01 (0.79-1.33) 1.23 (0.87-1.47) 1 (reference) 0.90 (0.68-1.15) 1.01 (0.80-1.23)	History of miscarriage, previous induced abortion, maternal vitamin supplementation, frequency of night shift, frequent staying up late, regular physical exercise, smoking, alcohol consumption Controls matched by maternal age ±3 years
	Average amount of cigarettes per day and alcoholic consumptions per week in three months before pregnancy Directly reported by the male partner	Average cigarette smoking Average alcohol consumption	AHR (95% CI)* 1.01 (0.95-1.07) 0.97 (0.72-2.81)	Maternal age, BMI, difference in partner's ages, prior pregnancy loss, smoking, alcohol consumption, caffeine consumption, vitamin adherence, average intercourse frequency Paternal BMI, smoking, alcohol consumption, caffeine consumption, vitamin adherence
	Average amount of alcohol consumptions per week in three months before pregnancy Indirectly reported by the female partner; a small subsample of men (n = 94) was interviewed for validation	Alcoholic consumptions/week <1/2 1-6 7-13 ≥14	AOR (95% CI) 1 (reference) 1.2 (0.95-1.6) 1.0 (0.74-1.4) 1.2 (0.84-1.7)	Maternal age, maternal smoking, passive smoking, nausea, maternal alcohol consumption
	Amount of alcohol consumptions in the cycle before conception Directly reported by the male partner	Alcoholic consumptions/week 0 1-4 5-9 ≥10	AHR (95% CI) 1 (reference) 2.7 (0.6-2.4) 1.6 (0.3-7.7) 4.3 (0.9-19.3)	Maternal caffeine intake, alcohol consumption, smoking, age, menstrual cycle length

Venners et al.(23) conducted a prospective study in a cohort of Chinese textile workers. Paternal smoking behavior was reported through a questionnaire, completed by the male partners. Both early pregnancy losses, detected by daily urine hCG assays, and clinically detected spontaneous miscarriages were taken into account. Compared to nonsmoking men, AORs for total pregnancy loss were 1.12 (95% CI 0.77-1.65) for smoking 1-20 cigarettes per day and 1.64 (95% CI 0.92-2.93) for smoking ≥20 cigarettes per day.

Blanco-Muñoz et al.(16) reported a nested-case control study in couples who were included during the obligatory prenuptial marriage counselling in Mexico. They found an increased risk of pregnancy loss in couples consisting of smoking men and nonsmoking women compared to couples consisting of 2 nonsmoking partners, although this was not statistically significant (AOR 3.60; 95% CI 0.80-16.3). The amount of smoking was not specified.

The most recent (2018) and largest study on paternal smoking and the risk of pregnancy loss was a Chinese population-based retrospective cohort study of nearly 6 million pregnancies by Wang et al.(26) The data used for this study derived from couples who participated in the National Free Pre-Pregnancy Checkup Project. During preconception health examinations, both partners were interviewed about their smoking behavior. Only nonsmoking women and their partners were included. Reported AORs for pregnancy loss increased from 1.03 (95% CI 0.96-1.11) for paternal smoking of 1-4 cigarettes per day to 1.23 (1.17-1.30) for ≥20 cigarettes per day, with nonsmoking men being the reference group.

Paternal smoking and paternal alcohol consumption

Maconochie et al. studied a wide range of socio-demographic and lifestyle behaviors in relation to first trimester pregnancy loss in the UK, including paternal smoking and alcohol consumption.(20) All data was collected from the participating women. They did not find any significant associations between these two factors and the risk of pregnancy loss. The odds ratios were adjusted for maternal age, year of conception, and previous pregnancy outcomes, but not for maternal lifestyle factors.

In a maternal age-matched case-control study in China, Xu et al.(19) evaluated a variety of potential risk factors for early pregnancy loss. They reported AORs for clinically confirmed first trimester pregnancy loss ranging from 1.05 (95% CI 0.81-1.27) for preconceptional paternal of smoking 1-10 cigarettes per day to 1.23 (95% 0.87-1.47) for >20 cigarettes per day, compared with nonsmoking men. All information on lifestyle factors was obtained through a questionnaire completed by the participating women.

Buck Louis et al.(17) investigated associations between couples' lifestyle behaviors in the preconception period and pregnancy loss in a prospective cohort study in the USA. Both members of the participating couples recorded their daily use of cigarettes. Pregnancy loss was detected by conversion to a negative pregnancy test or by clinical confirmation upon gestation. The investigators presented a multivariable model with AHRs for female and male lifestyle factors. The average daily number of cigarettes and alcoholic consumptions were included in the model as continuous variables, with AHRs of 1.01 (95% CI 0.95-1.07) and 0.97 (0.73-1.28), respectively.

Paternal alcohol consumption

Two studies entirely focused on alcohol consumption and the effect on pregnancy loss. In an American hospital-based case-control study, Windham et al.(22) found an AOR of 1.2 (95% CI 0.84-1.7) for men consuming 14 or more alcoholic consumptions per week during the preconception period (drinking behavior was reported by their partners). Henriksen et al.(24) conducted a prospective cohort study in Denmark and interviewed both members of the couples. They reported an AHR for pregnancy loss of 4.3 (95% CI 0.9-19.3) when men consumed 10 or more alcoholic consumptions per week, compared to non-drinking men.

Quantitative synthesis

Paternal smoking

Eight studies that evaluated the association between paternal smoking behavior in the preconception period and the risk of pregnancy loss were included in the meta-analysis.(16-19, 21, 23, 25, 26) One study was not included in the meta-analysis because it reported risk estimates without adjustment for maternal smoking status.(20) The meta-analysis (Fig. 2) showed significant increased risks of pregnancy loss if fathers smoked more than 10 cigarettes per day (pooled estimates 1.12; 95% CI 1.08-1.16 for 11-19 cigarettes per day and 1.23; 95% CI 1.17-1.29 for ≥20 cigarettes per day). No effects were found for smoking 1-10 cigarettes per day or for "any smoking" (i.e., taking into account all smoking fathers, regardless of the quantity of smoking).

A sensitivity analysis (Supplemental Fig. 1, available online) was performed by repeating the meta-analysis with exclusion of the study of Wang et al.(26), as the sample size and, thus, the weight of this study in the meta-analysis were relatively large compared to all of the other studies. A similar pattern of the paternal smoking association was observed, with a pooled estimate of 1.19 (95% CI 0.97-1.46) for smoking ≥20 cigarettes per day.

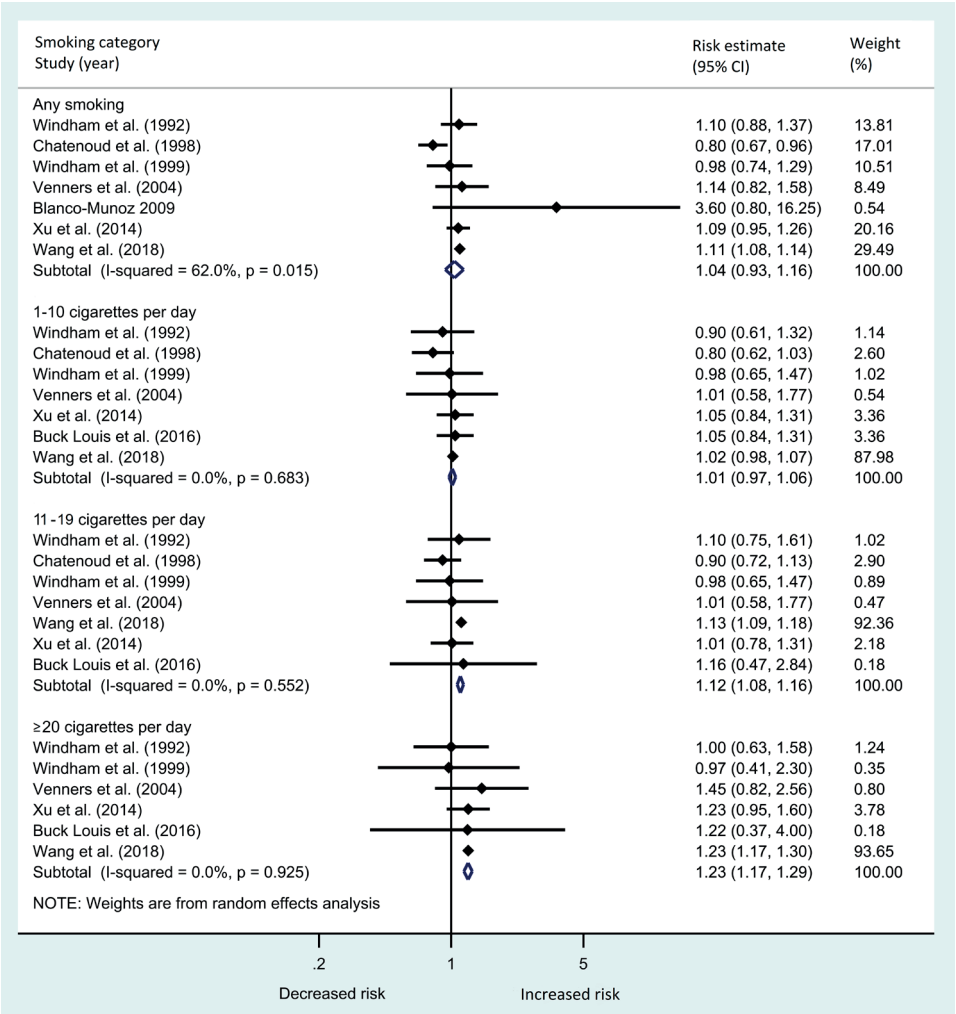

Figure 2. Forest plot describing the association between paternal smoking behavior in different categories of paternal smoking and the risk of spontaneous pregnancy loss

As indicated by I^2 (a statistic that indicates the percentage of variance in a meta-analysis that is attributable to study heterogeneity), heterogeneity was small for smoking categories 1-10, 11-19 and ≥20 cigarettes per day, whereas heterogeneity was substantial in the category "any smoking" because of the relatively extreme risk estimated reported by Blanco-Munoz et al.(16) A funnel plot showed some underrepresentation of small studies with negative effects (Supplemental Fig. 2, available online). There were no major differences in the pooled estimates provided by models with random and fixed effects (data not shown).

Paternal alcohol consumption

Five of the included studies evaluated the association between paternal alcohol consumption in the preconception period and the risk of pregnancy loss. Three studies(17, 19, 21) did not find any increased risks of pregnancy loss associated with paternal alcohol consumption, regardless of the quantity of alcohol consumption. Two studies(22, 24) reported increased AORs for large numbers of alcoholic consumptions per week, although these effects were not statistically significant (Windham et al.(22): AOR 1.2; 95% CI 0.84-1.7 for ≥14 alcoholic consumptions per week and Henriksen et al.(24): AOR 1.6; 95% CI 0.3-7.7 for 5-9 alcoholic consumptions per week and AOR 4.3; 95% CI 0.9-19.3 for ≥10 alcoholic consumptions per week). Because of the limited number of studies and substantial differences between studies in used subcategories for quantity and unity of alcohol consumption, no meta-analysis was performed.

DISCUSSION

In this systematic review and meta-analysis, paternal smoking in the preconception period of >10 cigarettes per day was found to be associated with a significantly increased risk of pregnancy loss, independent of maternal smoking habits. The study of Wang et al.(26) had relatively much weight in the meta-analysis due to its large sample size; however, we assessed this study as well conducted and with a low risk of bias. A sensitivity analysis excluding this study showed also a similar pattern of the paternal smoking effect. Based on few available studies, no clear evidence was found for a link between paternal alcohol consumption and pregnancy loss. No studies were identified that evaluated the association between paternal BMI and the risk of pregnancy loss.

Investigating the relation between paternal lifestyle factors and the risk of pregnancy loss from an etiological perspective is challenging for several reasons. First, the risk of bias due to confounding should be taken into account. For example, because smokers are more likely to have partners who smoke and maternal smoking is a known risk factor for pregnancy loss, it is crucial to control for the smoking status of the female partner when evaluating the paternal smoking effect.(27) For this reason, we restricted our meta-analysis to studies that appropriately adjusted their risk estimates for maternal smoking or that were conducted in non-smoking women. On the other hand, a risk may appear in controlling for too many variables. Risk of bias due to confounding occurs when there is a failure to adjust for common causes of both the exposure and outcome. Prior pregnancy loss, for instance, is a strong predictor for a next pregnancy loss but should not be treated as a confounder as explained by Weinberg(28) and Howards et al.(29). If one assumes that the exposure of interest (e.g., paternal smoking) is a cause of both prior and current pregnancy losses, controlling for prior pregnancy loss will result in overadjustment bias: the estimate of the total causal effect will be biased toward the null.(28-30) Likewise, some of the studies adjusted for socioeconomic status, which is associated with the risk of pregnancy loss.(31) However, indicators of socioeconomic status (e.g., education and income) are most likely non-causally related to pregnancy loss and mediated by lifestyle and behavioral factors.(30) From that perspective, not adjusting for socioeconomic status is appropriate to prevent overadjustment. Overadjustment bias may have been induced in some of the studies included in this review.

A second issue is that different study designs may introduce different types of bias. Although hospital-based case-control studies have the advantage of more certainty about the diagnosis of pregnancy loss, only a selection of all women who underwent a medical procedure for their pregnancy loss are included in these studies; women with early pregnancy loss are usually less well represented. Furthermore, in studies where the exposure status is obtained in retrospect (i.e., after the occurrence of pregnancy

loss or live birth), differential recall bias may arise. Women who miscarried (and their partners) could be more likely to report higher levels of possibly damaging exposures. (32) In addition, in retrospective studies, the selection of exposed or unexposed subjects may be somehow related to the outcome of interest, since women who suspect a relation between their exposure status and their pregnancy loss may be more inclined to participate. Besides this, self-reported socially undesirable lifestyle exposures are prone to underreporting, which may result in some nondifferential misclassification bias.(33) As shown by Windham et al.(21), maternal reporting of paternal smoking behavior may as well lead to non-differential misclassification, making a potential association more difficult to detect.

A third challenge is to differentiate between the impact of exposure in the preconception stage and exposure during pregnancy. For example, maternal passive smoking (second-hand smoke derived from their partner) may be a confounder for the direct effect of preconceptional paternal smoking on pregnancy loss. To assess the true effect of preconceptional paternal smoking, Wang et al.(26) did a separate analysis with exclusion of women whose partners still smoked during the early pregnancy follow-up. The effect estimates derived from this analysis were slightly lower compared to the non-restricted analysis (AOR for ≥20 cigarettes 1.23; 95% CI 1.1.17-1.30 compared to 1.33; 95% 1.30-1.35), suggesting that some confounding by maternal passive smoking was present indeed.

Despite these caveats, there are solid biological arguments supporting a causal relation between preconceptional paternal lifestyle factors and pregnancy loss. It has been shown that tobacco smoke constituents react directly with spermatozoa and can cause DNA damage.(34) Male cigarette smokers exhibit higher levels of reactive oxygen species in their seminal plasma, which may overwhelm seminal plasma antioxidant capacity and cause oxidative stress-mediated sperm DNA fragmentation.(35, 36) Similarly, both obesity and excessive alcohol intake have been linked to sperm DNA damage.(37, 38) Because of the minimal repair capacity of ejaculated sperm, changes in genomic integrity of spermatozoa may persist upon conception. A recent study showed that paternal lifestyle characteristics, potentially mediated by sperm DNA fragmentation, have significant effects on embryo developmental kinetics in couples that underwent intracytoplasmic sperm injection treatment.(39) In addition, impaired sperm DNA integrity has been associated with pregnancy loss in both spontaneous and assisted pregnancies.(40, 41) As the paternal genome is activated after 4-8 cell embryo stages, the effect of high sperm DNA damage is presumed to manifest after fertilization, in the later stages of embryonic development.(42) Defects in sperm DNA may impact blastocyst development and may as well lead to (post)implantation failures.(42-44)

The male contribution to adverse pregnancy outcome has been under evaluated for a long time. Here we show that paternal smoking in the preconception period is associated with an increased risk of pregnancy loss in a dose-dependent manner, irrespective of maternal smoking habits. This significant finding has implications for preconception counselling and is also of interest for couples with unexplained recurrent pregnancy loss. More research into other paternal lifestyle exposures, including alcohol consumption and obesity (or dietary intake), is needed since these factors have hardly been studied in the context of pregnancy loss. Future studies should preferably have a prospective design, appropriate ascertainment of exposures and outcomes and adequate adjustment for confounders. In addition to epidemiologic research, basic studies are desired to further explore underlying mechanisms.

REFERENCES

1. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE et al. Incidence of early loss of pregnancy. N Engl J Med 1988;319:189-94.
2. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. BMJ 2000;320:1708-12.
3. Pineles BL, Park E, Samet JM. Systematic review and meta-analysis of miscarriage and maternal exposure to tobacco smoke during pregnancy. Am J Epidemiol 2014;179:807-23.
4. Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. Fertil Steril 2008;90:714-26.
5. Sundermann AC, Velez Edwards DR, Slaughter JC, Wu P, Jones SH, Torstenson ES et al. Week-by-week alcohol consumption in early pregnancy and spontaneous abortion risk: a prospective cohort study. Am J Obstet Gynecol 2020.
6. du Fossé NA, van der Hoorn M-LP, van Lith JMM, le Cessie S, Lashley EELO. Advanced paternal age is associated with an increased risk of spontaneous miscarriage: a systematic review and meta-analysis. Hum Reprod Update 2020;26:650-69.
7. Oldereid NB, Wennerholm UB, Pinborg A, Loft A, Laivuori H, Petzold M et al. The effect of paternal factors on perinatal and paediatric outcomes: a systematic review and meta-analysis. Hum Reprod Update 2018;24:320-89.
8. Tremellen K. Oxidative stress and male infertility—a clinical perspective. Hum Reprod Update 2008;14:243-58.
9. Martin JH, Aitken RJ, Bromfield EG, Nixon B. DNA damage and repair in the female germline: contributions to ART. Hum Reprod Update 2018;25:180-201.
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. 2009;339:b2535.
11. Kolte AM, on behalf of the ESHRE Special Interest Group EP, Bernardi LA, on behalf of the ESHRE Special Interest Group EP, Christiansen OB, on behalf of the ESHRE Special Interest Group EP et al. Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group. Hum Reprod 2014;30:495-8.
12. Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S et al. ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open 2018;2018.
13. .ACOG Practice Bulletin No. 200: Early Pregnancy Loss. Obstet Gynecol 2018;132.
14. Steegers-Theunissen RP, Twigt J, Pestinger V, Sinclair KD. The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism. Hum Reprod Update 2013;19:640-55.
15. Dekkers OM, Vandenbroucke JP, Cevallos M, Renehan AG, Altman DG, Egger M. COSMOS-E: Guidance on conducting systematic reviews and meta-analyses of observational studies of etiology. PLoS Med 2019;16:e1002742.
16. Blanco-Muñoz J, Torres-Sánchez L, López-Carrillo L. Exposure to maternal and paternal tobacco consumption and risk of spontaneous abortion. Public Health Rep 2009;124:317-22.

17. Buck Louis GM, Sapra KJ, Schisterman EF, Lynch CD, Maisog JM, Grantz KL et al. Lifestyle and pregnancy loss in a contemporary cohort of women recruited before conception: The LIFE Study. Fertil Steril 2016;106:180-8.
18. Chatenoud L, Parazzini F, di Cintio E, Zanconato G, Benzi G, Bortolus R et al. Paternal and maternal smoking habits before conception and during the first trimester: relation to spontaneous abortion. Ann Epidemiol 1998;8:520-6.
19. Xu G, Wu Y, Yang L, Yuan L, Guo H, Zhang F et al. Risk factors for early miscarriage among Chinese: a hospital-based case-control study. Fertil Steril 2014;101:1663-70.
20. Maconochie N, Doyle P, Prior S, Simmons R. Risk factors for first trimester miscarriage—results from a UK-population-based case–control study. BJOG 2007;114:170-86.
21. Windham GC, Swan SH, Fenster L. Parental cigarette smoking and the risk of spontaneous abortion. Am J Epidemiol 1992;135:1394-403.
22. Windham GC, Fenster L, Swan SH. Moderate maternal and paternal alcohol consumption and the risk of spontaneous abortion. Epidemiology 1992;3:364-70.
23. Venners SA, Wang X, Chen C, Wang L, Chen D, Guang W et al. Paternal smoking and pregnancy loss: a prospective study using a biomarker of pregnancy. Am J Epidemiol 2004;159:993-1001.
24. Henriksen TB, Hjollund NH, Jensen TK, Bonde JP, Andersson AM, Kolstad H et al. Alcohol consumption at the time of conception and spontaneous abortion. Am J Epidemiol 2004;160:661-7.
25. Windham GC, Von Behren J, Waller K, Fenster L. Exposure to environmental and mainstream tobacco smoke and risk of spontaneous abortion. Am J Epidemiol 1999;149:243-7.
26. Wang L, Yang Y, Liu F, Yang A, Xu Q, Wang Q et al. Paternal smoking and spontaneous abortion: a population-based retrospective cohort study among non-smoking women aged 20-49 years in rural China. J Epidemiol Community Health 2018;72:783-9.
27. Okechukwu CA, Nguyen K, Hickman NJ. Partner smoking characteristics: Associations with smoking and quitting among blue-collar apprentices. Am J Ind Med. 2010;53:1102-8.
28. Weinberg CR. Toward a Clearer Definition of Confounding. American Journal of Epidemiology 1993;137:1-8.
29. Howards PP, Schisterman EF, Poole C, Kaufman JS, Weinberg CR. "Toward a clearer definition of confounding" revisited with directed acyclic graphs. Am J Epidemiol 2012;176:506-11.
30. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiology. 2009;20:488-95.
31. Norsker FN, Espenhain L, á Rogvi S, Morgen CS, Andersen PK, Nybo Andersen A-M. Socioeconomic position and the risk of spontaneous abortion: a study within the Danish National Birth Cohort. BMJ Open 2012;2:e001077.
32. Leviton A. Biases Inherent in Studies of Coffee Consumption in Early Pregnancy and the Risks of Subsequent Events. Nutrients 2018;10:1152.
33. Gorber SC, Schofield-Hurwitz S, Hardt J, Levasseur G, Tremblay M. The accuracy of self-reported smoking: A systematic review of the relationship between self-reported and cotinine-assessed smoking status. Nicotine Tob Res. 2009;11:12-24.
34. Zenzes MT. Smoking and reproduction: gene damage to human gametes and embryos. Hum Rep Update

2000;6:122-31.

35. Esakky P, Moley KH. Paternal smoking and germ cell death: A mechanistic link to the effects of cigarette smoke on spermatogenesis and possible long-term sequelae in offspring. Mol Cell Endocrinol. 2016;435:85-93.
36. Beal MA, Yauk CL, Marchetti F. From sperm to offspring: Assessing the heritable genetic consequences of paternal smoking and potential public health impacts. Mutat Res Rev Mutat Res. 2017;773:26-50.
37. Wright C, Milne S, Leeson H. Sperm DNA damage caused by oxidative stress: modifiable clinical, lifestyle and nutritional factors in male infertility. Reprod Biomed Online 2014;28:684-703.
38. Aboulmaouahib S, Madkour A, Kaarouch I, Sefrioui O, Saadani B, Copin H et al. Impact of alcohol and cigarette smoking consumption in male fertility potential: Looks at lipid peroxidation, enzymatic antioxidant activities and sperm DNA damage. Andrologia 2018;50:e12926.
39. Hoek J, Schoenmakers S, Baart EB, Koster MPH, Willemsen SP, van Marion ES et al. Preconceptional Maternal Vegetable Intake and Paternal Smoking Are Associated with Pre-implantation Embryo Quality. Reprod Sci. 2020;27:2018-28.
40. McQueen DB, Zhang J, Robins JC. Sperm DNA fragmentation and recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril. 2019;112:54-60.e3.
41. Robinson L, Gallos ID, Conner SJ, Rajkhowa M, Miller D, Lewis S et al. The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis. Hum Reprod 2012;27:2908-17.
42. Borges E, Jr., Zanetti BF, Setti AS, Braga DPdAF, Provenza RR, Iaconelli A, Jr. Sperm DNA fragmentation is correlated with poor embryo development, lower implantation rate, and higher miscarriage rate in reproductive cycles of non–male factor infertility. Fertil Steril. 2019;112:483-90.
43. Seli E, Gardner DK, Schoolcraft WB, Moffatt O, Sakkas D. Extent of nuclear DNA damage in ejaculated spermatozoa impacts on blastocyst development after in vitro fertilization. Fertil Steril. 2004;82:378-83.
44. Borini A, Tarozzi N, Bizzaro D, Bonu MA, Fava L, Flamigni C et al. Sperm DNA fragmentation: paternal effect on early post-implantation embryo development in ART. Hum Reprod. 2006;21:2876-81.