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INVITED REVIEW

Reproductive Health

Maternal cigarette smoking during pregnancy and reproductive health in children: a review of epidemiological studies

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Maternal cigarette smoking may affect the intrauterine hormonal environment during pregnancy and this early fetal exposure may have detrimental effects on the future trajectory of reproductive health. In this review, we discuss the epidemiological literature on the association between prenatal exposure to maternal cigarette smoking and several aspects of reproductive health. The literature points towards an increased risk of the urogenital malformation cryptorchidism, but a potential protective effect on the risk of hypospadias in sons following prenatal cigarette smoking exposure. Studies on sexual maturation find a tendency towards accelerated pubertal development in exposed boys and girls. In adult life, prenatally exposed men have impaired semen quality compared with unexposed individuals, but an influence on fecundability, that is, the biological ability to reproduce, is less evident. We found no evidence to support an association between prenatal cigarette smoking exposure and testicular cancer. Among adult daughters, research is sparse and inconsistent, but exposure to cigarette smoking *in utero* may decrease fecundability. In conclusion, prenatal exposure to cigarette smoking may cause some long-term adverse effects on the reproductive health.

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INTRODUCTION

Reproductive health has been subject to increasing interest and concern during recent years. Approximately 15% of the population in developed countries are affected by infertility,¹ there have been an increasing use of assisted reproductive technology, a decreasing trend in semen quality have been claimed,^{2,3} as well as increasing prevalence of urogenital malformations,⁴ and incidence of testicular cancer.⁵ These factors have contributed to a substantial public interest to the concern. Due to the rapid increase in these trends, some have argued that new or increasing exposures to lifestyle factors and environmental pollutants in fetal as well as adult life are involved in the etiology.⁶ Based upon the fetal-origins-of-disease hypothesis,⁷ it has been hypothesized that the reproductive disorders are interrelated and part of a so-called “testicular dysgenesis syndrome”⁶ with a common *in utero* etiological pathway. Subsequently, the “ovarian dysgenesis syndrome”-hypothesis has also been postulated.⁸ Although the empirical evidence behind these hypotheses have been much debated,^{9–11} there is an increasing awareness on the consequentiality of an altered intrauterine milieu and the potential early programming of reproductive health. The hypotheses have been widely adopted and the question on whether maternal lifestyle during pregnancy, for example, cigarette smoking affects offspring’s reproductive health persists.¹²

Smoking has, in some populations, been the most widely spread exposure with rapid changes in both prevalence and intensity over time, also during pregnancy. The known effects of cigarette smoking exposure

on the developing fetus are numerous; one of the best documented is the negative influence on fetal growth and pregnancy complications.^{13,14} Further, the harmful effects on several aspects of reproductive health have for years been a major research focus.

We reviewed the epidemiologic literature on the reproductive health of children exposed to cigarette smoking *in utero*.

MATERIALS AND METHODS

PubMed was searched from its inception until March 2013 for epidemiological studies on prenatal cigarette smoking exposure and one or more of the following outcomes: cryptorchidism, hypospadias, pubertal development, female fecundity, male fecundity, time-to-pregnancy (TTP) and testicular cancer. The following search MeSH-terms were used: maternal exposure, prenatal exposure delayed effects, smoking, congenital abnormalities, cryptorchidism, hypospadias, semen analysis, gonadal steroid hormones, sex characteristics, fertility, menopause, ovarian follicle, puberty and testicular neoplasms. Other search terms were also used: prenatal smoking, cigarette, semen, sperm counts, reproductive hormones, time to pregnancy, fecundity, menarche, age of menarche and Tanner stages. Furthermore, we identified articles in the referenced literature.

RESULTS

Cryptorchidism

Cryptorchidism (undescended testes) is the most common congenital malformation in boys with an estimated birth prevalence of 2%–5%

in Western countries.^{15,16} It is a major risk factor for testicular cancer¹⁷ and related to male subfertility.¹⁸ The most consistently reported risk factor is being small for gestational age (SGA),^{19–21} but maternal lifestyle factors may also play an important role.^{22,23}

We identified 20 epidemiological studies investigating the association between maternal cigarette smoking during pregnancy and cryptorchidism^{20,21,24–41} published from 1984 to 2011. A meta-analysis⁴² was published in 2011, summarizing the findings of the majority of the mentioned studies.

Figure 1 presents a summary of studies reporting an odds ratio (OR) or risk ratio (RR) with 95% confidence interval (CI) on the association between maternal cigarette smoking during pregnancy and cryptorchidism. In a large-scaled case-control study, Akre *et al.*²⁰ investigated risk factors for cryptorchidism in 2782 boys and five matched controls per case, using prospectively collected exposure data. The odds of having cryptorchidism among exposed boys were higher than among unexposed boys (adjusted OR: 1.19 (95% CI: 1.06; 1.33)). These results were supported by another large case-control study by Biggs *et al.*³¹ In 2007, Jensen *et al.*³⁸ performed a follow-up study of a pregnancy cohort, including 5716 boys (270 cryptorchid) with prospectively collected exposure data. They showed that mothers smoking >20 cigarettes per day had an adjusted RR of 2.3 (95% CI: 1.1; 5.0) for having a son with cryptorchidism compared with nonsmokers. Furthermore, the results indicated that the nicotine content of the cigarettes may be of importance. In accordance with these findings, Damgaard *et al.*²¹ reported a higher OR for having a cryptorchid son among mothers, who used nicotine replacement therapy (NRT). The tendency was observed both among women using nicotine substitutes who continued smoking throughout their pregnancy (OR: 2.42 (95% CI: 0.46; 12.70)) as well as users of nicotine substitutes who stopped smoking during pregnancy (OR: 4.60 (95% CI: 1.10; 19.23)). The analyses were, however, only based on a total of 40 women. Further, there was no information on when the substitute users stopped smoking during pregnancy or information on dose or duration of the use of nicotine substitutes.

However, the majority of the existing literature does not support an association between maternal cigarette smoking during pregnancy and cryptorchidism.^{21,24,25,27–30,32–34,36,37,39–41} These studies differed in several ways. Most of the studies that did not find associations

were case-control studies with data on maternal smoking obtained postpartum, thus liable to recall bias. Several studies were limited by retrospectively collected information on maternal cigarette smoking, which may result in recall bias. Further, self-reporting of smoking habits may be prone to misclassification, most probably due to underreporting. Studies comparing self-reported smoking information with cotinine levels (the proximate metabolite of nicotine) have concluded that women who are either smokers on a daily basis or nonsmokers report their smoking accurately, but there is a classification problem in occasional smokers.^{43,44} Serum cotinine levels may provide more precise measures of smoking habits; however, on the other hand, as the average half-life of cotinine is 18–20 h, it reflects exposure during a fixed time at pregnancy and when the interest is exposure in early pregnancy self-reported information may provide more valid measures.

In addition, several studies were limited by small sample sizes, and the majority performed no adjustment for potential confounders. Also, a major obstacle is the differences in relation to case definition. The diagnoses of cryptorchidism, in particular for the mild forms, may vary between observers and this may well explain the contradictory results. Therefore, caution is particularly prudent when comparing results.

Recently, Hackshaw *et al.*⁴² conducted a meta-analysis including 18 of the studies described above. The summary estimate indicated a small increased risk of cryptorchidism following maternal cigarette smoking exposure *in utero* (OR: 1.13 (95% CI: 1.02; 1.25)). Although well-conducted meta-analyses can provide valuable information, there are some potential pitfalls to take into account. Some of the concerns are publication bias and limitations in the quality of the original studies included. Observational studies are often prone to substantial heterogeneity due to discrepancies in study design, study populations, exposure and outcome assessment, statistical methods, as well as the way results are presented. Although Hackshaw *et al.*⁴² have conducted a comprehensive systematic review based on several papers, the studies included differed as mentioned in several ways and may have biased the meta-analysis.

In summary, the majority of studies found no association between maternal cigarette smoking during pregnancy and cryptorchidism, but the two largest case-control studies^{20,31} as well as a large pregnancy cohort study,³⁸ observed an increased risk after adjustment for

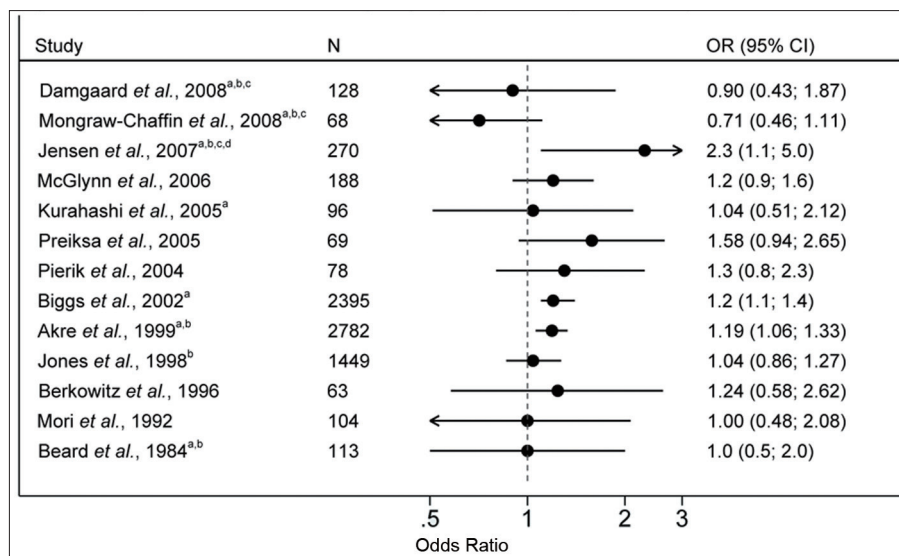


Figure 1: Summary of the studies on maternal smoking during pregnancy and risk of cryptorchidism in boys (a) Adjusted results. (b) Prospectively collected information on maternal smoking during pregnancy. (c) Dose-response studied. (d) Risk ratio with 95% confidence interval.

potential confounders. Further, the meta-analysis indicated a small increased risk for cryptorchidism.⁴² Taken together, this indicates a small-to-moderate increased risk of cryptorchidism following *in utero* exposure to cigarette smoking.

Hypospadias

Hypospadias is a malformation of the urethral opening originating in the first trimester of pregnancy with a birth prevalence varying between 1 and 6 per 1000 male births, depending on definition.^{45,46} Studies have reported an increasing prevalence during the 1970s and 1980s, but it appears that the trend has plateaued in recent years.^{47,48} Genetic factors seem to have a principle role in development of hypospadias;⁴⁹ but common risk factors, such as SGA, have been suggested for both hypospadias and cryptorchidism,²⁰ which may reflect a contribution of placental insufficiency.

We identified 14 case-control studies^{20,32,39,50-60} published from 1990 to 2010 and one meta-analysis⁴² on the association between maternal cigarette smoking during pregnancy and hypospadias.

A summary of studies reporting OR with 95% CI on the association between maternal cigarette smoking during pregnancy and hypospadias are presented in **Figure 2**. Four studies indicated that maternal cigarette smoking is associated with a reduced risk of having a child with hypospadias,^{20,50,52,57} two of these presented statistical significant results:^{52,57} in the study by Kallen,⁵² including 3262 boys with hypospadias identified among 1 413 811 infants in Swedish health registries, the OR of having a child with hypospadias was 0.81 (95% CI: 0.71; 0.92) among women smoking ≥ 10 cigarettes per day. The findings were corroborated in the study by Rodriguez-Pinilla *et al.*⁵⁷ with 2393 cases and 12 465 controls (OR: 0.86 (95% CI: 0.77; 0.96)).

To the contrary, Brouwers *et al.*⁵⁶ reported higher OR of hypospadias following prenatal cigarette smoking exposure (OR: 1.5 (95% CI: 1.0; 2.4)), among 769 cases and 440 controls. Yet, the exposure data were only specified as smoking or drinking alcohol during pregnancy joined together. Three studies did not report ORs: two of these observed a lower proportion of smoking mothers among cases than among controls;^{53,58} whereas, Carbone *et al.*³⁹ found the opposite.

The majority of publications reported no association between prenatal cigarette smoking exposure and risk of hypospadias.^{20,32,50,51,54,55,59,60}

Many of these studies were limited by small sample sizes and in some studies hypospadias was not studied separately, but included in a group of genitourinary malformations. Further, similar to the studies on cryptorchidism, the studies are strongly dependent on case definitions, which varied between studies. Several studies were limited by imprecise data on timing and frequency of maternal smoking habits during pregnancy, which may vary much in different societies. Moreover, women smoking cigarettes during pregnancy may, in relation to other characteristics, differ by country.

The meta-analysis by Hackshaw *et al.*⁴² that included 15 studies reported an OR of 0.90 (95% CI: 0.85; 0.95) for having a son with hypospadias.

In summary, although the majority of the studies points toward no association, there may be a protective effect of maternal cigarette smoking during pregnancy on the risk of having an offspring with hypospadias. A plausible biologic explanation does not exist and the protective effect may be due to confounding or differential survival during fetal life related to smoking.

Pubertal development

A secular trend towards earlier age at sexual maturation among girls has been proposed.⁶¹⁻⁶³ Whether the same decreasing trend is evident among boys is unclear.^{61,64}

We identified 12 studies exploring whether prenatal exposure to cigarette smoking affects timing of puberty. Of these, nine studies investigated female puberty⁶⁵⁻⁷³ and three studies investigated male puberty.⁷⁴⁻⁷⁶

Studies of female pubertal development have used age of menarche (AOM) as a marker of age of puberty. Shrestha *et al.*⁷¹ observed 2-4 months earlier AOM among women whose mothers smoked >10 cigarettes per day or stopped smoking during pregnancy compared with nonexposed. The association was more pronounced in the study by Ernst *et al.*⁷² in which daughters exposed to <10 cigarettes per day and ≥ 10 cigarettes per day experienced AOM 4.0 and 6.5 months earlier than nonexposed, respectively. These results corroborate previous indications of earlier AOM among heavily exposed girls,^{65,67-69} especially among Caucasians. Common for these studies are that the exposure information was collected prospectively from the mothers.

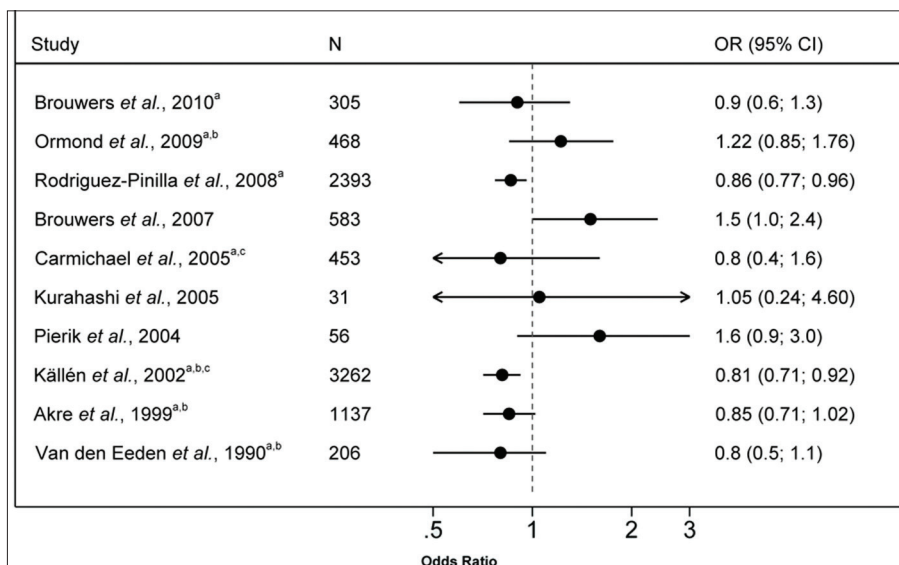


Figure 2: Summary of the studies on maternal smoking in pregnancy and risk of hypospadias in boys (a) Adjusted results. (b) Prospectively collected information on maternal smoking during pregnancy. (c) Dose-response studied.

Most recently, D'Aloisio *et al.*⁷³ performed a large study of 32 096 women and found that early menarche (≤ 10 or 11 years) was associated with *in utero* exposure to cigarette smoking. However, the study was limited by retrospectively collected data from the women (35–59 years of age) on both AOM and prenatal exposure to cigarette smoking.

To the contrary, Windham *et al.*⁶⁶ and Ferris *et al.*⁷⁰ observed a later AOM in women exposed to >20 cigarettes per day, but the results by Windham *et al.*⁶⁶ were attenuated when adjusting for possible confounders, and the study by Ferris *et al.*⁷⁵ was limited by a low participation rate and a long recall time, thereby increasing the risk of recall bias.

Results from the four studies on the association between prenatal cigarette smoking and pubertal development in boys show consistent results. The earliest study by Fried *et al.*⁷⁴ found that exposed men experienced an earlier self-reported age at voice break compared with nonexposed. These findings were based on only 83 boys and with no confounder adjustment. The results were corroborated by a large study ($N = 3486$) by Ravnborg *et al.*⁷⁵ They reported earlier voice break, growth of penis and pubic hair development among exposed boys; however, with limited confounder adjustment and retrospectively collected exposure information. The most recent study by Håkonsen *et al.*⁷⁶ with prospectively collected data on maternal cigarette smoking reported tendencies toward earlier age of first nocturnal emission, acne and voice break; indicating an earlier age of pubertal development among exposed men. However, the differences between exposure groups were not statistically significant. The findings were based on 2522 participants, and the analyses were adjusted for several important potential confounders. All three studies were limited by retrospectively collected self-reported data on pubertal development and due to the recall time, there may have been some misclassification.

In conclusion, although results for girls are conflicting and the number of studies for boys is sparse, the existing literature provides some evidence to support the hypothesis that exposure to cigarette smoking *in utero* may accelerate puberty in both sexes.

Female fecundity

The reproductive health of women is traditionally described by AOM, hormonal status, fecundability measured by TTP, menstrual cycle characteristics, number of follicles in the ovaries and age of menopause.⁷⁷

We identified five studies examining the association between *in utero* exposure to cigarette smoking and female fecundity, measured by other markers of reproductive health than AOM (described in paragraph 3.3) and TTP (described in paragraph 3.6) in adult daughters.^{72,78–81} In a recent Danish pregnancy cohort study ($N = 367$) by Ernst *et al.*⁷² tendencies towards lower levels of testosterone and dehydroepiandrosterone sulfate (DHEAS) with higher levels of cigarette smoking exposure *in utero* were observed among daughters, who were nonusers of hormonal contraceptives. They did not find associations with follicle number, cycle length, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, sex hormone binding globulin (SHBG), anti-Müllerian hormone (AMH), free testosterone or free estradiol. Kerkhof *et al.*⁸⁰ observed higher levels of AMH in exposed daughters but found no association with the level of other reproductive hormones. In line with these findings, Hart *et al.*⁷⁹ performed ultrasound examinations of adult women exposed *in utero* and did not observe a reduction in ovarian reserves. These findings are surprising and contradicts the results of animal studies.^{82,83}

In a study on prenatal exposure to diethylstilbestrol (DES), a synthetic nonsteroidal estrogen which suppresses FSH, Hatch *et al.*⁸⁴ raised the hypothesis that prenatal exposure to environmental factors with similar

hormonal disrupting properties, such as cigarette smoking, may influence the age at menopause. The hypothesis was examined by Strohsnitter *et al.*⁷⁸ using three cohorts, among these the cohort used by Hatch *et al.*⁸⁴ Strohsnitter *et al.*⁷⁸ observed that exposed nonsmoking women were more likely than unexposed nonsmoking women to reach menopause at an earlier age (HR: 1.38 (95% CI: 1.10; 1.74)), but with no indication of a dose-response effect. Since 80% of the women were prenatally exposed to DES, the results may not be applicable to other populations. Steiner *et al.*⁸¹ did not find prenatal tobacco exposure to be associated with higher risk of being postmenopausal, not even among nonsmoking women (HR: 1.04 (95% CI: 0.98; 1.11)). This study was strengthened by a large study population but limited by information on prenatal smoking exposure collected retrospectively and through the daughters.

In summary, it is almost unexplored whether maternal cigarette smoking during pregnancy affects female fecundity and further investigations are needed.

Male fecundity

Impaired male fecundity (i.e., the biological ability to reproduce) is commonly due to deficiencies in semen quality. The etiology underlying male reproductive dysfunction is poorly understood, but is predominantly of testicular origin rather than arising from gonadotropin deficiency or other extratesticular causes.⁸⁵ Spermatogenesis is hormonally regulated and maintenance of male reproductive function is dependent on the circulating levels of specific reproductive hormones.

We identified 12 papers^{75,86–96} covering 11 study populations that investigated the associations between maternal cigarette smoking and semen quality and level of reproductive hormones. All studies were observational follow-up studies and the majority included Danish^{75,87–90,93,95} and other European men,^{91,92} but also two studies on North American men have been conducted.^{86,96}

Table 1 provides a summary of the epidemiological studies on the association between maternal cigarette smoking during pregnancy and semen quality and reproductive hormones in male offspring.

In five studies, young men from Denmark, Norway, Finland, Lithuania, Estonia, Sweden and Germany at compulsory medical examination for possible military service were studied.^{75,88,91,92,95} These men were not selected according to fecundity status, thereby limiting the risk of selection bias, although low participation rates (13%–24%) may have posed a risk of the validity. In the studies of Jensen *et al.*⁸⁸ Paasch *et al.*⁹² and Ravnborg *et al.*⁷⁵ 15%–37% lower semen concentration and 18%–39% lower total sperm count were observed among exposed sons in comparison with nonexposed. These findings were not supported by the remaining two studies investigating young men at compulsory medical examination.^{91,95} Two of these five studies also measured the level of reproductive hormones:^{75,91} Richthoff *et al.*⁹¹ found no association with testosterone, SHBG, FSH or inhibin B levels; whereas, Ravnborg *et al.*⁷⁵ found lower inhibin B and inhibin B/FSH ratio among exposed compared with nonexposed. This indicates a primary reduction in the testicular spermatogenic capacity and altered hypothalamo-pituitary function. Further, they found lower free testosterone among nonsmoking men. All five studies were based on prenatal exposure information collected from the adult sons at the time of medical examination.

Four other studies also used retrospectively collected information on maternal smoking during pregnancy.^{86,87,89,94} Briefly, Ratcliffe *et al.*⁸⁶ examined sons of mothers who participated in a randomized clinical trial on exposure to DES during pregnancy, and no indication of an effect of prenatal cigarette smoking exposure on semen quality was

Table 1: Epidemiological studies on the association between maternal smoking during pregnancy and semen quality and reproductive hormones

Reference	N	Study population	Exposure information obtained		Dose response studied	Adjusted results for measures of semen quality ^a	Adjusted results for levels of reproductive hormones ^b
			From son or mother	Prospectively or retrospectively			
Ratcliffe <i>et al.</i> 1992 ⁸⁶ USA	292	Sons of women participating in a randomized clinical trial of diethylbestrol during pregnancy	Mother	Retrospectively	No	No association with semen volume, sperm concentration, TSC or percentage of viable or motile sperm	Statistically insignificant higher LH and FSH and lower T in exposed men compared with nonexposed men
Storgaard <i>et al.</i> 2003 ⁸⁷ Denmark	265	Twins and singleton brothers identified through Danish registers	Mother	Retrospectively	Yes	Lower sperm concentration and TSC among men exposed to >10 cigarettes per day. No association with sperm morphology	Lower inhibin B and higher FSH among men exposed to >10 cigarettes per day. No association with LH or T
Jensen <i>et al.</i> 2004 ⁸⁸ Denmark	1770	Men (Denmark, Norway, Finland, Lithuania, Estonia) at compulsory medical examination for possible military service	Son/ mother	Retrospectively	No	Lower sperm concentration, TSC, sperm motility and tendency toward lower sperm morphology among exposed	Not measured
Jensen <i>et al.</i> 2005 ⁸⁹ Denmark	522	Greenhouse workers, steel welders, pesticide-spraying farmers and first pregnancy planners	Mother	Retrospectively	Yes	Tendency towards lower sperm concentration and TSC among exposed. Higher risk of oligozoospermia among men exposed to >10 cigarettes per day	Exposure not associated with FSH or inhibin B
Ramlau-Hansen <i>et al.</i> 2007 ⁹⁰ and 2008 ⁹³ Denmark	347	Sons of women who participated in the Danish pregnancy cohort "Healthy Habits for Two"	Mother	Prospectively	Yes	Trend of lower TSC with higher exposure. Lower semen volume among high exposed men. Statistically insignificant lower TSC and sperm concentration in exposed. No association with motility or morphology	Trend of higher free T/free E2 ratio with higher exposure. Exposure not associated with free or total T, estradiol, SHBG, FSH, LH, inhibin B, LH/free T ratio or FSH/inhibin B ratio
Richthoff <i>et al.</i> 2008 ⁹¹ Sweden	269	Men at compulsory medical examination for possible military service	Son	Retrospectively	No	No association with semen volume, sperm concentration, TSC or sperm motility	Exposure not associated with T, SHBG, FSH, LH or inhibin B
Paasch <i>et al.</i> 2008 ⁹² Germany	791	Men at compulsory medical examination for possible military service	Son/ mother	Retrospectively	No	Lower sperm concentration and TSC among exposed. No association with semen volume, sperm motility or morphology	Not measured
Kerkhof <i>et al.</i> 2009 ⁹⁴ The Netherlands	207	Men from The Netherlands recruited from hospitals and schools	Son/ mother	Retrospectively	No	Not measured	Higher free T and LH among exposed compared with nonexposed. Exposure not associated with total T, SHBG, FSH, AMH or inhibin B
Jørgensen <i>et al.</i> 2010 ⁹⁵ Denmark	858	Men at compulsory medical examination for possible military service	Son	Retrospectively	No	No association with semen volume, sperm concentration, TSC, sperm motility or morphology	Not measured
Cirillo <i>et al.</i> 2011 ⁹⁶ USA	196	Sons of women who participated in the American pregnancy cohort "Child Health and Developmental Studies"	Mother	Prospectively	No	No association with sperm concentration, sperm motility or morphology	Not measured
Ravnborg <i>et al.</i> , 2011 ⁷⁵ Denmark ^c	3486	Men at compulsory medical examination for possible military service	Sons/ mother and/or father	Retrospectively	No	Lower sperm concentration and TSC among exposed. In subsample of nonsmoking men: Lower sperm morphology among exposed. No association with semen volume or sperm motility	Lower inhibin B and inhibin B/FSH ratio among exposed compared with nonexposed. Exposure not associated with total testosterone or estradiol. Association with FSH, LH, SHBG, free T, free T/LH ratio

^aTSC: total sperm count; ^bT: testosterone; LH: luteinizing hormones; FSH: follicle stimulation hormones; SHBG: sex hormone binding globulin; AMH: anti-Müllerian hormone
^cOverlapping study population (n=773) between the studies by Jensen *et al.*, 2004⁸⁸ and Ravnborg *et al.*, 2011.⁷⁵

found. They found a tendency toward higher LH and FSH and lower testosterone among exposed men compared with nonexposed men. The first to investigate a possible dose-response relationship between prenatal tobacco exposure and semen quality was Storgaard *et al.*⁸⁷ They reported about 50% lower sperm concentration and total sperm count among sons prenatally exposed to >10 cigarettes per day compared with nonexposed. Additionally, the exposed men had lower levels of inhibin B and higher FSH levels, but no association with LH or testosterone was found. Jensen *et al.*⁸⁹ also studied dose-response relationship

and observed a tendency towards lower sperm concentration and total sperm count with higher exposure levels. Men exposed to >10 cigarettes per day had about 2.5 higher risk of oligozoospermia than nonexposed. Exposure was not associated with FSH or inhibin B. In the study by Kerkhof *et al.*⁹⁴ higher free testosterone and LH were observed among exposed compared with nonexposed, but differences in total testosterone, SHBG, FSH, AMH or inhibin B were not found.

Only two studies have used prospectively collected information on maternal cigarette smoking obtained from the mothers at time of

pregnancy.^{90,96} The Danish pregnancy cohort study by Ramlau-Hansen *et al.*⁹⁰ found a trend towards lower total sperm count with higher exposure levels. In comparison with non-exposed sons, sons exposed to >19 cigarettes per day had 38% lower total sperm count and 17% lower sperm concentration, however, these differences did not reach statistical significance. Also, a trend of higher free testosterone/free estradiol ratio with higher smoking dose was observed, but no association with other hormones. This suggests a resetting of the negative feedback mechanism of the hypothalamo-pituitary-gonadal axis during fetal development. The study from USA by Cirillo *et al.*⁹⁶ reported no association between prenatal tobacco exposure and sperm counts. The discrepant findings of these two studies may be due to differences in the study populations. In the study by Ramlau-Hansen *et al.*⁹⁰ 248 men out of 347 men (71%) were prenatally exposed to cigarette smoking and a dose-dependent association between prenatal cigarette smoking exposure and semen quality were observed. Cirillo *et al.*⁹⁶ studied semen quality in prenatally exposed men where 47 out of 196 (24.5%) were exposed. Further, they only presented results based on binary cigarette smoking exposure which may explain the contradictory findings.

None of the studies found prenatal tobacco exposure to be associated with sperm motility or morphology.

In conclusion, the results on reproductive hormones are inconsistent, whereas the existing studies provide rather good evidence that maternal cigarette smoking during pregnancy has adverse effects on sperm concentration and total sperm count of the sons.

Time-to-pregnancy

Time-to-pregnancy, e.g., the number of menstrual cycles required for a couple to conceive, has been extensively used in epidemiological studies aiming to measure couples fecundity over time or in relation to potential detrimental factors.⁹⁷⁻⁹⁹

We identified six epidemiological studies investigating the association between prenatal exposure to cigarette smoking and TTP,¹⁰⁰⁻¹⁰⁵ of whom three also included sons.¹⁰²⁻¹⁰⁴ The studies were based on observational follow-up designs and included study populations from Norway, Denmark, Great Britain and USA that generally were Caucasians, well-educated and with no chronic or

fertility diseases. The same discrete-time survival model was used to evaluate the effect of *in utero* exposure to cigarette smoking in all studies with estimation of fecundability odds ratio (FOR), that is, the odds of conception within a cycle or month among the exposed group divided by the corresponding odds in the unexposed group.

Figure 3 shows a summary of studies on the association between *in utero* exposure to cigarette smoking and TTP, presented with FORs and 95% CIs. Four studies suggest a small-to-moderate decrease in fecundability among exposed women,^{101,102,104,105} and one study reported a similar association in men.¹⁰² Two studies did not observe an association;^{100,103} one of these was a study by Joffe and Barnes,¹⁰³ with information on maternal cigarette smoking during pregnancy collected during pregnancy, who reported an adjusted FOR of 1.02 (95% CI: 0.92; 1.13) among women and 1.01 (95% CI: 0.89; 1.15) among men. The most recent and largest study by Ye *et al.*¹⁰⁵ including 48 319 first pregnancy planning couples, observed a FOR of 0.96 (95% CI: 0.93; 0.98) in nonsmoking women exposed to cigarette smoking during fetal life.

In a study by Jensen *et al.*¹⁰² TTP was recorded prospectively, as 423 couples were followed cycle by cycle until a clinically recognized pregnancy or for a maximum of six menstrual cycles. They had the ability to adjust for a variety of potential confounding factors not included in the other studies, such as semen quality and sexual activity. The adjusted FOR in prenatally exposed currently smoking women was 0.53 (95% CI: 0.31; 0.91), while the adjusted FOR among prenatally exposed nonsmoking women was 0.70 (95% CI: 0.48; 1.03), suggesting that current smoking may exacerbate possible damages established during prenatal life. The effect of prenatal exposure seemed to be more pronounced in sons with an FOR of 0.68 (95% CI: 0.48; 0.97). Conversely, in another study by Jensen *et al.*¹⁰⁴ female twins had reduced fecundability after exposure to maternal cigarette smoking (FOR: 0.81 (95% CI: 0.67; 0.99)), while male twins were unaffected (FOR: 1.12 (95% CI: 0.89; 1.40)), even among dizygotic twins of opposite sex sharing the same exposures. Baird and Wilcox¹⁰⁰ found no significant reduction in the fecundability of daughters, but Weinberg *et al.*¹⁰¹ detected a large decrease in FOR (0.5 (95% CI: 0.4; 0.8)) following prenatal exposure to cigarette smoke.

All studies were to some extent limited by retrospectively collected information on either exposure, outcome or both; and a recall time

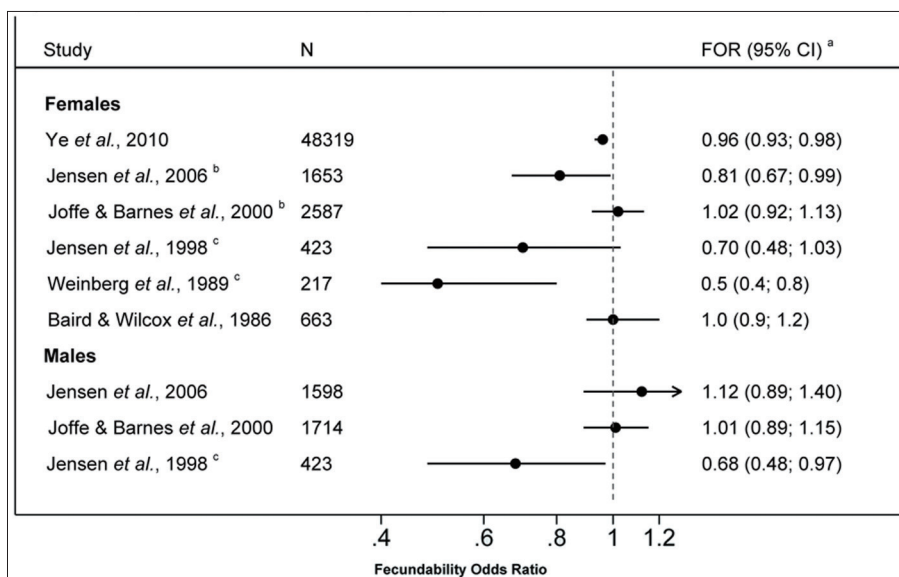


Figure 3: Summary of the studies on maternal smoking during pregnancy and time-to-pregnancy (TTP) in children. (a) Adjusted results. (b) Information on maternal smoking during pregnancy primarily collected with assistance from mothers. (c) Prospectively collected information on time to pregnancy.

on the exposure varying from 15 to 66 years. The studies^{100–105} used binomial exposure data on prenatal cigarette smoking (yes/no) which is easier to recall than actual number of cigarettes smoked per day and may reduce underreporting of maternal smoking, but eliminates the opportunity to examine possible dose-response effects.

In conclusion, although the reason for the inconsistent findings remains unclear, maternal smoking during pregnancy seems to induce a minor decrease in fecundability among daughters, but not among sons. Further studies are warranted, especially among males.

Testicular cancer

Evidence exist for a rapid increase in the incidence of testicular cancer in many affluent countries in the post-war period,^{106,107} which now may be attenuated and maybe even declining in some countries.^{106,107} The disease predominantly affects young adults, and although the etiology is mostly unknown, it is thought to derive from carcinoma *in situ* cells that develop in fetal life.¹⁰⁸

We identified 14 epidemiological studies exploring prenatal cigarette smoking and the risk of testicular cancer: three ecologic studies^{109–111} and 11 case-control studies.^{29,112–121}

Clemmesen¹⁰⁹ found a correlation between incidence rates of testicular cancer and rates of tobacco-induced neoplasms among the maternal generation, and another ecologic study found strong geographical and chronological correlations between female smoking habits and testicular cancer incidence rates in the presumed offspring cohorts in four Nordic countries.¹¹¹ In a Swedish study, sons of women diagnosed with lung cancer had increased risk of testicular cancer.¹¹⁰ However, whether the parallel trends represent a causal relationship or simply a spurious association cannot be concluded from these ecologic studies.

Results from the 11 case-control studies with data on individual level^{29,112–121} are inconsistent with the results from the ecologic studies. Eight studies with information on maternal cigarette smoking collected through self-administered questionnaires and interviews after identification of testicular cancer cases and controls found no evidence to support the hypothesis.^{29,112–118} Due to the retrospectively collected exposure information there may be recall bias; however, three studies with prospectively collected exposure data also failed to find an association.^{119–121} The study by Tuomisto *et al.*¹²⁰ assessed maternal serum cotinine levels, further limiting the risk of information bias. Tuomisto *et al.*¹²⁰ also performed a meta-analysis on seven of the mentioned studies,^{29,114–119} including a total of 2149 cases and 2762 controls, and the summary estimate gave an OR of 1.0 (95% CI: 0.88; 1.12).

To conclude, the ecologic studies suggest an association between cigarette smoking exposure and testicular cancer, but due to the use of data at the population level rather than the individual level they are vulnerable to the ecological fallacy as well as other biases. The case-control studies did not find evidence for an association, thus, we find no convincing evidence for an association between prenatal cigarette smoking exposure and testicular cancer. Yet, it is of interest to see whether the current changes in smoking habits at the population level will influence on future incidence of testicular cancer.

DISCUSSION

Epidemiological findings

In summary, the reviewed studies point towards a damaging effect of prenatal cigarette smoking exposure on several aspects of male and female reproductive health. In regard to the male urogenital malformations, we observed a complex relationship; a small increased

risk of cryptorchidism, but a potential protective effect on the risk of hypospadias. Pubertal development seemed to be accelerated in both exposed boys and girls. In adult life, an adverse effect on semen quality was rather consistently reported but less evident when looking at fecundability both among daughters and sons. Finally, we found no evidence to support an association with testicular cancer.

QUESTIONS FROM THE PANEL

Q1: Is there any evidence that maternal smoking alters the hormonal milieu of the developing fetus?

A1: Although the prevalence of smoking during pregnancy has declined in recent years, around 16% of pregnant women continue to smoke throughout their pregnancy.^{122,123} Smoking has an antiestrogenic effect,¹²⁴ and evidence points toward a disruption in the hormonal homeostasis - toward an androgenization in cigarette smoking women compared to nonsmokers.^{125–127}

Cigarette smoke contains many toxic components, including metals, nicotine, carbon monoxide and polycyclic aromatic hydrocarbons (PAHs), many of which has the ability to cross the placental barrier and have been detected in amniotic fluid and fetal serum.¹²⁸ Concentrations of nicotine and cotinine, the major nicotine metabolite, in the fetal blood are highly correlated with those of their smoking mothers, some have even reported higher levels in the fetal blood compared to their mothers.^{129–131} Consequently, cigarette smoke may well interfere with both the intrauterine environment as well as the fetal endocrine system; thus, affecting fetal growth and development.

The placenta has a principal role in the production of estrogens during pregnancy. Both animal- and human studies have found that placental aromatase, which converts testosterone into estradiol, is inhibited by cigarette smoke; thus, causing an irreversible alteration in the placental steroidogenic function.^{132,133}

In offspring exposed to cigarette smoking *in utero*, a reduced concentration of estrone and free β -human chorionic gonadotropin (β hCG) in umbilical cord blood have been reported,¹³⁴ which may indicate an altered hormonal exposure of the fetus. Umbilical cord blood is, in practice, only obtainable at birth. It is unclear whether umbilical cord blood provides valid information about effects of early hormonal exposure,¹³⁵ and it does not reflect exposure during the critical developmental time window of the reproductive organs. Evidence from experimental studies suggests a “male programming window” during gestational week 8–14, where development of the genitals depend on sufficient androgen action.^{136,137} In females, the ovaries starts developing around 5 weeks post-conception¹³⁸ and from around the 5th month the final pool of oocytes are arrested in the first meiotic division until puberty.¹³⁹

Hormonal levels in amniotic fluid may be a better indicator of fetal hormonal exposure during prenatal development,¹³⁵ since it measures the exposure more directly during the vulnerable period in early fetal life. However, due to the risk associated with sampling of amniotic fluid, data can only be obtained from women referred for amniocentesis. These women are highly selected and most possibly skewed in regard to age, socioeconomic status and smoking status.

As a consequence of these complexities, studies investigating the influence of cigarette smoking on the intrauterine hormonal milieu are not easily conducted and results are lacking.

Q2: What are the possible mechanisms of nicotine action on reproductive organs?

A2: Although studied extensively, the mechanisms behind the potential reproductive consequences of exposure to cigarette smoking *in utero* are not fully understood and a wide variety of mechanisms have

been proposed. A possible direct toxic effect on the developing gonads or an indirect negative influence on the hypothalamus-pituitary-gonadal axis¹⁴⁰ are both plausible biologic explanations.

In utero exposure to the fetotoxic components of cigarette smoke may well interfere with the delicate formation of gonads and cause deleterious effects on reproductive health in both sexes.^{82,83,141-144} Studies of male and female mice prenatally exposed to benzo[a]pyrene (BaP), a carcinogenic compound of PAH, have supported this assumption.^{82,145}

In females, a general ovarian toxicity has also been suggested,^{83,141-144} as *in utero* exposure to components in cigarette smoke have caused a reduction in the final pool of oocytes and altered ovarian steroidogenesis.¹⁴² Lutterodt *et al.*^{83,141-144} and Mamsen *et al.*^{83,141-144} investigated whether early *in utero* exposure to cigarette smoking affected the number of oogonia in ovaries from human embryos. They showed a negative effect on the growth of the developing gonads and a reduction in the number of germ cells. If these associations are true, an early exposure to cigarette smoke causes poor ovarian reserve which possibly affects fecundity in adult life. However, epidemiological studies have not supported this.^{79,80}

In males, Mamsen *et al.*¹⁴⁴ studied 24 human first-trimester testes and observed a detrimental effect on the growth and development of human embryonic testes with a significant reduction in the number of germ cells by 55% in prenatally exposed fetuses compared with unexposed. The significant negative effect of maternal smoking was dose-dependent and was consistent after adjusting for alcohol and coffee consumption. Also, Coutts *et al.*¹⁴⁶ observed germ cell apoptosis in the developing human testis following exposure to toxins in cigarette smoke. As the number of Sertoli cells determines sperm production, these findings are in accordance with the epidemiological findings of reduced sperm count and unaffected morphology or motility of the spermatozoa.

Q3: Is use of nicotine replacement in smoking cessation safe?

A3: An increasing number of pregnant women use NRT for smoking cessation;¹⁴⁷ and in many countries, NRTs are available as over-the-counter products. Although NRT is considered to be a good smoking cessation tool in the nonpregnant population¹⁴⁸ and may be a better alternative than continuing smoking during pregnancy, it is claimed to deliver higher concentrations of nicotine to the fetus than cigarette smoking.¹³³ Considering that many of the harmful fetal effects of cigarette smoking attributes to nicotine, it is reasonable to hypothesize a similar effect of NRT.

Only a few studies have investigated pregnancy and birth complications or fetal consequences of *in utero* exposure to NRT. The majority of research point toward no influence on birth weight.¹⁴⁹⁻¹⁵³ In a study by Strandberg-Larsen *et al.*¹⁵⁴ the use of NRT during pregnancy had no impact on the risk of stillbirth. Thus, it does not seem that nicotine alone is responsible for the well-known adverse fetal outcomes caused by cigarette smoking during pregnancy, which is not in accordance with experimental studies.

Although NRT had no negative influence on birth weight or stillbirth, a slightly increased risk of congenital malformations was observed in a large birth cohort.¹⁵⁵ Further, Damgaard *et al.*²¹ investigated the association between maternal use of NRT and risk of cryptorchidism in exposed sons and reported increased risk among NRT users. The OR was higher among women who ceased smoking and used nicotine substitutes (OR: 4.60 (95% CI: 1.10; 19.23)) during pregnancy than among women who mixed cigarette smoking with the use of nicotine substitutes (OR: 2.42 (95% CI: 0.46; 12.70)). The study was limited by a very small number of observations and further research is warranted.

Currently, there is insufficient evidence on the safety of NRT during pregnancy and little is known about adverse fetal outcomes and long-term consequences, including reproductive health.

Table 2: Summary of the main conclusions from the epidemiologic studies on the effect of maternal cigarette smoking during pregnancy on reproductive health in children

Outcome	Main conclusion
Cryptorchidism	Small increased risk following exposure, but only few large scaled studies
Hypospadias	Protective effect on the risk among exposed, but large discrepancies between studies
Pubertal development	Accelerated pubertal development in both sexes, but based on few studies
Female fecundity	Association almost unexplored, further studies warranted
Male fecundity	Adverse effect on semen quality, but some inconsistent results
Time-to-pregnancy	Small decrease in fecundability but only few studies
Testicular cancer	No evidence for an increased risk among exposed

FUTURE PERSPECTIVES: HOW TO MOVE FORWARD?

Although epidemiological studies point towards a negative influence of maternal cigarette smoking during pregnancy on some aspects of reproductive health, several questions remain unanswered. Some aspects are poorly investigated and some areas show inconclusive results. The fundamental concern when interpreting the existing literature is to disentangle whether the observed associations are due the direct toxic or indirect endocrine effects of cigarette smoking exposure *in utero* or confounded by characteristics of the smoking pregnant women. Observational studies are, due to unmeasured confounding and reverse causation, limited in making causal inferences. Further, for ethical reasons randomized control trials are not feasible. Thus, is it possible to overcome the potential bias created by unmeasured genetic or person-related confounding factors and provide solid evidence for a true association?

Over relatively short time periods, substantial changes in both active and passive smoking exposures have taken place. In many populations, cigarette smoking became very widespread during the 60s, 70s and 80s; also among females. During recent years, the habit has been rapidly declining, especially during pregnancy. The current trend towards a decrease in cigarette smoking should be identifiable in population statistics on reproductive failures and could possibly be utilized in ecologic studies; however, the study design is vulnerable to the ecological fallacy.

Mendelian randomization, an approach using genetic variants as proxy variables for modifiable exposures, such as cigarette smoking during pregnancy, is becoming commonly used in epidemiology. The method is less prone to confounding and suitable to distinguish causal effects from confounded associations in observational data,¹⁵⁶ which may provide new insights in this area. It will, however, require strong links between genetic factors and the tendency to smoke without any other causal links between the instrumental variable and the outcome.

CONCLUSIONS

In **Table 2**, a summary of the main conclusions from the epidemiologic studies on the effect of maternal cigarette smoking during pregnancy on reproductive health in children is presented. We conclude that the existing evidence indicates moderately impaired reproductive health in boys and girls exposed to cigarette smoking *in utero*.

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