

Maternal Smoking during Pregnancy: A Review of the Effects of Maternal Tobacco Use on Fetal Brain Development

Molonga Simon¹, Salim Serrano², Jaime R Lopez³ and Lee Geum Seon^{4*}

¹Department of Addiction Science, University of Sahmyook, Republic of Korea

²Department of Public Health, University of Sahmyook, Republic of Korea

³Department of Epidemiology and Biostatistics and Population, University of Loma Linda, Republic of Korea

⁴Department of Counseling Psychology, University of Sahmyook, Republic of Korea

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*For Correspondence

Lee Geum Seon, Department of Counseling Psychology, University of Sahmyook, Republic of Korea.

Tel: +821026458493

E-mail: sue7179@syu.ac.kr;
simonmolonga@yahoo.com

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ABSTRACT

Background: Maternal smoking during pregnancy (MSDP) is greatly associated with serious health outcome for offspring. Citing from past studies to present, experiments have been conducted to examine the association between maternal smoking and fetal brain development. A majority of these studies have focused more on indirect association and little or nothing on direct association. This review paper seeks to examine studies conducted on the direct relationship between maternal smoking and fetal brain development.

Method: A systematic search of Psyc-INFO, Medline, Scopus, Web of Science and Embase was conducted (1977-2017) and 116 studies were identified with eleven studies meeting inclusion criteria gathering data from over 4,000,000 participants. All studies measured outcomes using either internalizing (anxiety, depression, cognition) or externalizing (over action, aggressiveness, head circumference) behaviors or both.

Results: All the studies showed an indirect association between maternal smoking and fetal brain development and none could show how cigarette smoke affects fetal brain development directly. Six studies used internalizing behavior to show this indirect association and the remaining five used the externalizing behavioral outcome. Some studies predicted the smoke not to be the main cause for the abnormalities during brain development but the confounding factors are responsible for the unhealthy outcomes on brain development.

Conclusion: However, heterogeneity in the timing of brain development, assessment measures used for mother smoking habit and inconsistencies in adjustment for confounders, limits the synthesis and interpretation of findings. Moreover, if direct affect is to be attained, different measures and designs of prospect studies be required to investigate this complex association between maternal smoking during pregnancy and fetal brain development.

INTRODUCTION

During pregnancy, maternal smoking relatively remains a common but nonetheless hazardous in utero exposure. Previous studies have associated certain health conditions with smoke exposure. Reduced birth weight, poor psychological and developmental outcomes, increased risks for diseases and behavioral disorder are later experienced in life on smoke exposure^[1]. Children exposed to cigarette smoke end up having several health complications in their entire or at some stage of their lives, like impaired endocrine functioning, poor academic performance, respiratory, reproductive and behavioral disruption including aggressive behavior and ADHD^[2].

Nicotine-exposed children tend to have several health problems throughout their lives, including impaired function of the endocrine, reproductive, respiratory, cardiovascular, and neurologic systems. Poor academic performance and significant behavioral disruptions are also common, including ADHD, aggressive behaviors, and future substance abuse. But still, long term effect of this smoking during pregnancy on school performance or cognitive of the child remains a serious problem of understanding due to conflicting findings in previous research [3].

Tobacco use is the leading cause of preventable disease disability and death in the United States alone. A substantial number of women in the United States use tobacco and continue to smoke even when pregnant and each year alone contributes to roughly 161,000 perinatal and 4800 infant deaths compared to any other substance abuse in the United States [4,5].

Nicotine is the main component of tobacco smoke with a concentration of about 15% higher in fetal tissues than mother tissues [5]. Fetal can also suffer health from passive or environmental smoke, with fetal of smoking mothers having an average 200 g lighter and 1.4 cm shorter compared to fetal from non-smoking mothers [4].

Tobacco being one of the most commonly used substances during pregnancy, which suggest that about 25% of women use tobacco during pregnancy [6]. In 2005 in the United States, 12% of women were reported smoking during pregnancy and 22.4% of women were tobacco dependent at reproductive age [7]. In another study by Key 18.5% of women in the United States used tobacco and 11.4% smoked during pregnancy whereas on average, each state reported a 26% of tobacco use during pregnancy. Referencing from Centers for Disease Control and Prevention (CDC) 2015, out of the 15.1% of all adults (36.5 million people) that smoked, 16.7% were males and 13.6% females. According to the World Health Organization (WHO) fact sheet for May 2017, second hand smoke accounted for more than 890,000 premature deaths in infants and 28% of children died in 2004.

Maternal smoking during pregnancy has showed to alter the health of the unborn child making offspring to suffer unhealthy outcomes such as conduct disorder, cognitive problems and reduction in head size [8-13]. It is still unclear how the relation between maternal smoking's during pregnancy affects fetal brain development. Studies have been carried out on animals and the results showed to be a direct effect even at very low concentrations of nicotine. For humans, most studies have showed to be an indirect association between maternal smoking and fetal brain development [13,14].

According to Slotkin the nicotine is not really the main effect for the abnormal fetal brain development [14]. What really brings the alteration on or in the fetal brain development are the confounding factors because significant changes could only be seen after adjusting for the confounding factors [12]. This issue of smoking during pregnancy is now everywhere in the world. Perinatal outcome of smoking during pregnancy is well known but the public and even the Doctors themselves have limited knowledge on the long term health outcome on the fetus [15].

Maternal smoking during pregnancy has so many health effects on the offspring but still little has been done concerning the direct effect of this habit on the baby's brain development [16]. It would be good to have a contextual understanding of the impact of maternal smoking during pregnancy on the fetal brain development [10]. A narrow understanding would not be enough since, it is a lifetime issue. Therefore, it would be essential to have a consideration on a long-term implication for the fetal externalizing behavior (head circumference, over action, organ sizes and social-interaction) and internalizing behaviors (anxiety, depression, cognitive, stress). More is still to be done on this issue of fetal brain development and maternal smoking during pregnancy so as to have more data and statistics to support future studies. This fact of little data availability accounts for one of the main motives for writing this paper.

Like any living organ would need its optimal condition for growth, so too the human brain. When these conditions are not fully met, the said living-thing is obvious to have an abnormal growth and likewise a poor health. At the early begin of brain development, oxygen as one of the most important elements for brain development is needed. Smoking of cigarette would hinder the proper supply of oxygen to the brain. The problem here is the biochemistry of the brain. When nicotine comes in, it disrupts the biochemistry of the fetal with the metabolite ratios predict the neuro-developmental outcomes [17]. For example, carbon monoxide that is found in smoke would compete with the oxygen for binding space on haemoglobin, causing the insufficient amount of oxygen to be supplied to the brain. Insufficiency of oxygen and other elements and nutrients would lead to abnormal fetal brain development. These abnormalities can be physical, psychological. The physical characteristics of an abnormal fetal brain can be seen on the head circumference [18]. Physical can also be on the morphology of the fetal brain for the psychological characteristics, the behavior of the child prove abnormality in the brain development [8,11,16-20]. The fetal refers to the baby before delivery and after delivery. The mean age for the fetal we decided to include in our study ranges from mechanisms for the impact of maternal smoking during pregnancy on the development of the fetal brain (**Figure 1**).

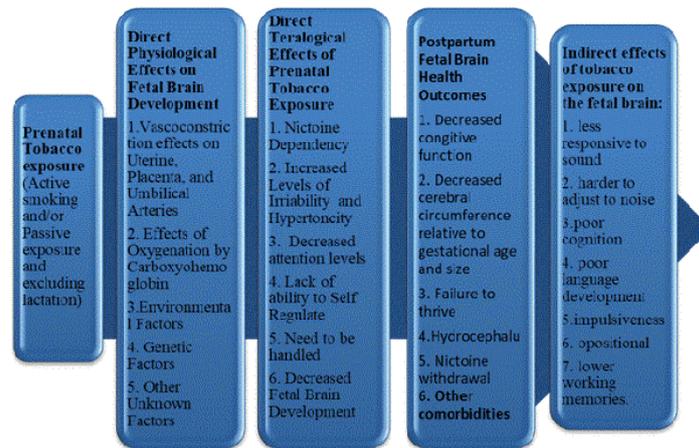


Figure 1. Biological model.

The neuro system which is composed of the brain and spinal cord is the first system to be formed immediately after conception. The development of human brain is a continuum process that begins in gestation and continues during childhood and right up to early adulthood (according to a 2016 report in the journal Environmental Health Perspectives), in this nervous system, are neural cells or neurons which help in message transmission throughout out body. These cells keep on multiplying, differentiating and maturing during this continuum process of brain development. So, any interference during the process can lead to a permanent defect on the baby’s outcome

Even though, knowledge about the negative effects of tobacco smoke on the development of the fetal brain is very limited, maternal nicotine addiction still poses great danger. Currently, the mechanisms to explain the biological interference would be unclear but still we can use other biological areas to try and explain the different processes involved. Our biology knowledge teaches us that mother and fetus are connected through the placenta, which main function is to permit the movement of food and other useful elements (like blood and oxygen) from the mother into the child’s circulation and waste material from the child back to the mother. The fetus has no fully developed organs or system, therefore, solely depends on the mother for nutrients and many other elements and nutrients. Whatever the mother consumes, some will definitely reach the baby too.

Thousands of harmful chemicals do exist in tobacco smoke that are detrimental to fetal brain development. Among these thousands of chemicals, studies have laid more interest on 2 components, nicotine and carbon monoxide. First thing we need to know is that nicotine from the mother will compete with endogenous acetylcholine receptor in the brain, provoking abnormalities during development of the brain because neurotropic actions would be disrupted. Nicotine reduces the amount of oxygen to the brain causing neurological damage by lessening the quantity of oxygen that moves into the brain. The results can also be Sudden Infant Death Syndrome (SIDS). The experiments have been performed mostly on animals, which shows that exposure to nicotine during pregnancy will lead to changes in the brain morphology due to disruption in replication and differentiation of brain cells [21,22].

Carbon monoxide on the other side competes with oxygen for binding sites on haemoglobin. In this way inhibits oxygen from binding on haemoglobin to form oxyhaemoglobin that is delivered to tissues and other parts of the body [23]. This way carbon monoxide is delivered to the cells in the present of cigarette smoke rather than oxygen. Fetal with deficient in oxygen supply may likely suffer from hypoxia and ischemia which has a serious effect on brain development. This is called oxygen starvation which may also cause injury to the heart of the unborn child. Most of these mechanisms are epigenetic in nature, affecting DNA methylation and dysregulated expression of microRNA [24]. DNA, the main component in genes is so important for brain development but the epigenetic mechanism still remains a matter of clarity. A gene regulated by DNA methylation, brain-derived neurotrophic factor (BDNF), is a very important gene for normal brain development. In an experiment on mice, lower quantities of BDNF gene, protein and mRNA suffered behavioral changes due to exposure to cigarette smoke [25]. Yochum and his colleagues also suggested that changes in epigenetic can lead to long-lasting neurodevelopmental problem in the brain [25].

Figure 2 below is a simple biological model. It shows the direct and indirect effects of cigarette smoking on the fetal brain. Beginning from the prenatal tobacco exposure to direct psychological to direct Tera logical to postpartum and indirect effects. Borrowing from genetics on how our genetics constitutions differ, so too the responds and effects to nicotine differ.

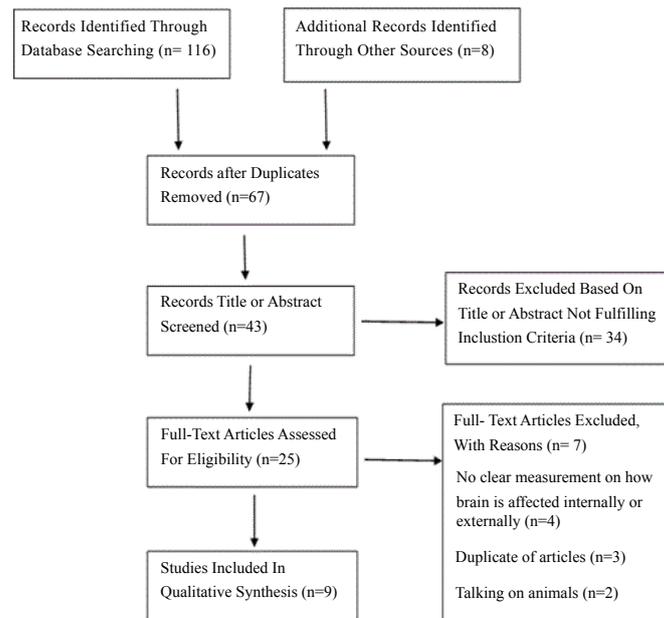


Figure 2. PRISMA flow diagram.

The current state of policy and practices of tobacco

With all the public health policies and control about the harmful effects of tobacco, the knowledge about the harmful outcomes of using the substance during pregnancy has been well-established. However, debate concerning the impact of using the substance during pregnancy on fetal brain development remains a serious issue [17].

Created on May 21st, 2003 and going into effect on 27 February, 2005, the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) has been the main force to tackle the growing global tobacco problems in public health. Since, its creation, it has been the ever first public health treaty under the United Nation.

Differing from Nation to Nation, tobacco policies and practices also differs. Although some of the policy maybe the same (like increase tobacco prices or taxes, smoke free houses, restricting cigarette smoking in public places, restaurants, workplaces and many others. Like in the United States of America, the policies are not the same in all the States. States like Arizona, New Mexico and more than twenty others have one way legalized the use of marijuana for medication and recreational purposes. Not only allowing the growing of up to six Marijuana plant at their homes, the State of California recently ratified 64 laws allowing individuals of ages 21 and above to use up to one ounce of marijuana a day (state marijuana laws in 2017 map Governing magazine). As part of protecting children from tobacco exposure display in the UK, the Scottish parliament in 2015 passed a law that banned the exposure of tobacco products in small or retailing shops [26]. In the year 2004, the Norwegian government banned indoor smoking by disallowing the use of tobacco products in public places [27]. The main reason was to control for second handed smoking. Norway has a long history of tobacco control due to a high prevalence rate of smoking among individual between the ages of 13-79. One of huge fight was to cut down the prevalence to less than 10% between 2013 and 2016. What they did was a nationwide fight that included the increase of tax on tobacco products, graphic health post on the cigarette packets, banning tobacco adverts and banned of smoking in public places [28]. Most countries put children on high priority for prevention against tobacco and cigarette smoking. Since, the year 2000, the Netherlands passed on ban on cigarette sales to youths under sixteen years of age. The ban stretches to sponsoring and advertisement [29]. The Dutch government has equally banned the use of tobacco products in public vicinities like hospitals and nursing homes. These different laws are good but we still have a long to go, although they help in curving down the use and prevalence of cigarette smoking, a lot more of damages are still recorded from tobacco use.

This review paper seeks to examine studies conducted on the direct relationship between maternal smoking and fetal brain development. Moreover, if direct affect is to be attained, different measures and designs of prospect studies be required to investigate this complex association between maternal smoking during pregnancy and fetal brain development.

MATERIALS AND METHOD

Search strategy

Health-care A systematic search of abstracts and titles of peer-reviewed articles was conducted using Google scholar, PsycINFO, Medline, Web of Science, Embase and Scopus database including papers from 1997 up to January 2017. Search terms included two key terms: maternal smoking and fetal brain development. In other to identify studies investigating maternal smoking during pregnancy and fetal brain development the following terms were used to systematically search databases: Fetus

or fetal or foetus or foetal or grow or develop, pregnancy, prenatal exposure, maternal smoking, and environmental tobacco smoke exposure, neurodevelopment, neurobehavioral, psychomotor development, behavior problems, cognitive development, IQ, mental health, and school achievements learning ability. To narrow the search further in PsycINFO and Scopus the following terms were also included: Pregnant mother or maternal woman.

The lists of identified relevant articles were searched for other appropriate articles. Data from review articles were excluded. When multiple publications from the same cohort containing overlapping participants were available, the article with the most applicable information, strong methods and little bias was preferred.

SELECTION OF STUDIES

Inclusion and exclusion

Based on the selection criteria, this review relied mostly on epidemiological studies that focused on maternal tobacco use (prenatal, postnatal or during) and fetal brain development or neurodevelopment were identified by a search on the different search engines mentioned above. For eligibility, each study must have used a measure of exposure to maternal active or passive smoking during pregnancy period and at least one measure of neurocognitive function in the offspring.

Articles were included for review if they met the following criteria:

- (a) If any of this was measured during pregnancy, anxiety or depression or stress.
- (b) Cognitive or hyperactivity or ADHD was also measured after pregnancy. The instrument used for measurement must be a valid one if not the study was not included.

Studies were excluded if the exposure to different types of toxicants were combined into a single variable, making it impossible to determinate the association between exposures of interests and fetal neurodevelopment. Exclusion criteria included:

- (a) Studies that were not conducted in humans.
- (b) Studies that were conducted using animals.

Data extraction

Two authors reviewed the literature independently and extracted the information following a formal protocol written in advance that clearly stated the objectives, the hypotheses to be tested, the subgroups of interest, the proposed methods, and the criteria for extracting information. To avoid discrepancies in the data collection process, consensus was reached through conferral. There was considerable heterogeneity in study methodology making the studies not suited for meta-analysis. The data was highly minimized from the original paper. Besides, if studies reported the risk estimates from several adjustment models, the estimates from maximum extent of adjustment for potentially confounding variables were extracted.

The following information was extracted from each eligible article: First author, year of publication, country location, sample size, design of study, study population, smoking status, test for brain effect, confounding factors and result (**Table 1**).

Table 1. Studies and Key Findings.

Authors	Design of study	Sample (n)	Exposure information	Test for brain effect	Confounding factors	Results
Jacob F. Orlebeke et al.		n=1365 pregnant women and their healthy twins (2-3 years)	Completion of questionnaires by mothers about their pregnancy and their sad twins	The authors used the Child Behavior Checklist for ages 2-3 to assess behavioral problems in healthy twin pairs	socioeconomic status, maternal age, and having been breast- or bottlefed, birth weight, gestational age, health problems, smoking and of the mother during pregnancy	There was a significant effect of maternal smoking on so-called externalizing behavior problems (oppositional, aggressive, overactive), but not on internalizing behavior problems (withdrawn, depressed, anxious), in both first and second born twins

Wakschlag et al.	longitudinal assessment	n=177 clinic referred boys, ages 7 to 12 years	annual structured diagnostic interview	Each child, his parent, and his teacher were interviewed separately each year using the National Institute of Mental Health Diagnostic Interview Schedule for Children	Age of mother at birth, prenatal alcohol and illicit drug use, pregnancy and birth complications, prematurity, and low birth weight	Mothers who smoked more than half a pack daily during pregnancy were more than 4 times as likely to have a child with CD than mothers who did not smoke (odds ratio, 4.4; 95% confidence interval, 1.87-10.27; P=001). Attention-deficit hyperactivity disorder was not significantly associated with maternal smoking (MantelHaenzel $\chi^2=0.09$; $df=1, 177$; P=0.76)
Lambe et al.	cohort study, population based	n=400,000+ children at the age of 15 years	From the medical birth register about maternal smoking	School performance from National School Register	Maternal age, parity, maternal education, maternal socioeconomic category, home ownership, sex of the child, birth weight, birth length, head circumference, gestational age and Appa score at 5 min	In a model adjusted for maternal characteristics, maternal smoking during pregnancy was associated with an increased risk of poor scholastic achievement: For 1-9 cigarettes per day, the or was 1.59 (95% confidence interval 1.59-1.63) and for 10 or more cigarettes per day, the or was 1.92 (1.86-1.98)
Roza et al.	Population-based prospective cohort study	n=7042 pregnant women	Assessments in pregnancy, including physical examinations, ultrasound assessments and questionnaires	longitudinal multilevel analysis using fractional polynomials	Maternal age, foetal gender, maternal height, maternal body mass index, maternal educational level, maternal ethnicity, parity, maternal alcohol consumption, maternal prenatal anxiety and maternal prenatal depression	Smoke during pregnancy, foetal head circumference showed a growth reduction of 0.13 mm [95% confidence interval (CI): -0.18; -0.09] per week. Biparietal diameter of fetuses with smoking mothers grew 0.04 mm (95% CI: -0.05; -0.02) less per week than that of fetuses of non-smoking mothers. Atrial width of lateral ventricle was 0.12 mm (95% CI: -0.22; -0.02) smaller and trans-cerebellar diameter was 0.08 mm (95% CI: -0.15; -0.00) smaller if mothers smoked, but growth per week of these characteristics was not affected by maternal smoking in pregnancy
Julvez et al.	population-based birth cohort	n=420 pregnant mothers and children at age 4	Interviewer-administered questionnaires were completed by mothers during the third trimester of pregnancy and then every year up to age 4 years of their child	A standardized version of the McCarthy Scales of Children's Abilities (MCSA) was used to evaluate the child's motor and cognitive capabilities at pre-school	home location, maternal alcohol consumption, mother's social class and level of education during pregnancy, parity, marital status, father's education level, child's gender, birth weight and height, breastfeeding duration, passive smoking, school season, age during test administration and evaluator (psychologist)	Maternal smoking during pregnancy (in cig./day) was associated with a decrease (in points) of children's global cognitive score [$\beta = -0.60$, (95% CI: -1.10; -0.09)]; as well as global cognitive sub-areas like verbal score [$\beta = -0.59$ (95% CI: -1.11; -0.07)]; quantitative score [$\beta = -0.57$, (95% CI: -1.08; -0.06)]; executive function score [$\beta = -0.71$, (95% CI: -1.23; -0.20)]; and working memory score [$\beta = -0.46$, (95% CI: -0.92; -0.01)]

Gilman Stephen et al.	Birth cohort study	n = 52,919 mother and child	Using data from the Collaborative Perinatal Project (1959–1974). Data from examinations and interviews were recorded by trained staff beginning at the time of registration for prenatal care	At age 4 cognitive ability was assessed with the Stanford-Binet Intelligence Scale. Wechsler Intelligence Scale assessed verbal intelligence quotient (IQ), performance IQ, and full-scale IQ age 7 years. Academic performance at age 7 years was assessed using the Wide Range Achievement Test (WRAT)	Socioeconomic status, maternal and paternal age, maternal marital status, maternal employment status, household crowding, prior pregnancies, maternal and paternal history of mental illness and psychiatric or neurologic problems during pregnancy	Results from the conditional analyses indicated a birth weight difference of –85.63 g associated with smoking of ≥ 20 cigarettes daily during pregnancy (95% confidence interval: –131.91; –39.34) and 2.73 times higher odds of being overweight at age 7 years (95% confidence interval: 1.30; 5.71)
Brian B Boutwell et al.	Early Childhood Longitudinal Study, Birth Cohort (ECLS-B)	n = 10,600 mothers, fathers, and their biological children	interviewed via telephone surveys, questionnaires	Preschool and Kindergarten Behavior Scales–Second Edition (PKBS-2) to measure problem behaviors and social adjustment in children and ECLS-B to assess behavioral, cognitive, and emotional development in preschool aged children	Maternal Age, Family Adversity, Delivery Intervention Index, Labor Complications Index, Apgar Scores, and Paternal Antisocial Behavior, Paternal Substance Abuse, Paternal Depression, Demographic Characteristics	The children of mothers who smoked during their pregnancy exhibited higher levels of externalizing problem behaviors (mean difference = 1.80, t-value =6.98, P ≤ 0.05). prenatal exposure to cigarette smoke was no longer a significant predictor to externalizing behavioral problems (mean difference=0.30, t-value=0.74, P>0.05)
Devasuda et al.	case-control study	n=26 pregnant women, age ≥ 18	questionnaires administered by their obstetricians	magnetic resonance imaging (MRI) scanner (1.5 T)	maternal age, parity, BMI, and education level	Exposed fetuses showed lower brain volumes, kidney volumes, and total fetal volumes. This effect greater at visit 2 than at visit 1 for brain and kidney volumes, and greater at visit 1 than at visit 2 for total fetal volume. Exposed fetuses also demonstrated lower lung volume and placental volume, and this effect was similar at both visits. No difference was found between the exposed and nonexposed fetuses with regards to liver volume
Shahrdad Lotfipour et al.	first cross-sectional in Canada and second is longitudinal in Finland	n=2,137 adolescence (12-18 years) from Canada and Finland	data obtain about adolescence from two distinct geographical location; the Saguenay Youth Study (SYS) in Canada (47% with PEMCS) and (49% with PEMCS) from the Northern Finland Birth Cohort	The Saguenay Youth Study (SYS) in Canada (i) the Diagnostic Interview Schedule for Children (DISC) predictive scales (ii) Questionnaire asking if adolescent has ever used any or all of a list of 14 drugs. The Northern Finland Birth Cohort, (iii) The Rutter B scale and a postal questionnaire concerning their life habits (e.g. smoking) (iv) postal questionnaires and (v) questionnaire that the participants received during a clinical examination	(i) distal exposure (maternal in-utero alcohol use), (ii) concurrent exposure (the number of peers reported to be taking drugs) and (iii) salient background risks (sex, family income and mother's education)	Both populations showed higher likelihood of adolescent drug use with PEMCS. In the NFBC1986 cohort, exposed (versus non-exposed) adolescents experiment with an extra 1.27 [B=0.24, 95% confidence intervals (CI) =0.15; 0.33 P<0.001] drugs. In the SYS cohort, a clear protective effect of not being exposed is shown: non-exposed (versus exposed) adolescents are 1.5 times [B=-0.42, 95% CI =-0.75; -0.09, P=0.013] less likely to take drugs

Steven Moylan et al.	Norwegian Mother and Child Cohort Study	n = 90,040 mother-child	report from mother through questionnaires	Mothers reported their child's internalizing behaviors by answering questions taken from a condensed 25 question version of The Childhood Behavior Checklist (CBCL) [37] at ages 18 months, 36 months, and 5 years	Paternal smoking, maternal education, maternal age, maternal depressive and anxiety symptoms, maternal alcohol consumption, parity, gestational age at birth, and smoking in previous pregnancies	MSDP was associated with increased internalizing behaviors when offspring were aged 18 months (B=0.11, P<0.001) and 36 months (B=0.06, P<0.01), Higher rates of smoking (e.g. >20 cigarettes per day) were associated with higher levels of internalizing behaviour
Sandra M. Meier et al.	nationwide cohort study	n=957,635 pregnant mothers and children (age from 5)	linkage of six Danish population-based registries	Using the Danish Psychiatric Central Register and the Danish National Patient Register	sex, calendar year, mother's parity, parental age at childbirth, parental psychiatric history, substance abuse, divorce, abuse, parental highest education at time of birth, and parental income at time of birth	offspring exposed to MSDP were at increased risk for both severe depression [HRR 1.29, 95% confidence interval (CI) 1.22-1.36] and severe anxiety disorders (HRR 1.26, 95% CI 1.20-1.32) However, there was no association between MSDP and internalizing disorders when controlling for the mother's propensity for MSDP (depression: HRR 1.11, 95% CI 0.94-1.30; anxiety disorders: HRR 0.94, 95% CI 0.80-1.11) or comparing differentially exposed siblings (depression: HRR 1.18, 95% CI 0.75-1.89; anxiety disorders: HRR 0.87; 95% CI 0.55-1.36)

RESULTS

Study selection

A search identified 116 studies and only 9 reached the inclusion criteria. Majority of the studies were excluded because they fail to provide vivid information on data extraction like “test for brain effect” and very few because their research was not on humans but animals. Each of the 9 studies examined different aspects of maternal smoking on fetal brain development. Based on the effect, these studies were classified under two main categories: Internalizing brain effects and externalizing brain effects.

Study characteristics

Internalizing brain effect studies (4 articles) out way the externalizing brain effect studies (5 articles). More of the selected tried as much as possible to use the cognitive effect to assess brain damage. Only one study talked about twins [30]. This study was good because it did not only research about twins but comparing male and female effects. It as well proven that males are more likely to suffer externalizing behavior than female in a set of twin. All of the studies used different assessment tools for brain test. The majority used longitudinal and cohort study designs.

Systematic review

Maternal smoking and internalizing brain effects:

After a careful inclusion and exclusion study, a total of 4 articles have investigated the link between maternal smoking and the internalizing brain effect (anxiety and depression) of the fetus. Parameters by measuring the effects include; self-reporting from parents and children, interviewing of mother and child, cognitive ability from school scores. Co-factors such as socioeconomic status of parents, maternal age, and having been breast- or bottle-fed, birth weight, gestational age, health problems, smoking and of the mother during pregnancy, mother education, occupation and financial contribution. All articles proved the effect of maternal smoking and internalizing brain effects of fetus.

Only one article tried to research about the risk of conduct disorder in boys [40]. Wakschlag and his colleagues tried to investigate the effects of maternal smoking during pregnancy and the risk of conduct disorder in boys. They recruited 177 clinic-referred boys, who were of ages 7 to 12 years. The data was from two main cities in United States; Pennsylvania (n=96) and Georgia (n=81). 88.5% participated at the first assessment and four annual assessments were conducted. Maternal mothers were assessed via a structural interview on the number of packs smoked on a daily base during their pregnancy. These were categorized into 3 groups: none (occasionally), half a pack or less daily and more than half a pack daily. Each child, his parent and teacher were also interviewed each year using the National Institute of Mental Health Diagnostic Interview Schedule for Children. They used the DSM-III-R criteria for the diagnostic.

The results report that only one hundred five boys (59.3%) met the DSM-III-R criteria. However, the study did report the significance

between maternal smoking and the risk of conduct disorder in boys of mothers who did smoked during pregnancy. Therefore, mothers who smoked more packs per day or more cigarettes during pregnancy were significantly more likely to have children who met the DSM-III-R at least once in the assessment (Mantel-Haenzel $X^2=13.74$; $df=1,177$; $P=0.001$). mothers who smoked more than half a pack daily during pregnancy were more than 4 times likely to have a child with conduct disorder (CD) than mothers who did not smoke (odds ratio: 4.4; 95% confidence interval: 1.87-10.27; $p=0.001$). No significance of maternal smoking and Attention-deficient hyperactivity disorder (Mantel-Haenzel $X^2=0.09$; $d=1,177$; $P=0.76$). We noticed the following limitation or backdrop of this article. All research that has been carried on large samples has always showed results that are almost accurate. Limiting your sample to a very number makes the results to be far from the real approximate. Looking at this article, their findings was limited only to a small number of boys ($n=177$); making the results less accurate. Another limitation is the period of data collection. Their data was based on maternal retrospective reports 7 to 12 years. Researching all about connecting the past and the future because there emerging evidences every day. There was no data on the pre and postnatal environmental smoke exposure. This study will be strong enough if the assessment was done on the prenatal and postnatal smoking. With this lack of data, they could not examine the association of diagnostic status during the 6 years. Only one year assessment was done (Table 2).

Table 2. Maternal smoking and internalizing brain effects.

Author, year	Investigation	Results
Wakschlag et al.	Research about the risk of conduct disorder in boys	Mothers who smoked more than half a pack daily during pregnancy were more than 4 times as likely to have a child with CD than mothers who did not smoke (odds ratio, 4.4; 95% confidence interval, 1.87-10.27; $P=0.001$). Attention-deficit hyperactivity disorder was not significantly associated with maternal smoking (Mantel Haenzel $2=0.09$; $d=1, 177$; $P=0.76$).
Steven Moylan et al.	Impact of maternal smoking during pregnancy on depression and anxiety behavior	MSDP was associated with increased internalizing behaviors when offspring were aged 18 months ($B=0.11$; $P<0.001$) and 36 months ($B=0.06$; $P<0.01$). Higher rates of smoking (e.g. >20 cigarettes per day) were associated with higher levels of internalizing behaviors.
Lambe et al.	Assessed the association of maternal smoking and school performance at age 15 of more than 400,000 males and females students born between 1983 and 1987.	Smoking compared with no tobacco use during pregnancy was associated with an increased risk of poor scholastic achievement: For 1–9 cigarettes per day, the OR was 1.59 (95% confidence interval 1.59 –1.63) and for 10 or more cigarettes per day, the OR was 1.92 (1.86 –1.98).
Sandra M. Meier et al.	Familial confounding of the association between maternal smoking during pregnancy and internalizing disorders in offspring	Offspring exposed to MSDP were at increased risk for both severe depression [HRR 1.29, 95% confidence interval (CI) 1.22–1.36] and severe anxiety disorders (HRR 1.26; 95% CI 1.20–1.32) However, there was no association between MSDP and internalizing disorders when controlling for the mother’s propensity for MSDP (Depression: HRR 1.11; 95% CI 0.94–1.30; anxiety disorders: HRR 0.94, 95% CI 0.80–1.11) or comparing differentially exposed siblings (Depression: HRR 1.18, 95% CI 0.75–1.89; Anxiety disorders: HRR 0.87; 95% CI 0.55–1.36)

Maternal smoking and externalizing brain effects

Table 3. Maternal smoking and externalizing brain effects

Author, year	Investigation	Results
Jacob F. Orlebeke et al.	Investigated the effect of maternal smoking during pregnancy on behavioral problems (such as oppositional, aggressiveness and over action) of 2 to 3 year old healthy twin pairs	There was a significant effect of maternal smoking on so-called externalizing behavior problems (oppositional, aggressive, overactive), but not on internalizing behavior problems (withdrawn, depressed, anxious), in both first- and second-born twins
Brian B Boutwell et al. (2010)	Effect of maternal smoking during pregnancy on offspring externalizing behavioral problems	The children of mothers who smoked during their pregnancy exhibited higher levels of externalizing problem behaviors (mean difference=1.80, t-value=6.98, $P \leq 0.05$). prenatal exposure to cigarette smoke was no longer a significant predictor to externalizing behavioral problems (mean difference =0.30, t-value=0.74, $P>0.05$)
Devasuda et al.	To study whether maternal cigarette smoking during pregnancy is associated with alterations in the growth of fetal lungs, kidneys, liver, brain, and placenta	Exposed fetuses showed lower brain volumes, kidney volumes, and total fetal volumes. This effect greater at visit 2 than at visit 1 for brain and kidney volumes, and greater at visit 1 than at visit 2 for total fetal volume. Exposed fetuses also demonstrated lower lung volume and placental volume, and this effect was similar at both visits. No difference was found between the exposed and nonexposed fetuses with regards to liver volume
Shahrdad Lotfipour et al.	Maternal smoking during pregnancy is associated with the probability drug use by the children at adolescent age.	Both populations showed higher likelihood of adolescent drug use with PEMCS. In the NFBC1986 cohort, exposed (versus non-exposed) adolescents experiment with an extra 1.27 [$B=0.24$, 95% confidence intervals (CI)=0.15, 0.33 $P<0.001$] drugs. In the SYS cohort, a clear protective effect of not being exposed is shown: non-exposed (versus exposed) adolescents are 1.5 times [$B=-0.42$, 95% CI=-0.75, -0.09; $P=0.013$] less likely to take drugs

Gilman Stephen et al.	The authors investigated the relation between maternal smoking during pregnancy and 14 developmental outcomes of children from birth through age 7 years, using data from the Collaborative Perinatal Project (1959–1974; n=52,919)	Results from the conditional analyses indicated a birth weight difference of –85.63 g associated with smoking of ≥ 20 cigarettes daily during pregnancy (95% confidence interval: –131.91; –39.34) and 2.73 times higher odds of being overweight at age 7 years (95% confidence interval: 1.30; 5.71)
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In all, 5 studies investigated the association of maternal smoking during pregnancy and external behaviors in children (like over action, aggressiveness, oppositional, disobedient, fighting, loss of focus). Most the parameters were measured using ultrasound after adjusting for possible confounding (like socioeconomic status, maternal education, financial status, marital status, breast or bottled felt, marital age, ethnicity, fetal sex, twin or not twin). Of all these articles, only one article distinguished from the other four articles. Each report has reported the association with a single baby. The only article that did not report association with a single child was a study conducted by Orlebeke JF who investigated the effect of maternal smoking during pregnancy on behavioral problems (such as oppositional, aggressiveness and over action) of 13377; 2 to 3 year old healthy twin pairs [30]. They used the child behavior checklist (CBCL) for 2 to 3 year old twins to assess the behavioral problems. The authors collected pre and perinatal information immediately after the birth of the twins including mother’s smoking behavior during her pregnant period. After the collection of data, the authors analyzed the effect and found significant association on the external behavior and not on the internal behavior. Actually, not that there was no effect on internal behavior. Using the CBCL, the total score for external behavior was so high while that on internal behavior was very low or negligible. They also saw that the CBCL score was higher in boys than for girls (Table 3).

DISCUSSION

This review paper brings a new fresh idea of evidence suggesting how maternal smoking during pregnancy effect fetal brain development. However, neurologically and physically, fetal development is consistently associated with the mother’s lifestyle during pregnancy. All the articles we came across show some consistency of earlier and current findings on the development of the child’s brain. Some articles have revealed the detection of these effects on the developmental brain using medical procedures (Ultrasound and magnetic resonance imaging) to follow-up the fetus from the first to the second gestation [13,31]. Notable inconsistencies in the results of the specific fetal brain development parameters associated with maternal smoking habits. Also, contradictory findings with maternal lifestyle and the fetal brain development. Inconsistencies exist because there is no article that has revealed the direct link between maternal smoking during pregnancy and effect on the fetal brain development. Following our critical and detailed findings, cigarette smoking during pregnancy is forcefully responsible of the effects on the fetal health but was fully accounted for by confounding factors [12].

Many findings, current and past have made our understanding of the neurobiology development of the brain. Human brain begins forming immediately after conception (3 weeks old pregnancy). This developmental process of the fetal brain is a life process because the elements that aid in brain development are equally needed to help in the storing of information and other skills at adolescent and adult stage. Many factors from the mother play vital role in this process of development. This simply says that the child is dependent on the mother for every developmental element for growth. If the mother is addicted, then the fetus health is at play also. Oxygen, nutrients from the mother goes to the child through the placenta to assist in the development of the child.

Answering the research question of this review article, “Does maternal smoking during pregnancy affects the development of the fetal brain?” Many articles have tried to give valid evidences on how smoking during pregnancy affects fetus brain development. Although, these evidences are not directly linked, smaller but highly significant association was found to affect the externalizing behaviors like the head circumference, biparietal and arterial diameter. Since, the link between maternal smoking during pregnancy and baby’s brain development is not yet clearly proven. Mechanisms have been used to show the untoward effects of maternal smoking during pregnancy on the neurobiological outcome of the fetus. One mechanism explains that smoking causes fetal hypoxia resulting in interference with regulating state mechanism and alteration of cellular growth [32].

Smoking habits during pregnancy is a cultural practice mostly exercised in the western world and other developed nations, while it is kind of limited in Africa. Exposure of the fetus to this smoke has a kind of reducing-like effect on the fetus. As expected, the fetuses exposed to maternal smoking are smaller in size compared to non-exposed fetuses [33-37].

LIMITATIONS

Being a review paper that deals with a vast collection of different articles and different aims, the limitations are obvious. We discovered that almost all of the articles were bias in the aspect of “Exposure Information” because they use self-reporting to collect information from parents and children [38-45]. Interviewing cannot be 100% reliable and should be counted too as being bias as well. Some comparable studies were done comparing boy and girl twins, who is affected more [9,46-49]. This is not really clear how the measures were done. Therefore, future research should be conducted about twins and comparing boys and girls. One serious

limitation was the fact that none of the included studies could not establish a relationship between maternal tobacco use and fetal brain development. Since, the articles were more on showing how cigarette smoke could affect the fetal brain indirectly; our suggestion is more focus should be on how cigarette smoke affects the fetal brain development directly^[50,51].

CONCLUSION

This review paper shows that very little has been done to show a direct link between maternal smoking during pregnancy and fetal brain development. The past work on the topic is small in number but very rich in content as concerns the idea of how smoking during pregnancy could be very dangerous for the baby. The direct link was not there to really prove these effects of smoking during pregnancy on fetal brain development. As earlier said the few papers written on this area are really rich in ideas in the sense that they could not show that direct link but they suggested psychological distress such as anxiety, depression, cognitive and stress to show how the development of fetal brain is affected internally. These were not really clear because this behavior of smoking during pregnancy only indirectly affecting the fetal brain development and not directly. So, for direct affects to attained, different measures and designs of prospect studies are required to investigate this complex association between maternal smoking during pregnancy and fetal brain development. If new mechanisms about the transmission are put in place, then the study of smoking during pregnancy and fetal brain development would gain more grounds and be advanced as well. However, heterogeneity in the timing of brain development, assessment measures used for mother smoking habit and inconsistencies in adjustment for confounders, limits the synthesis and interpretation of findings.

More studies should be conducted on the domain of mothers' behaviors during pregnancy not only to improve the mother's wellbeing but to prevent unhealthy outcome on the offspring. Also studies should consider differences in timing, intensity and of brain development during and after pregnancy and should employ diagnostic assessment of mother smoking addiction. Further work is also needed to establish the biological mechanism involved.

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