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Use of Nicotine-Containing Products During Pregnancy: Effects on Fetal Development

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Abstract: Currently, the usage of tobacco products among adult females is prevalent, representing 10 out of 100 adult females (CDC, 2023). In addition, 4.0% of adult women have been reported as using e-cigarettes. This is mainly due to the addiction to nicotine, which releases dopamine in the brain, ultimately causing the user to want to consume more nicotine-containing products. When used during pregnancy, nicotine-containing products could be harmful to both the mother and the growing fetus. Nicotine consumption during pregnancy may impact the critical brain development period of the fetus, thus resulting in several serious birth defects. Among those who use nicotine-containing products, Nicotine Replacement Therapy (NRT) may be used to facilitate reducing addiction to nicotine. NRT can be used as an ideal therapy to help quit smoking tobacco or e-cigarettes as it replaces much of the nicotine in nicotine-containing products, thus decreasing motivation to use tobacco. Despite the reduced nicotine levels, NRT is reported to show that it may pose a threat when used during pregnancy. As a whole, a few studies have revealed the potential detrimental connection between the usage of nicotine-containing products - including tobacco, e-cigarettes, and NRT - during pregnancy and its effects on the fetus. In spite of this, there has been little research done on the subject, which may lead to further complications if the public is largely unaware. This literature review aims to investigate the effects of nicotine-containing products on the developing fetus.

Keywords: Nicotine, Nicotine Replacement Theory, Tobacco, E-cigarettes

1. Introduction

Tobacco smoking accounts for more than eight million deaths globally each year, as well as 1.3 million deaths among non-smokers (WHO, 2023). The majority of smokers use tobacco due to their addiction to nicotine, the primary alkaloid in tobacco smoke and the major modulator of addiction-related psychopharmacological effects (Benowitz et al., 2009). Addiction refers to the behavior of compulsive drug use in spite of adverse health consequences (Picciotto & Kenny, 2021). In addition, the introduction of the e-cigarette provided an alternative to tobacco smoking yet still poses major health risks due to its nicotine content and its links with its ability to adversely affect the body's blood vessels, increasing cardiovascular risk (Feeney et al., 2022). About half of tobacco smokers addicted to nicotine attempt to stop permanently each year, which involves the use of nicotine replacement therapies (NRT). Through nicotine delivery, NRT reduces the desire to consume tobacco as well as the related physiological and psychomotor withdrawal symptoms (Silagy et al., 2004). However, even though these alternatives eliminate other harmful components of cigarettes, nicotine still poses a threat to the developing fetus when used during pregnancy.

In spite of these consequences, there is still much to learn about the effects of nicotine-containing products, especially NRTs, in pregnancy (Bednarczuk et al., 2022).

2. The impact of tobacco smoking on the fetus

Nicotinic acetylcholine receptors (nAChRs), neurotransmitter-gated transmembrane ion channels that open upon ligand binding, enable fast synaptic transmission located in the central and peripheral nervous system (Karlin & Akabas, 1995). While acetylcholine is the endogenous ligand for nAChRs, nicotine can also bind with these receptors (Gotti & Clementi, 2004). A study of animal models has shown that nicotine exposure can impair the development of nAChRs during critical periods of brain development through inappropriate activation or deactivation (Dwyer et al., 2008).

2.1. Orofacial Clefts

Nicotine levels were found to be present in the infants of smokers during pregnancy (Yang et al., 2016) (Spector et al., 2014), which has been associated with birth defects in some cases. One case involves an offspring with orofacial clefts (Cnattingius, 2004) (Meyer et al., 2004). A case-control study showed that prenatal smoke exposure increased the risk of cleft lip or palate by 1.6 to 2.0 times if these defects were not associated with other birth defects (Khoury et al., 1989). Another study also found that pregnant women who used Swedish snuff had a higher odds ratio of having offspring with an oral cleft when compared to nontobacco users (Gunnerbeck et al., 2014). Based on these studies, it appears that nicotine affects in-utero palate development with abnormalities.

2.2. Preterm Birth

Another known effect of nicotine on the fetus is preterm birth. A study in New Zealand showed that maternal smoking during pregnancy led to an independent increase in preterm birth, and a case-control study from Stockholm also reported the same results for heavy smokers (Cnattingius et al., 2004) (Kyrklund-Blomberg et al., 2005). In addition, a study linking nicotine to preterm birth found that pregnant mothers using snuff had an increased odds ratio of 1.58 for premature birth compared to the control group of pregnant mothers not using any nicotine-related substances (Dahlin et al., 2016)

2.3. Intrauterine Growth Restriction

Intrauterine growth restriction can also be associated with maternal smoking during pregnancy (Cnattingius et al., 2004) (Bernstein et al., 2005). Nicotine preclinical studies have been found to support this relationship as well. The intake of nicotine during pregnancy resulted in reduced fetal growth and reduced blood flow in the uterus and placenta of rats (Birnbaum et al., 1994). Another study also reported that pregnant mice treated with nicotine had reduced placental and fetal weights (Rowell & Clark, 1982). Preclinical and human studies indicate an association between nicotine exposure and adverse pregnancy outcomes in pregnant women who smoke or use smokeless tobacco products.

3. The impact of E-cigarettes on the developing fetus

Electronic cigarettes produce an inhalable aerosol by heating a mixture of nicotine, propylene glycol, glycerin, and flavorings. Propylene glycol contains a faintly sweet taste and is a viscous, colorless liquid; it is used to make plastic, but it is also used in food processing as a fluid for low-temperature heat exchange.

Glycerol exists as an odorless, colorless, viscous liquid that is sweet tasting and nontoxic and is used as a sweetener and humectant (e.g., to retain moisture). There is generally no information available on the effects of inhaling these substances (Whittington et al., 2018). Electronic nicotine delivery systems (ENDS) are noncombustible and contain fewer toxins than regular cigarettes, including carbon monoxide, one of the most potent fetotoxins (Aubard & Magne, 2000). Due to their noncombustible nature, ENDS do not emit carbon monoxide or contribute to second-hand smoke (Peterson & Hecht, 2017). Nevertheless, nicotine levels delivered by traditional cigarettes and ENDS appear to be comparable (St Helen et al., 2016) (Etter et al., 2014).

3.1. Decreased Body Weight and Impaired Pulmonary Growth

Most of the data available indicate that ENDSs may be harmful to a developing fetus. Developing fetuses are at risk from nicotine transmission; a study of neonatal mice found that exposure to e-cigarettes for 10 days decreased the body weight of newborns and impaired pulmonary growth after birth (McGrath-Morrow et al., 2015). Furthermore, it has been demonstrated that intravenous nicotine administration in rats increases the risk of intrauterine infection and decreases the infectious dose needed to cause infection (von Chamier et al., 2017).

3.2. Impaired Production of Placental Protein

There is also evidence that perinatal nicotine exposure without tobacco smoke impairs the production of placental protein disulfide isomerase in rodents. As a result of decreased protein disulfide isomerase levels, oxidative damage, and mitochondrial damage are induced, leading to premature cardiac deterioration (Barra et al., 2017). Additionally, the effects of nicotine administered to fetal lung and placental tissues were shown to affect DNA methylation when the main addictive alkaloid found in tobacco was present (Chhabra et al., 2014).

3.3. Altered RNA Levels

In another study, the effect of e-cigarettes with and without nicotine on mice offspring was studied with bulk RNA-sequencing of frontal cortex tissue. Transcriptomic analysis revealed enrichment of pathways involved in cancer, organismal injury and abnormalities, neurologic disease, gastrointestinal disorders, and psychiatric disorders after exposure to e-cigarettes both with and without nicotine (Lauterstein et al., 2016). The following studies demonstrate that the smoking of e-cigarettes can lead to various consequences, such as impaired immune function, adverse neural development, and decreased lung and cardiac function.

4. Nicotine Replacement Therapy's Known Effect on Fetus

Nicotine Replacement Therapy (NRT) was devised for tobacco consumers who find it difficult to quit smoking due to the addictiveness of nicotine. NRT substitutes for a large amount of nicotine in tobacco, thus reducing motivation to consume tobacco and withdrawal symptoms, allowing the user to quit tobacco use more easily. In particular, this therapy is intended to diminish the desire to consume tobacco and the psychological and physiological withdrawal symptoms related to it (Silagy et al., 2004). To date, there has been a wide variety of alternative nicotine sources integrated into programs for tobacco cessation.

In managing nicotine dependence and withdrawal, nicotine-containing medications are the most commonly studied and used pharmacology (Henningfield et al., 2005). NRT products come in various

forms including nicotine gum, transdermal patches, nasal sprays, oral inhalers, and tablets. The transdermal patch provides a sustained release of nicotine. The use of other products including gum, nasal spray, oral inhalers, and tablets provides acute doses of nicotine. As a result, they provide immediate relief from cravings and provide general craving relief as well as breakthrough craving relief (Sweeney et al., 2001) (Fagerström, n.d.). Despite varying levels of effectiveness and different rates of nicotine absorption, all of these products are effective even in the absence of behavioral guidance.

U.S. Food and Drug Administration has classified NRT in pregnancy categories C or D based on the galenic form (Siu & U.S. Preventive Services Task Force, 2015). It has generally been concluded that NRT use is safer than smoking during pregnancy (Coleman et al., 2007). It has also been recommended by several scientific societies in obstetrics and gynecology that NRT be prescribed to pregnant smokers who have failed to quit on their own (Guerby et al., 2020) (Grangé et al., 2020). Although a number of systemic reviews on the risks and advantages of the use of NRT during pregnancy exist, there is insufficient information about health outcomes in offspring whose mothers used NRT during pregnancy.

4.1. Infantile Colic

A 2012 study by Milidou et al. investigated whether nicotine exposure is linked to infantile colic (Milidou et al., 2012), which describes unusual crying behavior in otherwise healthy infants (Sung et al., 2018). The participants were pregnant Danish women, whose data was collected through interviews. There were four groups of participants categorized by the researchers: NRT users, smokers, those who smoked and used NRT simultaneously, and those who were not exposed to NRT during pregnancy. Based on specific criteria, they evaluated infant behavior, development, nutrition, and crying frequency. As a result, 7.9% of 63,128 infants met the criteria for infantile colic. Prenatal exposure to NRT (but not postnatal exposure) had similar odds of colic as prenatal exposure to tobacco smoke. This finding held even after accounting for various influencing factors.

4.3. Attention-Deficit/Hyperactivity Disorder (ADHD)

In 2014, a study by Zhu et al. examined maternal use of NRT and parental smoking during pregnancy (Zhu et al., 2014). In the study, both mothers and fathers were asked about their smoking habits, while only the mother was also asked for her NRT usage. When the children were 7 years old, their parents filled out the Strengths and Difficulties Questionnaire (SDQ). ADHD occurs when there is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with function and development (Lange et al., 2010). There were 2.4% of children with ADHD diagnoses or medications in the sample. As a result, a higher risk of ADHD was seen in children whose mothers used NRT and whose fathers did not smoke. Additionally, the study found that NRT use during pregnancy was associated with higher hyperactivity and inattention scores in 7-year-old children compared to nonsmokers.

4.4. Infant Impairment (Developmental or Behavioral Issues)

The Smoking, Nicotine And Pregnancy (SNAP) trial evaluated NRT use during pregnancy (Coleman et al., 2012). In the trial, a total of 521 women used nicotine patches, and 529 used placebo patches. Data was also collected on two-year-old infants born to these women in the Midlands and North-West of England (Cooper, Taggar, et al., 2014) (Cooper, Lewis, et al., 2014). As part of the evaluation, questionnaires were used to gather information about infant disability behavior, development, and respiratory symptoms. The severity of infant impairments was divided into three categories: "survival with no impairment,"

"survival with definite impairment," and "survival with suspected impairment." As a result of a secondary analysis, it was found that compared to a placebo group, infants whose mothers used nicotine patches were more likely to survive without impairment. However, there was no significant difference between the two groups when it came to respiratory disorders.

Another secondary analysis of the SNAP trial investigated whether maternal smoking status at different points during the trial was associated with the absence of developmental impairments at age 2 (Iyen et al., 2019). The study found no significant association between maternal tobacco smoke exposure and infant development impairments at age 2 after adjusting for confounding factors. Based on the study's findings, it cannot be concluded that improved infant development observed in the nicotine patch group was caused by smoking cessation.

5. Conclusions

According to the World Health Organization (WHO), tobacco kills more than 8 million people each year, including 1.3 million non-smokers who are exposed to second-hand smoke. It is also concluded that e-cigarettes carry and emit substances that are potentially toxic. One of the addicting agents in tobacco and e-cigarettes is nicotine, which interacts with the acetylcholine receptors, stimulating dopaminergic transmission (Tiwari et al., 2020). Access to nicotine through tobacco and e-cigarettes can result in several adverse consequences to the fetus when consumed during pregnancy.

Several studies conclude that the smoking of tobacco during pregnancy can lead to an increased risk of oral cleft palates. Also, a study in New Zealand and another in Stockholm showed that smoking during pregnancy was also associated with an independent increase in preterm birth. The effects of smoking during pregnancy can additionally result in intrauterine growth restriction. The use of nicotine during pregnancy resulted in reduced fetal growth and blood flow in the uterus and placenta of rats, and another study also reported that pregnant mice treated with nicotine had reduced placental and fetal weights.

In addition, it has been reported that e-cigarette exposure decreased newborns' body weight and impaired their ability to develop lungs after birth. Studies also show that the use of e-cigarettes during pregnancy impairs the production of placental protein disulfide isomerase in rodents. It has also been demonstrated that RNA levels may potentially be altered learning to various outcomes such as impaired immune function, adverse neural development, and decreased lung and cardiac function.

For smokers who are unable to quit due to nicotine addiction, Nicotine Replacement Therapy (NRT) was developed. By substituting nicotine for tobacco, NRT reduces motivation to consume tobacco and withdrawal symptoms, enabling users to stop smoking more easily. However, the delivery of nicotine through NRT has been found to bring some negative effects to the fetus when used during pregnancy. Infantile colic, an unusual crying behavior in healthy infants, has been reported to have a larger rate in the children of mothers exposed to NRT. ADHD, a persistent pattern of inattention and/or hyperactivity-impulsivity, was shown to be at higher risk for children whose mothers used NRT. Likewise, various forms of infant impairment were shown in infants of mothers using NRT.

Through these studies, a link between the use of nicotine-containing products (e-cigarettes, tobacco, and NRTs) during pregnancy and the effects it brings to newborns has been established. However, there are a limited number of related studies in the current field, especially for the investigation of NRTs, which can be a barrier to the results of the review. In addition, most of the results of the studies are associations, which leaves the relations debatable. Furthermore, there are a number of nonpharmaceutical approaches to quitting smoking during pregnancy, including behavioral therapies or motivational interviewing. Thus, further investigation into more ideal ways of NRTs through safer and clearer implications would be beneficial.

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