ORIGINAL ARTICLE

Maternal Smoking during Pregnancy and its effects on Neural Tube Defects

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ABSTRACT

Objectives

Maternal smoking is a potent teratogen among congenital malformations, however its role in the development of Neural Tube Defects (NTDs) is still unclear. In this systematic review, we intend to further investigate the interaction of smoking during pregnancy and the incidence of NTDs.

Materials & Methods

This article was written according to PRISMA criteria from February 2015 and August 2022. After examining the four stages of PRISMA criteria, we selected clinical articles. These articles were selected from PubMed, Scopus and Google scholar (for results follow-up) databases. We gathered NTDs effect and types, smoking type and habit of parents, from neonates.

Results

Eventually, 8 articles were included by two separated authors, Smoking was associated with an increase NTDs in the population of pregnant mothers and also among children whose fathers smoked. The main side effects that were considered to be the cause of NTDs besides smoking were alcohol and BMI (18.5-24.9). Smoking also affects the level of folic acid as a substance with an essential role that affects the closure of the neural tube. folic acid available to infants changing along with the level of other blood elements such as zinc, that necessary prevent for NTDs condition.

Conclusion

Parental smoking can be considered as one of the strong teratogens in the occurrence of NTDs. Smoking, whether active or passive by the mother, or by the father, is associated with the occurrence of NTDs, In order to reduce the prevalence this disorder, we advise pregnant mothers and neonate's fathers to quit smoking.

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Introduction

Neural tube defects (NTDs) are congenital defects in the nervous system characterized by either open or closed neural tube dysraphism, stemming from incomplete or insufficient neural tube closure (1, 2). These conditions include anencephaly, spina bifida, and encephalocele, making NTDs among the most common birth defects (3, 4). . 3% of live births in the world are generally attributed to it (5),the most severe type of which is craniorachischisis, characterized by an open spine from the midbrain, and no maternal treatment has been defined for it (6). Anencephaly occurs when the upper part of the neural tube does not close, while myelomeningocele refers to the condition where the lower part of the spine remains open. . In myelomeningocele, a swollen mass is formed at the end of the neural tube. Encephalocele in the closed type is identified by a hernia or protrusion in the upper end and Meningocele in the lower end. It is the abnormal growth of the fetal tail bud. This defect introduces the lower back and sacral areas of spina bifida, classified as closed type (2, 3, 7-9). Stillbirth, neonatal death, and post-neonatal death are the most common result of these disorders, which can be diagnosed by ultrasound imaging or screening of the alpha-fetoprotein level of the mother's serum (10, 11). The prevention and prognosis of these disorders have attracted the scientific community's attention (12-14), implying the need to know the risk factors of their occurrence. Normal body mass index, consumption of nutritional supplements such as folic acid or multivitamins, proper health habits of the mother, presence of dangerous teratogens such as alcohol consumption or smoking, folic acid deficiency, family marriage, and genetic issues are the leading causes of NTD in pregnant mothers (9, 15-19).

Smoking is one of the factors affecting diseases such as heart and respiratory diseases (20-23). As the World Health Organization (WHO) stated on its website, the harmful effects of tobacco on the pathogenesis of many diseases have impaired the health of many people around the world and have put a lot of pressure on governments (24, 25) so that the WHO announced: Considering that about 1.3 billion people worldwide use tobacco products, 5 million deaths have been reported, which will increase to more than 8 million by 2030 (26). Maternal smoking is a way that determines the effects of smoking on children's health and causes birth defects (27-29) that can be referred to as NTDs. The impact of tobacco and its related products, especially cigarettes, on NTDs has been a new and interesting topic in recent years. In 2021, a meta-analysis was conducted on the effect of parental smoking on the probability of NTD occurrence (30), concluding that parental smoking is associated with a higher probability of NTD occurrence in infants However, in this study, the types of maternal and paternal smoking were examined together with each other, and we felt it necessary to examine the relationship between active maternal smoking, passive maternal smoking, and maternal secondhand exposure to NTDs in newborns. In addition, this study investigated the folic acid element as one of the factors whose reduction is one of the main causes of NTD incidence under the influence of cigarettes and tobacco products. The missing link in this topic is how smoking interacts with the mother's body to create conditions in favor of NTDs. What this research intend to reveal by responding to the research question (PICO criteria) in this systematic review is the unknown link between tobacco products and the incidence of NTDs.

This systematic review intends to answer the research question based on the PICO (Problem/ Population, Intervention, Comparison, and Outcome) criterion is as follows.

Does maternal tobacco exposure cause congenital NTDs in infants?

Materials & Methods

Search strategy:

This review started by tracking the results by searching in PubMed, Scopus, and Google Scholar databases. The researchers extracted the keywords used from the MESH database and wrote this review article based on the PRISMA checklist (Figure 1).

First, the articles related to the studied NTDs, and in addition, this study used tobacco epidemiological statistics from the official WHO website. Keywords were Tobacco/Smoking, Maternal smoking and NTDs, Maternal smoking and Folic acid, and Maternal smoking and NTDs. Finally, the researchers followed up on the obtained results in Google Scholar based on the principle of non-bias, mentioning conflicting results. This review also matched the studied articles with the systematic reviews of the Cochrane database in

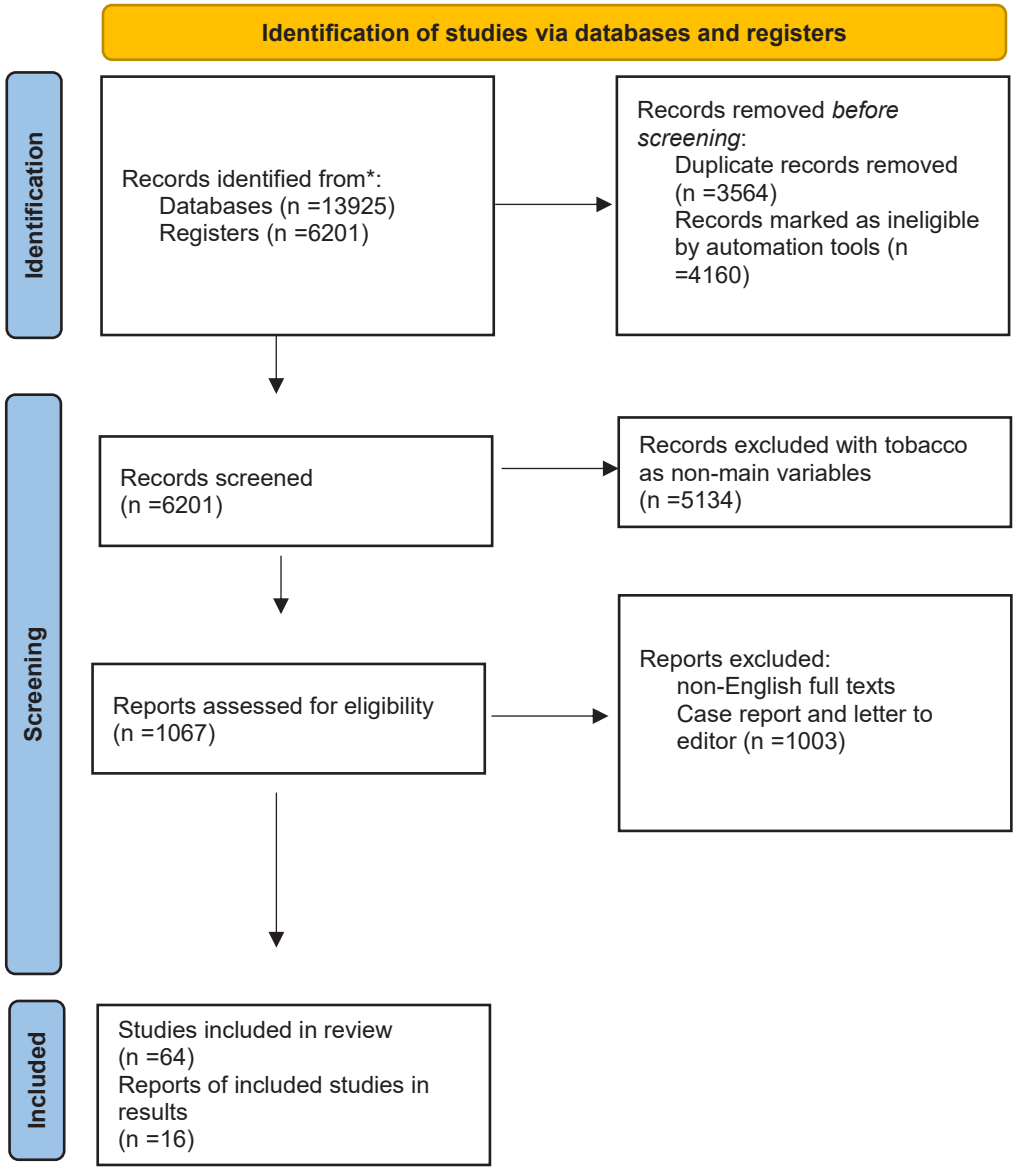

Fig 1. *PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only*

terms of similarity.

Include and Exclude criteria:

NTDs were investigated based on the international definition of ICD 11 (International Classification of Diseases) accepted in 2022. Articles that examined congenital brain abnormalities were excluded from the study. After screening, articles in which Smoking was not evaluated as the main variable and was only calculated as a confounding factor, were not included in the study. The review was completed searching between February 2015 and August 2022.

Original articles of all kinds, including observational, comparative, clinical trials, and the like, were excluded from the screening section. Studies that did not mention congenital abnormalities in detail were also excluded. The team of authors selected articles that examined one of the types of tobacco as an independent variable. This study also excluded case report articles, reviews, and non-English articles from the article community. This review did not exclude animal articles.

First, the researchers removed duplicate, non-English and articles without summary or incomplete articles. This study implemented the specified exclusion criteria before proceeding to review the full texts. Two authors independently assessed the articles. In cases of disagreement regarding the selection of an article, the issue was resolved under the guidance of the lead author (Tables 1 and 2).

Data collection:

After reviewing the articles that measured the relationship between smoking, tobacco, and NTD, this study looked for an effective factor to create a stronger correlation between smoking and NTD. After carefully examining the article and its authors' perspectives, this study explores the connection between folic acid and tobacco products, focusing particularly on commercially purchased cigarettes. . Two authors read the articles, and in case of disagreement, the differences were resolved under the refereeing of the responsible author. The following information was extracted from the final statistical population.

- First author
- Type of study
- Population
- Smoking habit and type
- NTDs effect and types
- Side risk factors
- Age means
- Geographical location

Content extraction was centered on the answer to the research question based on the PICO criteria mentioned in the introduction, and the accuracy of the extracted articles and content was checked under the supervision of a specialist in infants (from the named authors).

Results

Study selection:

The articles without free access were evaluated by the eligibility of the summary of the articles, and upon necessity and need more information; the first author was contacted via email. Articles were extracted from PubMed and Scopus databases. Finally, this review evaluated the results by searching Google Scholar. In all stages, the non-biased rule was observed under the supervision of the responsible author, and conflicting results were considered.

Smoking during pregnancy was a preeminent reason associated with an increase in the incidence of NTDs in articles and specifically in Chinese infants (31).The highest occurrence was found in mothers under 25 years of age (32) with a BMI of

Table 1. The information obtained from the available articles, the type of smoking was mostly passive and exposed, the BMI of the mothers was not comprehensively available, so it was difficult to extract them from the articles. The scattered geographical distribution is a sign of the comprehensiveness of the subject in different locations

first author (year)	*study setting*	*population*	*age mean*	*smoking type*	*smoking habit*	*NTDs effect*	*NTDs types*	*Side Risk factors*	*Additional Results*
Chuanhui Yin(2021)	NM	Hamsters	-	Passive	NM	Yes	NM	noggin expression reduced and BMP2 expression increased	ell apoptosis and accelerate placenta maturation by smoking
Birhane Alem Berihu(2019)	Ethiopia	Maternal study	NM	NM	NM	Yes	NM	Chemicals population, paternal history, and folic acid utilization	-
Liu Luo(2020)	British	Father smoking	NM	NM	Half a pack	Yes	Anencephaly Encephaloceles	-	-
Adrienne T Hoyt(2016)	NM	Neonates Defect	NM	secondhand smoke (SHS)	NM	Yes	Anencephaly spina bifida	body mass index, periconceptional alcohol consumption	-
Yali Zhang(2021)	China	Maternal	<25:82 25–29: 71 30–34: 43	passive smoking	1–3 times/week:37 4–6 times/week:24 >6 times/week:72	Yes	Anencephaly:78 Spina bifida:121 Encephaloceles:25	-	-
Alison K Krajewski(2021)	Texas	Maternal	<19:169 20–24:327 25–29:321 30–34:239 35–39:106 >40:36	NM	NM	Yes	Anencephaly Spina Bifida	Sociodemographic environmental quality	-
Farzaneh Zaheri (2017)	Iran	Maternal	16–25:28 26–35:15 36<:3	secondhand smoke	1–9 cigarettes per day paternal smoking 28.7%	Yes		alcohol multivitamins folic acid	
Q Zhou(2020)	NM	Father Smoking	NM	secondhand smoke	13.3% decreased their smoking 6.6% continued smoking	Yes	NM	-	congenital heart diseases, limb abnormalities, digestive tract anomalies and neural tube defects than those whose fathers continued smoking.

Table 2. Articles related to blood elements, articles related to smoking and genetic pathways were not included in this table. We also included articles that examined the effects of smoking on components other than NTDs

first aouthor (year)	*study setting*	*population*	*smoking*	*element*	*NTDs effect*	*Results*	*Side Risk factors*	*Additional Results*
Chuanhui Yin (2021)	Non-Mentioned (NM)	Hamsters	Yes	Cadmium Lead zinc	NM	smoking is associated with elevated levels of metals	-	-
Katrine Bilde (2019)	NM	NM	Yes	metallothionein 1 and 2	NM	smoking is associated with a significantly reduced expression	Zinc	zinc deficiency-can affect pregnancy outcome and growth
Anna Bizoń (2021)	Poland	Maternal	Yes	antioxid copper zinc cadmium	NM	tobacco smoke is associated with significant alteration in antioxidant status and copper, zinc, and cadmium concentration	-	-
Nihat Demir (2017)	Turkey	NM	Yes	copper zinc selenium cobalt	Yes	High plasma levels of heavy metals As, Pb, and Cd and trace element Cu were identified as risk factors for the development of NTD	no association between Hg and Co plasma levels and increased risk for the development of NTD was observed	Zn and Se were also found to be risk factors for NTD
Mengyuan Liu (2021)	China	Maternal	No	cadmium and lead	Yes	Higher concentrations of Cd were observed in the NTD group than in the control group, but no difference was found for Pb	enhanced in fetuses who carry the G allele of rs4880 in SOD2 and T allele of rs1801133 in MTHFR	-
Shazia H Chaudhry (2020)	Canada	Maternal	Yes	folic acid	Yes	factors significantly associated with higher homocysteine concentration were nulliparous, smoking and chronic hypertension,	Sociodemographic environmental quality	Folic acid supplementation of >1 mg/d during pregnancy did not substantially increase folate concentration
Minxue Shen (2016)	Canada	Maternal	NM	folate	Yes	This indicates that the current RBC folate cut-off approach for assessing risk of neural tube defects in obese women may be limited	BMI	BMI is inversely associated with serum folate and positively associated with RBC folate in pregnant women

18.5-24.9, while in a study in western Iran(19), the BMI index was 26.1-29.9 for mothers with a greater number of NTDs were associated in births. Furthermore, this study added that the incidence of NTDs in male neonates is more than that of girls (54.3 boys). In both articles, increasing smoking to six times per week was associated with a higher risk for NTDs. Zhou states that even infants whose fathers were active smokers (secondhand smoke (SHS) for mothers) and who quit during pregnancy show lower numbers of NTDs (33). In a similar systematic study, the father's smoking cessation was associated with a reduction of anencephaly and encephalocele (34). Adrienne Hoyt recommends further studies to prove the effectiveness of SHS for impacting NTDs, specifically spina bifida, and also recommends that mothers use folate supplements during pregnancy to prevent the effects of smoking on neonates (35).

Folic acid or folate supplementation has a significant effect in preventing NTDs (36). This systematic study stated that folic acid (B9) is associated in the blood of pregnant mothers and even in the blood of the umbilical cord by cigarette, and the level of this vitamin decreases in neonates by maternal smoke(37, 38). In this context, Korede Yusuf reported that smoking, in addition to reducing the level of folate, is also associated with a decrease in its biological level (39). In the previous article, he states that the brain-body weight ratio (BBR) of infants with pregnant mothers who received folic acid supplements showed a higher level and also noted that smoking probably affects the level of micronutrients (folate) by controlling stress and BMI (40). It was necessary to use folic acid supplements to reduce the amount of 40cysteine and also to deal with the effects of the mutation of the 10-methylenetetrahydrofolate reductase gene (MTHFR) (41, 42). MTHFR causes a decrease in density in the cranial mesenchyme; however, using folic acid supplements controls this condition and reduces its effect (43). Using food supplements compensates for the lack of folic acid and other micronutrients, such as zinc, which are useful in forming the neural tube and are reduced under the influence of smoking (44). Anna Bizoń compared zinc and cadmium in pregnant smoking mothers with controls; smoking mothers generally showed lower zinc levels (45). The decrease in zinc levels in smoking mothers raises the possibility of reducing its transfer to the placenta during the fetal period, and besides that, smoking induces zinc homeostasis in the body of smoking mothers by expressing a decrease in metallothionein protein and a decrease in zinc available to the mother (46). Cadmium decreases with folate supplementation, and melatonin substitutes its capacity for zinc. The increase of cadmium and lead in pregnant smoking mothers was based on this issue (47). In another study, zinc and selenium in pregnant mothers with active smoking were significantly lower compared to the control group. Yet, this study contradicted the association between other elements, such as mercury (Hg), cobalt (Co), and NTD, with its results (44).

Cell apoptosis significantly affects the closure of the neural tube and the occurrence of NTDs, whose process is enhanced by noggin. Smoking during pregnancy reduces the expression of noggin, resulting in neural tube closure (48). Smoking controls these elements and even affects the genetic pathway of NTDs. Cell apoptosis is associated with a decrease in fetal DNA methylation (mDNA) under the influence of smoking during pregnancy. This condition, under the influence of mDNA, is associated with

accelerated fetal growth and decreased placental maturation. These conditions ultimately favor stillbirth (49, 50).

This review did not find a conflicting topic regarding the effect of smoking on the occurrence of NTDs; besides that, all the cases were in favor of using folic acid supplements during pregnancy and their positive effect on the prevention of NTDs. Only in some cases did we find contrasting blood elements that did not make much difference in our topic, and the focus of these articles was the effect of smoking on the blood level of elements such as copper, mercury, and others. The results were tracked in Google Scholar. The number of outlier searches was high, but the general results confirmed the obtained findings.

Discussion

Smoking, as an essential teratogen in congenital malformations, this time plays a prominent role among the risk factors of NTDs. BMI, mother's age, proper nutrition and, and explicitly using nutritional supplements along with the history of stillbirth and genetics all provide the necessary conditions for NTDs. Usually, smoking mothers younger than 25 years old showed the most cases of NTDs among births, either in the form of active or passive use and even in SHS. The reduction of micronutrients such as folic acid was seen in mothers. Stillbirths of NTDs were higher in infants whose fathers smoked, and the father's smoking cessation before pregnancy significantly reduced this statistic, which indicates the impact of smoking on the prevalence of NTDs even in SHS. In general, smoking increases lead, cadmium, and copper in pregnant mothers and provides the conditions for a general reduction of folate, which eventually leads to neural tube closure under the influence of folate.

The interaction of folic acid and smoking can be examined from several perspectives. Firstly, the direct effect of smoking is on folate itself, and the result of this relationship is the reduction of folate during pregnancy. Consequently, the overall level of maternal folate decreases, lowering the level of folic acid transfer from the placenta (51, 52). This is the interaction of smoking with the level of folate in the blood through mediators such as MTHFR. The involvement of smoking in the level of folate homeostasis ultimately affects the level of its absorption and blood transfer (53-55). On the other hand, smoking affects the absorption of folate and vitamin B12 in the stomach and reduces their absorption by mothers during pregnancy (56-58). Decreased absorption and reduced folate availability ultimately create a strong cycle for NTDs. Besides, other particles under the influence of smoking provide the conditions for NTDs. Lead, copper, and cadmium increase with smoking (53, 59, 60), and cadmium blocks folate transporters to the fetus. Finally, smoking reduces the level of folic acid necessary for the formation of the neural tube of the baby by increasing cadmium (53).

Indicatively, one of the most significant effects of smoking is creating oxidative stress during pregnancy. Oxidative stress primarily affects the mother's mood, which means that the mother's diet (61) is affected, and the substances needed to supply nutrients, such as folic acid and zinc, are disturbed (62, 63).

Oxidative stress by itself reduces folate loss during pregnancy and makes infants susceptible to neurological abnormalities such as NTDs and autism (64). Oxidative stress also interferes with the blood level of zinc and reduces the level available from the mother to the fetus. In this context, YuYan states an interesting conclusion

that exposure to zinc oxide causes apoptosis caused by endoplasmic reticulum stress, which ultimately causes distribution in neural tube closure and incidence of NTDs (62).

The effect of smoking on the genetics of newborns is still under many studies, but the articles show that the effect of smoking on DNA methylation will eventually disrupt the development of the fetus; as we said, more studies are needed to cite it.

In summary, we examined the effect of smoking directly and indirectly from the channel of blood elements and micronutrients as well as the genetic channel, all of which emphasized the positive effect of smoking on the occurrence of NTDs.

In Conclusion

Even though many studies were not available, this study could find substantial evidence to answer the research question. According to the results obtained from the available articles, smoking can be considered one of the strong teratogens in the occurrence of NTDs. Considering the importance of NTDs and the fact that these abnormalities are common in the world, we recommend that, first, more studies be conducted on how smoking during pregnancy affects the occurrence of NTDs. Moreover, measures should be taken to prevent smoking during pregnancy in communities.

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Authors' Contribution

Zeynab Elahi developed the theoretical formalism, performed the analytic calculations and performed the numerical simulations. Both Mohammad Satarzadeh and Farideh Hassanzadeh authors contributed to the final version of the manuscript. Mohammad Satarzadeh supervised the project.

Conflict of Interest

The authors have no conflicts of interest to declare.

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