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ORIGINAL ARTICLE

Maternal smoking during pregnancy and risk of cryptorchidism: a systematic review and meta-analysis

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Abstract

The risk factors for undescended testes in male infants and the underlying pathogenesis still remain unclear. The aim of this study is to identify the relationship between maternal smoking during pregnancy and risk of cryptorchidism. A systematic review was conducted using appropriate search terms to identify articles pertaining to maternal smoking during pregnancy and risk of cryptorchidism. Entries up to December 23, 2017 were taken into consideration, without any language or regional restriction. The crude ORs and their 95% CIs were computed by using the fixed-effect model. Twenty studies involving 111,712 infants were included in our meta-analysis. The risk of having a male infant with cryptorchidism was significantly different between mothers who smoked during pregnancy and those who did not (pooled crude OR 1.18, 95% confidence interval [CI] 1.12–1.24, $p < 0.00001$).

Conclusion: Our findings suggest that smoking during pregnancy increased the risk of cryptorchidism by 1.18 times. Further investigations that are well-designed, multicentric studies measuring variables, such as the number of cigarettes smoked in a day and the stage of pregnancy during which the mothers smoked, are necessary to precisely determine the relationship between maternal smoking and risk of cryptorchidism.

The authors consider that the first author should be regarded as joint First Author.

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What is Known:
• *Preterm and low birth weight have been definitively shown to be risk factors for cryptorchidism.*
• *The relationship between with maternal smoking during pregnancy and risk of cryptorchidism remains controversial all the time.*

What is New:
• *Mothers who smoked during pregnancy had a 1.18 times higher risk of having a child with cryptorchidism as compared to those who did not smoke.*
• *Evidence has been found that maternal smoking during pregnancy is a definitive risk factor for cryptorchidism.*

Keywords Cryptorchidism · Maternal smoking · Meta-analysis

Abbreviations
CI Confidence interval
OR Odds ratio

Introduction

Cryptorchidism, or undescended testes, is the failure of the testes to descend permanently into their terminal scrotal position. It is one of the most common congenital anomalies in young boys, especially those who are preterm, occurring at a rate of 1.0–4.6% and 1.1–45.3% among full-term and preterm neonates at birth [8]. The cryptorchidism also results in an abnormal appearance of the male external genitalia, instead of only serves as a potential risk factor for serious conditions such as testicular cancer and infertility [21, 29]. Despite the large number of studies on this topic, the risk factors and exact pathogenesis of cryptorchidism still remain elusive. Nevertheless, studies have shown that preterm delivery and low birth weight are risk factors for cryptorchidism [6]. Maternal smoking is frequently recorded in clinical practice. Although several investigations have been conducted to assess the relationship between smoking during pregnancy and the risk of cryptorchidism, the exact nature of this relationship still remains unclear.

Therefore, we conducted a systematic review and meta-analysis to clarify the statistical significance of the risk of cryptorchidism due to maternal smoking.

Materials and methods

In this study, we conducted a systematic review and meta-analysis of articles on the risk of cryptorchidism associated with maternal smoking, without any regional or language restriction. In this group, we regard mothers who smoked during pregnancy as the study (case) group, and those who did not smoke as the control group; we focused on the number of infants with cryptorchidism and total number of infants in each group, and in addition, the proportion of infants with cryptorchidism to the total number of infants across a large database.

Search strategy

This study was performed in accordance with the PRISMA guidelines [31] and was registered with PROSPERO: CRD42018086522, with complete descriptions of the aims and methods of our investigation.

Information sources and search terms

In this study, we included manuscripts about maternal smoking during pregnancy and risk of cryptorchidism published before May 1, 2018, without any regional or language restriction. Using the Boolean approach, various databases, namely, Pubmed, Cochrane library, Web of Science database, China National Knowledge Infrastructure (CNKI), WanFang Data, VIP database, and China Biology Medical disc (CBM), were searched for relevant papers. The following search terms were used in various combinations to retrieve articles based on their titles, key words, and abstracts: gestational smoking OR gestational cigarette exposure OR gestational tobacco exposure OR smoking OR cigarette OR tobacco AND cryptorchidism OR cryptorchidism OR undescended test* OR non-descended test* OR non descended test*. Additionally, we invited an outstanding expert (Professor Wei) in this field to screen the included manuscripts and recommend missed target articles regarding potential risk factors/smoking and congenital malformations/cryptorchidism, or nicotine exposure and cryptorchidism, in order to ensure that our analysis included all relevant manuscripts.

Inclusion criteria

Articles that met the following criteria were included in this study: (1) research objective was the diagnosis of cryptorchidism at the age of 1 year; (2) availability of the statistical data for each group and sample size of > 200; (3) patients included did not have any other factors that may have effects similar to smoking.

Exclusion criteria

Manuscripts were excluded from the analysis if they met any one of the following conditions: (1) studies in which mothers

who smoked in the past had quit before pregnancy; (2) manuscripts without relevant statistical data on the case group and control group or non-availability of the initial data even after contacting the authors for assistance; (3) articles that included subjects with other factors similar to smoking, e.g., intrauterine nicotine exposure; (4) studies focusing on paternal smoking or passive smoking and its effect on the occurrence of undescended testes.

Study selection and data extraction

Study selection

Figure 1 provides a schematic representation of the process of study identification and inclusion. In all, 65 duplicative papers were removed before abstract screening; titles and abstracts of 204 papers were screened; and 170 papers were removed since they were irrelevant to the current meta-analysis. After comprehensively screening 34 full texts, 15 papers were found to meet our inclusion criteria. Furthermore, we searched for papers regarding (potential) risk factors/smoking and congenital malformations/cryptorchidism, nicotine exposure, and cryptorchidism and found five additional papers (*Berkowitz* 1996 [6], *Brouwers* 2012 [9], *Wagner-Mahler* 2011 [42], *Shiono* 1986 [37], and *Davies* 1986 [12]), as advised by the external expert. However, we found that the data did not meet sufficiently with our search strategy since our study criteria were only a small part of their target research. For example, Shiono et al. [37] conducted a study on maternal smoking during pregnancy and different types of congenital malformations (including cryptorchidism). Thus, such studies may have been missed by our search criteria. This is also one of the limitations of this study.

Data extraction

We carefully assessed each selected paper and extracted the fundamental information, including first author, year of publication, location of initial study, study type, study period, sample size, method of exposure measurement, and others (Table 1). Most importantly, we determined the number of infants born with cryptorchidism, total number of mothers who smoked during pregnancy, and those who did not after repeated screening and calculation, for our systematic review and meta-analysis (Table 2).

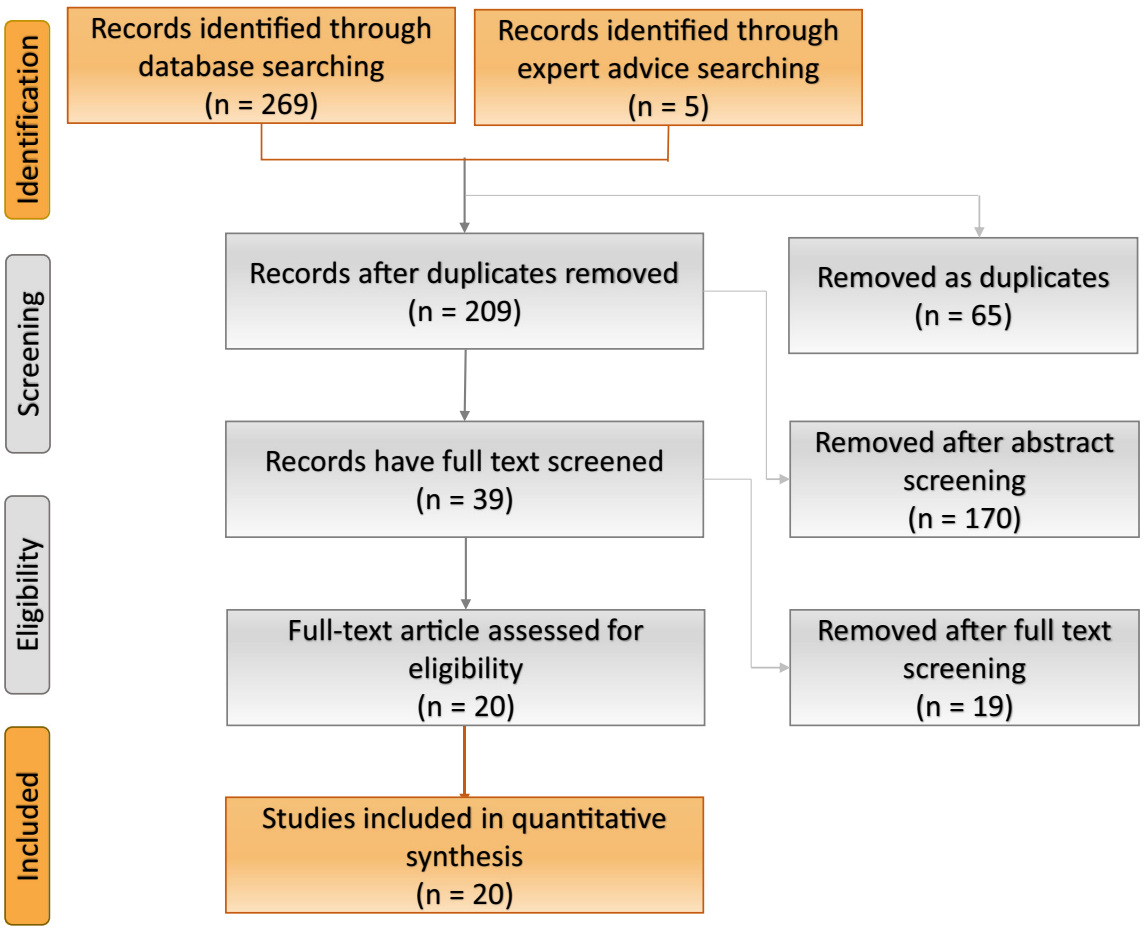

Fig. 1 Flow diagram shows studies identified from the literature and their subsequent selection or omission for the meta-analysis

Table 1 Extracted fundamental information of papers included in meta-analysis between maternal smoking during pregnancy and risk of cryptorchidism

First author	Year	Location	Study tapes	Sample size	Study period	Method of exposure measurement	The time mothers smoked	The number of cigarette mothers smoked
Biggs et al	2002	Washington USA	CCS	11975	1987–1996	birth and hospital discharge records	NA	NA
Jensen et al	2007	Odense and Aalborg Denmark	Cohort	5716	1984–1987	Questionnaires and medical records	Before pregnancy only; stopped before week 36; throughout pregnancy	Divided into 4 groups: 0 cigarettes/day; 1–9 cigarettes/day; 10–19 and ≥ 20
Kurahashi et al	2005	Sapporo Japan	CCS, cohort	212	Cases: 1990–2003 controls: 1985–2001	Mailed questionnaires and hospital records	Before pregnancy; during pregnancy and passive smoking	NA
Mongrawchaffin et al	2007	California USA	Cohort	334	1959–1967	Interview during early pregnancy		0 cigarettes/day; 1–9 cigarettes/day; 10–19 and ≥ 20
Moller et al	1996	Copenhagen Denmark	CCS	571	Cases: 1949–1960 controls: 1946–1970	Mail or telephone interview	Smoked regularly during pregnancy	NA
Adams et al	2011	Washington USA	CCS	40386	1992–2008	Records from CHARS data	NA	NA
Virtanen et al	2006	Turku Finland	CCS	1284	1997–2001	Hospital records	NA	NA
Mcbride et al	1991	Columbia Britain	CCS	732	1982–1984	Hospital and Health Surveillance Registry records, letters, postal questionnaire and phone calls	Among first birth; among later birth	NA
Akre et al	1999	Sweden	CCS	16698	1983–1993	Medical Birth Register and Inpatient Register records, Interview and antenatal examination	Daily and non–daily smoking	NA
Damgaard et al	2008	Copenhagen Denmark and Turku Finland	Cohort	2496	Denmark: 1997–2001, Finland: 1997–1999	Mail, antenatal clinical data, questionnaires, interviews, hospital records and birth records	Cessation before pregnancy; occasional smoker; cessation during pregnancy; current smoker	NA
Beard et al	1984	Minnesota USA	CCS	565	1943–1973	Medical records	NA	NA
Pierik et al	2004	Rotterdam, Netherlands	CCS, cohort	391	1999–2001	Home visit, interview, questionnaire	NA	NA
Berkowitz et al	1996	New York, USA	CCS, cohort	422	1987–1990	Questionnaire, perinatal database	NA	NA
Wagner–Mahler et al	2011	Nice area France	Cohort	6246	2002–2005	Questionnaire, examination	NA	NA
Davies et al	1986	Cambrige, England	ccs	212	Since1978	Hospital notes, interview, telephone	NA	NA
Brouwers et al	2012	Netherland	CCS	829	1996–2004	Hospital records, interview and telephone	NA	NA
Carbone et al	2007	Ragusa, Italy	CCS	384	1998–2002	Public pediatric records, interview	NA	NA
Shiono et al	1986	California, USA	CCS	33434	1974–1977	Questionnaire and hospital records	NA	NA
Mori et al	1992	Japan	CCS	208	1978–1986	Mailed questionnaires, interview	NA	NA
Fernandes et al	2007	Granada, southern Spain	Cohort	702	2000–2002	Examinations, blinded interviews, questions	NA	NA

Table 2 Summarized data of papers included in the meta-analysis between maternal smoking during pregnancy and risk of cryptorchidism

Study	Case group		Control group	
	Boys with cryptorchidism	Total no.	Boys with cryptorchidism	Total no.
Biggs et al. 2002	536	2347	1706	8874
Jensen et al. 2007	131	2519	137	3186
Kurahashi et al. 2005	19	41	74	167
Mongrawchaffin et al. 2007	41	84	144	250
Moller et al. 1996	39	75	60	123
Adams et al. 2011	423	5146	2300	32,481
Virtanen et al. 2006	14	288	111	996
Mcbride et al. 1991	86	205	158	527
Akre et al. 1999	808	4431	1768	11,055
Damgaard et al. 2008	38	728	89	1767
Beard et al. 1984	41	188	40	197
Pierik et al. 2004	22	93	56	298
Berkowitz et al. 1996	11	43	52	239
Wagner-Mahler et al. 2011	17	44	75	233
Davies et al. 1986	23	51	60	161
Brouwers et al. 2012	39	148	161	681
Carbone et al. 2007	4	16	44	235
Shiono et al. 1986	65	9481	137	23,954
Mori et al. 1992	18	104	18	104
Fernandes et al. 2007	11	46	36	106

Quality assessment

The methodological quality of this study was assessed using the Newcastle-Ottawa Scale (NOS), which is recommended by the Agency for Healthcare Research and Quality (AHRQ) and is available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. This scale uses a star system to assess the quality of a study across three domains: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively. The details are provided in Table 3.

Statistical analysis

We calculated the crude odds ratio (ORs) and their 95% confidence interval (CIs) provided in the 20 manuscripts that were appropriate for our target meta-analysis. The calculations were made using Revman 5.3, by using the fixed-effect model. First, we pooled the ORs and 95% CIs of maternal smoking during pregnancy and risk of cryptorchidism, using the available data, as shown in Table 2. Second, we calculated the independent ORs and 95% CIs in the 5 cohort studies and 15 case–control studies (case–control studies nested with cohort studies were regarded as case–control studies here, including *Berkowitz* 1996, *Pierik* 2004, and *Kurahashi* 2005). We then tested the heterogeneity of these manuscripts, using both the chi-square test (with a low p value indicating high heterogeneity, and p value of ≥ 0.1 indicating low heterogeneity) and I^2 index statistics (0% indicating no inter-study heterogeneity) [19], which varied from 0 to 100% and was described as low (0–40%), moderate (30–60%), substantial (50–90%), and considerable (75–100%) [43]. The fixed-effect model was applied when slight heterogeneity ($I^2 \leq 50\%$) as noted; otherwise, the random-effect model was used [20]. We also generated and visually analyzed funnel plots for testimonies of publication bias.

Results

In all, 20 articles pertaining to investigations on 111,712 infants were identified as meeting the inclusion criteria. All these studies had provided pertinent statistical data on the association between maternal smoking during pregnancy and risk of cryptorchidism; the selection process and flow diagram are shown in detail in Fig. 1. These 20 studies comprised 5 cohort studies [11, 14, 25, 33, 42] and 15 case–control studies [1, 2, 5, 7, 9, 10, 12, 30, 32, 34, 41]. Case–control studies nested with cohort study were regarded as a case–

Table 3 Quality assessment of included studies (case–control study or cohort study) according to Newcastle-Ottawa Scale (NOS)

Quality assessment of case–control studies

Reference	Selection				Comparability	Exposure			Scores
	Adequacy of case definition	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same ascertainment for cases and controls	Non-response rate	
Adams et al. 2011	*	*	NA	*	*	NA	*	NA	5
Akre et al. 1999	*	*	NA	*	*	NA	*	NA	5
Beard et al. 1984	*	NA	*/NA[&]	*	*	NA	*	NA	4 or 5
Berkowitz et al. 1996	*	*	NA	*	*	NA	*	NA	5
Biggs et al. 2002	*	*	NA	*	*	*	*	NA	6
Brouwers et al. 2012	*	*	NA	NA	*	*	*	NA	5
Carbone et al. 2007	NA	*	*	*	*	*	*	NA	6
Davies et al. 1986	*	*	NA	NA	*	*	*	NA	5
Kurahashi et al. 2005	NA	NA	NA	*	*	*	*	*	5
Mcbride et al. 1991	*	*	NA	*	*	*	*	NA	6
Moller et al. 1996	*	*	NA	NA	*	*	*	*	6
Mori et al. 1992	*	*	NA	*	*	NA	*	NA	5
Pierik et al. 2004	*	*	NA	*	*	*	*	NA	6
Shiono et al. 1986	*	*	NA	NA	*	*	*	NA	5
Virtanen et al. 2006	NA	NA	NA	*	*	*	*	NA	4

[&]Community controls and hospital controls account for half of total controls

Quality assessment of cohort studies

Reference	Selection				Comparability	Outcome			Scores
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstrated outcome was not present at start of study	Comparability of cohorts	Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Damgaard et al. 2008	*	NA	*	*	NA	*	*	*	6
Fernandes et al. 2007	*	NA	*	*	NA	NA	*	NA	4
Jensen et al. 2007	*	*	*	*	*	*	*	NA	7
Mongrawchaffin et al. 2007	*	NA	*	*	NA	*	*	NA	5
Wagner-Mahler et al. 2011	*	NA	*	*	*	*	*	NA	6

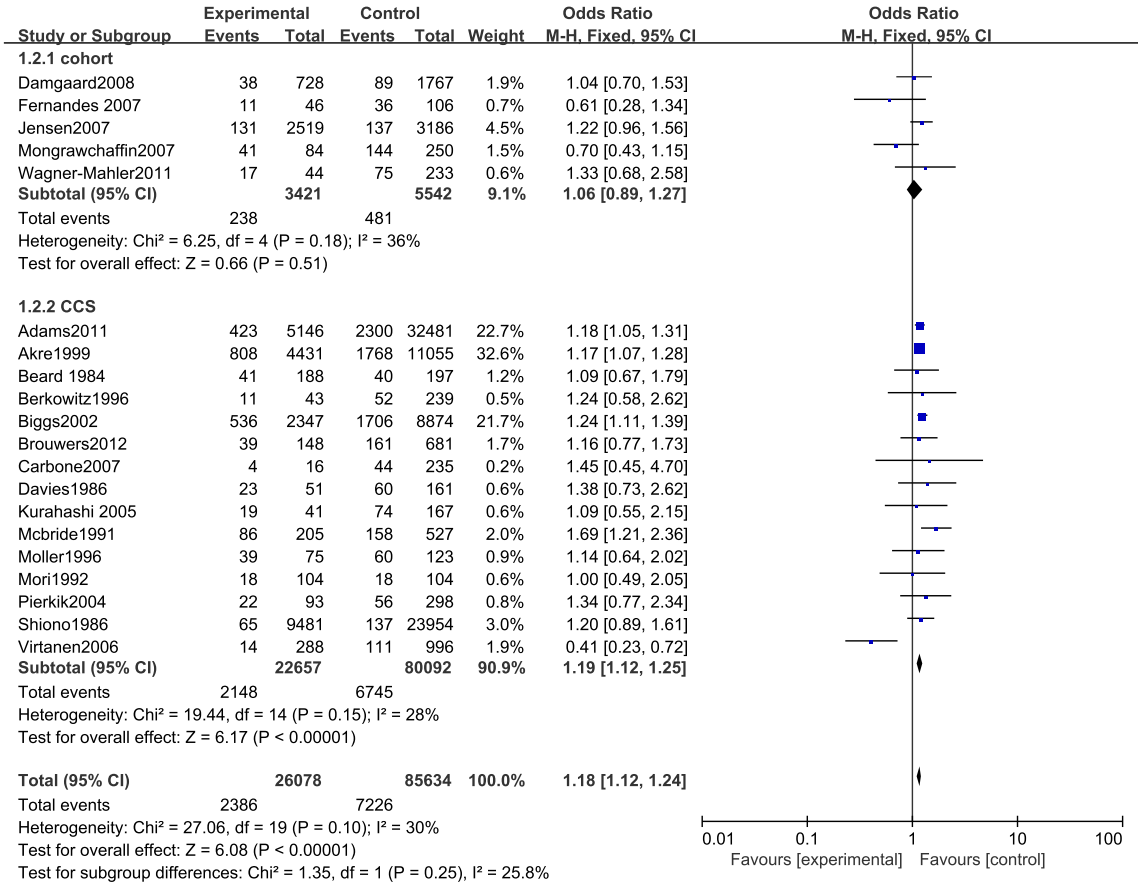

Fig. 2 Data showing outcomes between maternal smoking during pregnancy and risk of cryptorchidism, the total and by study tape (cohort studies and case–control studies)

control study here [6, 28, 36]. All the included studies were case–control studies or cohort studies, and their quality assessment scores are listed in Table 3. In all, 80% of these studies (16/20) had 5 or 6 points, while only one study had 7 points of a total of 9 score of Newcastle-Ottawa Scale for both case–control studies and cohort studies. Thus, these scores indicate that the studies included in this meta-analysis were of medium.

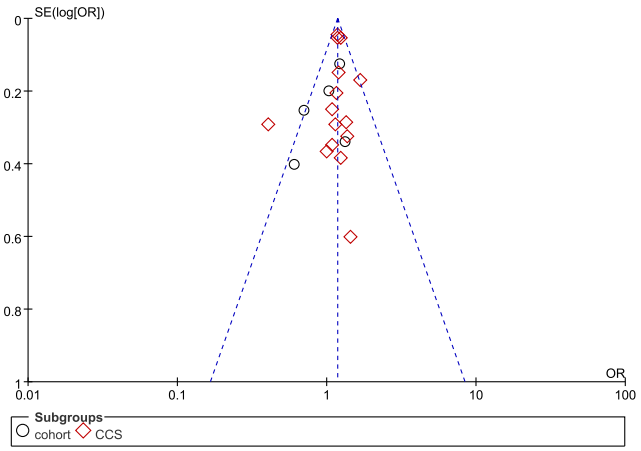

Fig. 3 A funnel plot of publication bias

Unfortunately, the earlier clinical studies were conducted between 1943 and 2008, and we could not retrieve any studies conducted after 2012 on the link between maternal smoking during pregnancy and risk of cryptorchidism. The total data in each group was adequate for our analysis (26,078 cases in the case group and 85,634 cases in the control group). For the first analysis, we pooled the ORs and 95% CIs obtained for maternal smoking during pregnancy and risk of cryptorchidism; the data are provided in Table 2. Next, we conducted a subgroup analysis for the cohort studies and the case–control studies. The results of the analysis are showed in Fig. 2.

The meta-analysis of the crude ORs (Fig. 2) revealed sufficient evidence to show a significant statistical relationship between maternal smoking during pregnancy and the risk of cryptorchidism in the male infants. In other words, mothers who had smoked during pregnancy had a significantly higher risk of delivering infants with cryptorchidism as compared to those who did not smoke (pooled crude OR 1.18, 95% CI 1.12–1.24, $p < 0.00001$). The pooled studies, cohort studies, as well as the case–control studies were of low heterogeneity (when combined, $I^2 = 30\%$, $p = 0.10$; cohort studies: $I^2 = 36\%$,

Table 4 The number of cigarettes mothers smoked during pregnancy and number of cases of cryptorchidism

Study		Number of cigarette mothers smoked per day		
		1–9	10–19	> = 20
Jensen 2007	No. of cases	51	56	9
	Total no.	1085	1037	89
Mongrawchaffin 2007	No. of cases	21	7	13
	Total no.	87	38	60
Carbone 2007	No. of cases	4	0	
	Total no.	13	3	

$p = 0.18$; case–control studies: $I^2 = 28\%$, $p = 0.15$), indicating that all the selected manuscripts were of acceptable homogeneity, and a fixed-effect model was applied to analyze the data (Fig. 3).

Since the available data were inadequate to arrive at a definitive conclusion based on the combined data, we attempted to conduct a subgroup analysis to identify any trend, if possible, regarding the association between the risk of cryptorchidism and the number of cigarettes smoked or the stage of pregnancy during which the mothers smoked. We sought to collect substantial data to determine the possible dose–response relationship between maternal smoking during pregnancy and risk of cryptorchidism; based on the results of previous investigations, the cut-off point was set at 10 cigarettes per day [33]. However, only three studies (*Jensen* et al., *Mongrawchaffin* et al., and *Carbone* et al) provided statistical numeric data for the above cut-off point. The obtained data were not sufficient to fix a model for the analysis. One of the studies, namely, *Jensen* et al., showed a trend wherein the higher the number of cigarettes the mothers smoked, the higher was the risk of cryptorchidism (in less than 10 cigarettes group and more than 10 cigarettes group, the mobility varies from 4.7 to 5.8%). However, the opposite trend was noticed in the study by *Mongrawchaffin* et al. (24.1 to 20.4%). The study by *Carbone* 2007 failed to draw a comparison. The detailed data showed in Table 4. In summary, we could not determine the exact dose–response relationship between the number of cigarettes the mothers smoked during pregnancy and the risk of cryptorchidism. Most unfortunately, we were unable to obtain any data on the stage of pregnancy during which the mothers smoked and the risk of cryptorchidism.

Discussion

Our meta-analysis revealed that maternal smoking during pregnancy significantly increases the risk of male infants being born with undescended testes (pooled crude OR 1.18, 95% CI 1.12–1.24, $p < 0.00001$). However, the lacking of exact association between the number of cigarettes mothers smoked during pregnancy and risk of cryptorchidism made it difficult for us to arrive at a more precise and definitive conclusion. When we pooled the data, both mothers who smoked only one cigarette during pregnancy and those who smoked a random number of cigarettes were included. This was because no studies were available despite placing no language or regional restrictions, possibly because of excessive workload and cost involved.

On performing subgroup analysis of maternal smoking during pregnancy and risk of cryptorchidism in cohort studies (OR 1.06, 95% CI 0.89–1.27, $p = 0.51$) and case–control studies (OR 1.19, 95% CI 1.12–1.25, $p < 0.00001$), we found that there was a marginal difference between the ORs obtained for the two study groups. We believe that there is a possibility of reporting bias in such studies, with only those studies obtaining the strongest effect being more likely to get published. Further, there may also be some degree of recall bias, since mothers of children with cryptorchidism who may have quit smoking at the start of the pregnancy may consider themselves to have been smoking during the pre-conception and conception period. This is another inevitable limitation of our study as well as many other systematic reviews.

When we attempted to collect data for an analysis on the dose–response relationship, between maternal smoking during pregnancy and risk of cryptorchidism, using a cut-off point of 10 cigarettes per day, we could identify only three original studies and still could not identify a common trend. As discussed above, this is a limitation of our study and highlights the need for well-designed, multicentric studies on this topic.

Preiksa et al. [36] and Jones et al. [26] have quantified the relationship between maternal smoking during pregnancy and risk of cryptorchidism (OR 1.58, 95% CI 0.94–2.65, $p = 0.08$, and RR 1.04, 95% CI 0.86–1.27). However, we could not obtain the original data of either of these studies and were unable to include these data into our meta-analysis, though we made efforts to e-mail the correspondence author for assistance.

Both the pooled studies and subgroups were of low heterogeneity (pooled studies, $I^2 = 30\%$, $p = 0.10$; cohort studies: $I^2 = 36\%$, $p = 0.18$; case–control studies: $I^2 = 28\%$, $p = 0.15$). By preparing a funnel plot, we could easily find the article (*Virtanen* et al. [41]) that contributed to the heterogeneity the most. We organized a sensitivity analysis, after eliminating the abovementioned article, and the pooled crude OR was 1.19, with 95% CI of 1.13–1.25 ($p < 0.0001$; and $I^2 = 0\%$, $p = 0.75$) for the same outcome with perfect homogeneity. Thus, we reviewed the full text of the abovementioned article and found that the heterogeneity may be attributed to the fact that they considered prospective cohort study on urogenital malformations for 1997–1999 and a case–control study on cryptorchidism for 1997–2001.

Lin Zhang et al. [43] conducted a systematic review related to this topic, and he concluded that mothers who smoked during pregnancy had a 1.17 times higher odds of delivering a male infant with cryptorchidism, without any statistical significance. However, we found some limitations that can be improved; for example, the included studies Carbone et al. [10] and Giordano et al. [11] used similar initial data from the province of Ragusa (Sicily, Italy) for analysis, the data was duplicated twice during the systematic review. After comparing the methods of these two articles, we chose *Carbone* et al. for extracting data, since it was more consistent with our inclusion criteria. Furthermore, Lin Zhang et al. did not provide specific data for the case group and control group; therefore, we are skeptical about the stringency of data collection, although their conclusion was very similar to ours. Besides, we rigorously strict the inclusion and exclusion criteria, performed subgroup analysis, and made effort to clarify the relationship of dose–response and timing of gestation and risk of cryptorchidism, though data were not enough to draw a more professional conclusion.

In the transabdominal phase, testosterone plays only a minor role [23]. Recent research has shown that the Leydig cell hormone, insulin-like hormone 3 (INSL3), primarily controls the transabdominal descent phase and leads to the enlargement of gubernacular bulb [35, 44], by binding to its receptor, RXFR2 [4]. Although an animal model was developed for abnormal *INSL3* function [3], the underlying mechanism still remains unclear. The inguinoscrotal phase is mainly controlled by androgens, which are thought to exert their effects by masculinizing the genitofemoral nerve [23]. In addition, Tanyel et al. pointed out a novel possible pathogenesis that androgens may affect the descent of testis by influencing the sympathetic tonus, for the sympathetic is androgen-dependent, and they had conducted an animal model for evidence [38, 39]. This possible pathogenesis still needs further investigations to determine, for small sample size and confused bias performed by Tanyel.

Ion RC et al. [24] and Ko TJ et al. [27] explained that cigarette smoke contains mutagenic and carcinogenic agents, in addition to other toxic agents; these can lead to serious alterations in the different stages of embryonic development (folliculogenesis, steroidogenesis, embryo transport, endometrial receptivity, angiogenesis), the uterine environment (uterine blood flow and myometrium), and chromosomal alignment [13]. Maternal smoking is associated with reduced hormone levels (e.g., human choriogonadotropin [hCG], follicle-stimulating hormone [FSH], and luteinizing hormone [LH]) [17, 40]; these changes may be related to the disruptions in normal endocrine function that may sometimes occur in between two embryonic phases [19, 22].

Fowler PA et al. [16, 18] have highlighted a recent, controversial documentary on how maternal smoking alters fetal testosterone levels. Smoke-induced changes in the descent of testes may occur to the indirect changes in androgen levels. However, circulating testosterone levels may not be the most accurate indicator of androgen exposure to the external genitalia since studies have shown that alternative pathways of androgen synthesis may also be important in humans [15]. Thus, a more comprehensive analysis of the levels of circulating androgens and effects of maternal smoking on the human male fetus is warranted to comprehensively characterize the impact of smoking on steroidogenesis. Alternatively, maternal smoking may directly affect the descent of the testes via the effects of androgen and other hormones. This effect, for example, may be medicated by changes in the expression or activity of androgen receptors.

Flück CE et al. [15] and Fowler PA et al. [18] have suggested that reduced fetal expression of some genes (e.g., *DHH*) may be a possible mechanism that links maternal gestational smoking and impaired reproductive development of the male offspring. However, the exact pathogenesis of cryptorchidism still remains unclear, and there is a clear need for a considerable research effort in this direction.

There are a few limitations to our study. In this study, we were unable to quantify the link between the risk of cryptorchidism and the different levels of smoking, e.g., the number of cigarettes the mothers smoked per day, the curve of smoking, and the stage of pregnancy at which the mothers smoked. Therefore, future research addressing these points are necessary to elucidate the link between maternal smoking during pregnancy and risk of cryptorchidism in a more precise and quantitative manner. In addition, as mentioned above, there may be a possibility for reporting bias and recall bias in the enrolled studies.

Conclusions

Our study yielded evidence of a statistically significant increase, specifically 1.18 times higher, in the risk of delivering a male infant with cryptorchidism among mothers who smoked during pregnancy, as compared to those who did not

smoke. Therefore, cryptorchidism can be also be included among conditions that are likely to occur in infants born to mothers who smoke during pregnancy. With a view to maintaining their own and their child's health, pregnant women should be strongly advised to quit smoking consciously, even if there is a 1% increased risk of cryptorchidism in their baby sons.

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Authors' contributions CJY and SDW conceived and designed the meta-analysis. CJY and YW independently searched the Pubmed, Cochrane Librery, Web of Science database, China National Knowledge Infrastructure (CNKI), WanFang Data, VIP database and China Biology Medical disc (CBM), and independently extracted the data. CJY led analysis and interpretation of data, drafted the manuscript and revised content based on feedback. YW acted as second reviewer. XLT and BL assisted with the retrieval of the database and acquisition of data. LJS and CLL assisted with the interpretation of data and provided critical revision of drafts. TL, DWH, and GHW assisted with the conception and design, interpretation of data, and critical revision of drafts. SDW acted as the corresponding author, provided funding support, assisted with interpretation of data, provided critical revision of drafts and acted as the third (mediating) reviewer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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