

Review Article

## Electronic Cigarettes Use During Pregnancy - Is it Safe or Not? A Literature Review

Iana Malasevskaia<sup>1\*</sup>, Ahmed Ali Al-Awadhi<sup>2</sup>, Fatima Ali Raza<sup>3</sup>

<sup>1</sup>Clinic of Obstetrics and Gynecology, Yemen-German Hospital, Sana'a, Republic of Yemen

<sup>2</sup>Yemen-German Hospital, Sana'a, Republic of Yemen

<sup>3</sup>MBBS Student, Karachi Medical and Dental College, Karachi, Pakistan

**\*Corresponding Author:** Iana Malasevskaia, Clinic of Obstetrics and Gynecology, Yemen-German Hospital, Sana'a, Republic of Yemen, Tel: 00967730552191; E-mail: [malasevskaia.iana@gmail.com](mailto:malasevskaia.iana@gmail.com)

**Received:** 09 April 2021; **Accepted:** 21 April 2021; **Published:** 23 April 2021

**Citation:** Iana Malasevskaia, Ahmed Ali Al-Awadhi, Fatima Ali Raza. Electronic Cigarettes Use During Pregnancy - Is it Safe or Not? A Literature Review. Fortune Journal of Health Sciences 4 (2021): 310-323.

### Abstract

Recently, the use of e-cigarettes has increased highly rapidly, especially among middle school and high school students and pregnant women who are concerned about tobacco effects on baby's health. There is little understanding of the effects of exposure to e-cigarette on human reproductive health, human development, or pregnant women. Human and animal data support that nicotine exposure during periods of development has multiple adverse health consequences, including impaired fetal brain, lung, cardiac development, and altered development of cerebral cortex and hippocampus in adolescents.

However, the effects of e-cigarettes are completely unknown regarding human development.

**Aim:** In this article, we are reviewing the most recent findings on the effects of e-cigarettes during pregnancy and early life.

**Method:** A literature search in PMC, PubMed, Google, ResearchGate, MEDLINE and Google Scholar was carried out using the following keywords: "Electronic cigarettes", "E-cigarettes and pregnancy", "ENDS and pregnancy". Study selection was in the language (English only), model (humans and animals), open accesses, and all types of studies

were included as long as they were relevant to our study.

**Limitation of study:** While we were collecting the information for this review, there were some limitations. Our data was primarily obtained from articles with free full access and written in English language only. This review article is a traditional review and, therefore, does not follow the Standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews.

**Keywords:** E-cigarettes; Electronic cigarettes; Nicotine; ENDS; E-cigarettes in pregnancy; E-cigarettes effects on intrauterine fetus

### Introduction & Backgrounds

Due to the high demand to quit cigarette smoking during pregnancy and the potential efficacy of e-cigarettes as a smoking cessation device, pregnant

women may be particularly interested in using e-cigarettes to stop or reduce cigarette smoking [1].

Electronic cigarettes (E-cigarettes) are called "e-cigs", "vape pens", "vapes", "e-hookahs" and "electronic nicotine delivery systems (ENDS)". E-cigarettes look like regular cigarettes, cigars, pipes, USB flash drives, pens, and other like everyday items [2]. E-cigarettes were invented by Chinese pharmacist Hon Lik in 2003 and subsequently became available globally, entering the European (EU) and American (US) markets in 2006 and 2007, respectively [3]. The Food and Drug Administration (FDA) has not begun its review of e-cigarette and their ingredients, nor has it issued any standards on the products or E-cigarette composition [4]. However, researchers do know that toxic chemicals and metals have all been found in e-cigarettes. Bellow in Table 1, are noted and described the most common chemicals detected in electronic nicotine delivery systems:

Nicotine	A highly addictive substance.
Propylene glycol	An additive in food; also used to make things like antifreeze, paint solvent, and artificial smoke in fog machines.
Acetaldehyde and formaldehyde	Carcinogens-chemicals are known to cause cancer.
Acrolein	An herbicide used to kill weeds and can cause irreversible lung damage.
Diacetyl	A chemical that can cause a lung disease called bronchiolitis obliterans, aka "popcorn lung".
Diethylene glycol	A toxic chemical used in antifreeze and is linked to lung disease.
Nickel, tin, lead	Heavy metals
Cadmium	A toxic metal found in cigarettes that causes breathing problems and disease.
Benzene	A volatile organic compound (VOC) was found in car exhaust.
Ultrafine particles	They can be inhaled deeply into the lungs and cause lung problems.

**Table 1:** The most common toxic chemicals found in electronic cigarettes

Whilst, some E-cigarettes/E-liquids do not contain Nicotine, the majority do, and the nicotine contents of e-cigarettes are variable. The Nicotine content on the label of some products is qualitative (e.g., zero, low, medium, high, super high) or quantitative on others [5]. Intrauterine babies will be exposed to Nicotine which has been shown to have a negative impact on neurobehavior. Nicotine negatively affects the central nervous system (CNS), with the deficits reflecting the biological and behavioral systems [6]. Prenatal nicotine exposure is associated with subtle changes in learning and behavior problems and morbidity from cognitive difficulties, ADHD, conduct disorders, behavioral problems, depression future in their life [6]. Exposure to Nicotine has been associated with attention deficit hyperactivity disorder (ADHD) later in childhood [6]. Nicotine easily crosses the placental barrier, detected in the fetal circulation and amniotic fluid. This transfer is rapid, with peak concentrations in the fetus after 15-30 minutes [7].

Propylene glycol, a chemical which is found in E-cigarettes, is unsafe for infants and pregnant women as it's harder for them to break down the ingredient. Cardiovascular issues and heart disease symptoms have been commonly associated with propylene glycol exposure [8].

Formaldehyde, one of the components found in E-cigarettes, recently classified as a carcinogen and ubiquitous environmental contaminant, has been suspected of causing adverse reproductive and developmental effects. A meta-analysis revealed an increased risk of spontaneous abortion [9]. Potential

mechanisms underlying formaldehyde-induced reproductive and developmental toxicities, including chromosome and DNA damage (genotoxicity), oxidative stress, altered level and function of enzymes, hormones and proteins, apoptosis, toxicogenomic and epigenomic effects (such as DNA methylation), were identified [9].

Prenatal exposure to high doses of acrolein significantly reduced fetal weight and testicular volume and testicular testosterone production capacity due to oxidative stress damage, which may contribute to the impairment of steroidogenesis [10].

Additionally, E-cigarettes contain heavy metals like lead, nickel, and tin. Maternal and fetal nickel exposure is possibly associated with the risk for heart defect [11]. Prenatal lead exposure has been known to negatively affect maternal health and infant outcomes across a wide range of maternal blood lead levels. It has been associated with gestational hypertension, spontaneous abortion, low birth weight, and impaired neurodevelopment [12]. Kippler et al. found significant inverse associations between maternal Cadmium exposure and birth anthropometry, especially head circumference and birth weight in girls, but no associations in boys [13]. Cadmium exposure during pregnancy results in a combination of factors, which will cause changes in the Zinc availability that will eventually affect the mother and the embryo/fetus or the newborn to a greater or lesser extent [14]. Maternal exposure to Cadmium seems to increase the risk of early delivery, leading to lower birth weight [15].

"High exposure to benzene during pregnancy is associated with low birth weight, an increased risk of childhood leukemia, and a greater incidence of

congenital disabilities such as spina bifida," said Caron-Beaudoin [16]. In Figure 1 are presented the most common chemicals used in electronic cigarettes.



**Figure 1:** The most common chemical components of E-cigarettes

In utero Ultrafine particles (UFP) exposure promotes placental stress through inflammation and oxidative stress, and programs renin-angiotensin system-related elements result in altered blood pressure in the offspring. Exposure to UFP during fetal development could influence susceptibility to cardiovascular disease in adulthood [17].

The present study aims to revise the current studies and literature to identify the effects of e-cigarettes on pregnancy and intrauterine babies.

### Review and Discussion

Studies reveal that e-cigarette use is increasing among adolescents and young adults. However, the long-term health effects are unknown, especially with regards to pregnancy [18].

### E-cigarettes and human studies

A cross-sectional analysis of the 2016 Pregnancy Risk Assessment Monitoring System used data on self-reported use of ENDS and cigarettes during the

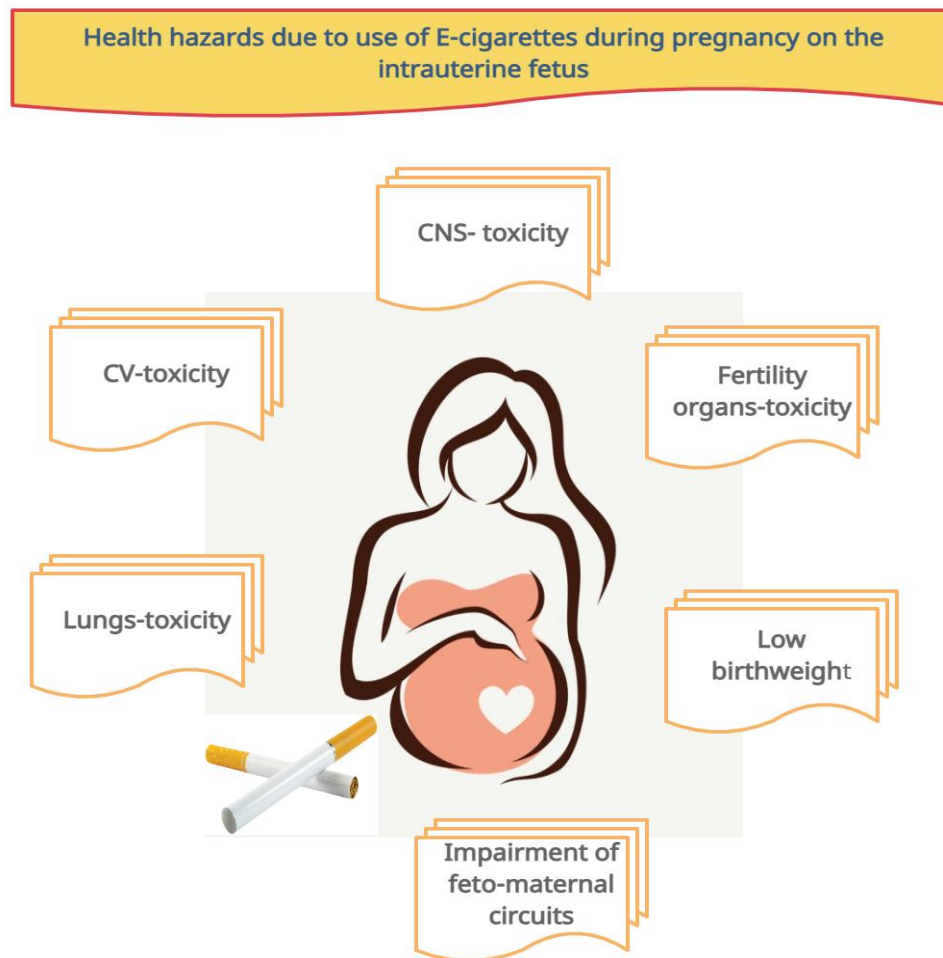
last three months of pregnancy among 33,964 women from 29 states and New York City [19]. The prevalence of prenatal ENDS use was 1.2%, varying from 0.6% to 1.8% in New York City and 4.4% to 22.7% in West Virginia. White women used ENDS more likely than black women. Women with education were also less likely to use ENDS. Those who used cigarettes during pregnancy were 11.05 times more likely to use ENDS prenatally [19].

Additionally, Cardenas et al. conducted a cohort study with 248 pregnant women using questionnaire data and biomarkers (salivary cotinine, exhaled carbon monoxide, and hair nicotine). They evaluated the association between birth weight and small-for-gestational-age (SGA) risk by applying multivariate linear and log-binomial regression to reproductive outcome data for 232 participants [20]. The prevalence of current ENDS use among pregnant women was 6.8% (95% CI: 4.4-10.2%), SGA risk ratios for ENDS users were 6.5-8.5 times that of the unexposed [20].

Froggatt et al. assessed the neurological outcome as a result of E-cigarette exposure. Eighty-three infants were involved in the study, exposed prenatally to cigarettes or E-cigarettes or not exposed to either [21]. Differences for birth outcomes were assessed between these three groups and scored on the Neonatal Behavioral Assessment Scale (NBAS) at

one month of age. The cigarette and E-cigarette exposed infants showed a greater number of abnormal reflexes ( $p=0.001$ ;  $p=0.002$ ), decreased motor maturity ( $p=0.036$ ) abilities, and marginally decreased for self-regulation ( $p=0.057$ ) on E-cigarettes exposed infants [21]. However, birth weight and head circumference did not differ for e-cigarette exposed infants than infants who were not prenatally exposed to nicotine [21].

Kim and Oancea examined the effects of prenatal E-cigarettes use on neonatal birth outcomes compared to conventional cigarette smokers and complete tobacco abstainers. Data of 55,251 pregnant women were analyzed [22]. Participants were classified into three groups based on their smoking behaviors in the third trimester: complete tobacco abstinence, exclusive conventional cigarette smoking, or exclusive E-cigarettes use [22]. Neonates of E-cigarettes users were significantly more likely to be small-for-gestational-age (SGA) (OR 1.76; 95% CI 1.04, 2.96), have low birth weight (LBW) (OR 1.53; 95% CI 1.06, 2.22), or be born preterm (OR 1.86; 95% CI 1.11, 3.12) compared to tobacco abstainers. However, odds of E-cigarettes users' pregnancies resulting in SGA, LBW, or preterm birth were not significantly lower than those of conventional cigarette smokers [22]. The Figure 2, summarize in short, the negative effects of electronic cigarettes on intrauterine babies.



**Figure 2:** Health hazards due to use of E-cigarettes during pregnancy. CNS- central nervous system, CV- cardiovascular system

### E-cigarettes and animal studies

Lauterstein et al. tested the hypothesis of neurotoxicity of nicotine component of E-cigarettes on pregnant mice. Pregnant C57BL/6 mice were exposed daily to whole-body inhalation throughout gestation to aerosols produced from E-cigarettes either with nicotine or without nicotine. Additionally, following birth, pups and dams were exposed together to E-cigarette aerosols throughout lactation beginning at postnatal day four-six and using the

same exposure conditions [23]. Female offspring exposed to E-cigarettes with or without nicotine and male offspring exposed to E-cigarettes without nicotine all showed neurological disease and psychiatric disorders, including decreases in memory, cognition, and learning [23]. They concluded that early life exposure to non-nicotine-containing aerosols produces greater frontal cortex gene expression changes; it is likely that one or more of

the aforementioned E-cigarette constituents, besides nicotine, could be driving the observed effects [23].

Additionally, Church et al. investigated the neurodevelopmental consequences of maternal E-cigarette use on adult offspring behavior and neuroimmune outcomes [24]. Twenty-seven pregnant female CD-1 mice were randomly assigned to one of three treatment groups and exposed daily to either filtered air, propylene glycol (PG), and vegetable glycerol (VG) or to PG/VG with nicotine. Whole-body exposures were carried out for three hours/day, seven days/week, from gestational day (GD) 0.5 until GD 17.5 [24]. Adult male and female offspring (eight weeks old) were assessed, and the nicotine-exposed group exhibited elevated locomotor activity in the elevated plus-maze and altered stress-coping strategies in the forced swim task [24]. However, male and female offspring exposed to PG/VG with and without nicotine had lower object discrimination. Maternal E-cigarette exposure with nicotine showed a reduction in interleukin (IL)-4 and interferon-gamma (IFN $\gamma$ ) in the diencephalon and a low level of hippocampal IFN $\gamma$  (females only). E-cigarette exposure without nicotine revealed a 2-fold increase of IL-6 in the cerebellum [24].

Al-Sawalha et al. examined the effect of E-cigarettes aerosol exposure during gestation and lactation on learning and memory of adult male offspring rats [25]. Rats were exposed to either fresh air or E-cigarettes' aerosol for one hour daily during the gestational period as well as the first 21 days of lactation [25]. Exposure to E-cigarettes aerosol during gestation/lactation increased activity of superoxide dismutase in the hippocampus impairing

long-term memory in adult offspring. However, brain-derived neurotrophic factor and the other tested oxidative stress biomarkers were not affected ( $p>0.05$ ) [25].

Wetendorf et al. examined whether e-cigarette exposure impairs implantation and offspring health on C57BL/6J mice, exposing them five times a week to E-cigarette vapor or sham [26]. After four months, a significant delay in the onset of the first litter was observed [26]. Additionally, a significantly impaired embryo implantation, at day 5.5, despite high levels of progesterone was also observed [26]. A significant change in the integrin, chemokine, and JAK signaling pathways were detected. Moreover, female offspring exposed in utero to E-cigarettes exhibited a significantly low weight, whereas males exhibited a slight deficiency in fertility [26].

Noël et al. assessed whether in utero exposures to e-cigarettes aerosols compromised lung development in mice. A third-generation E-cigarettes device was used to expose pregnant BALB/c mice by inhalation of nicotine cinnamon-flavored E-cigarette's aerosols for 14-31 days, and control mice were exposed to filtered air [27]. Both preconception and prenatal exposures to E-cigarette's aerosols significantly decreased the offspring's birth weight and body length. Altered fetal lung structure and dysregulating of the Wingless-related integration site (Wnt) signaling, which is essential to lung organogenesis, also was detected [27].

Wang et al. evaluated the biochemical and molecular implications of maternal exposure during pregnancy to E-cigarette aerosols on the adult offspring of both

sexes, with a focus on pulmonary extracellular-matrix (ECM) remodeling and myogenesis [28]. Pregnant CD-1 mice were exposed to E-cigarette aerosols with or without nicotine during pregnancy, and the lungs of adult male and female offspring were collected and examined [28]. Compared with the air-exposed control group, female mice exposed to E-cigarette's aerosols, with or without nicotine, demonstrated increased lung protein abundance of LEF-1 (lymphoid enhancer-binding factor 1), fibronectin, and E-cadherin, whereas altered E-cadherin and PPAR $\gamma$  (peroxisome proliferator-activated receptor  $\gamma$ ) levels were observed only in males exposed to e-cigarette's aerosols with nicotine [28]. Lipogenic and myogenic messenger ribonucleic acid (mRNAs) were dysregulated in adult offspring in a sex-dependent manner [28]. PAI-1 (plasminogen activator inhibitor-1) was significantly increased in females and males exposed prenatally to e-cigarette aerosols with nicotine, while MMP9 (matrix metalloproteinase 9) was downregulated in both sexes exposed to e-cigarette's aerosols with nicotine. These findings suggest that vaping during pregnancy is unsafe and increases the risk for later-life interstitial lung diseases [28].

McGrath-Morrow et al. investigated the effects of E-cigarette emissions on systemic cotinine levels, weight, and postnatal lung growth in neonatal mice. Neonatal mice were exposed the first ten days of life to E-cigarettes containing either 1.8% nicotine in propylene glycol (PG) or PG alone. The result showed that mice exposed to nicotine/PG had a 13.3% decrease in total body weight, modestly impaired lung growth, and elevated plasma cotinine compared to room air controls [29].

Palpant et al. investigated the impact of standard tobacco cigarettes and E-cigarettes on heart development in vitro and in vivo. Zebrafish and human embryonic stem cells (hESCs) were used as a model for in vivo and in vitro experiment [30]. Exposure to both types of cigarettes resulted in broad, dose-dependent heart malformation, pericardial edema, and reduced heart function. Both types of cigarettes decreased the expression of cardiac transcription factors in cardiac progenitor cells, suggesting a persistent delay in differentiation [30]. In definitive human cardiomyocytes, both E-cigarette- and tobacco cigarette-treated samples showed reduced expression of sarcomeric genes such as ventricular myosin light chain-2 (MLC2v) and myosin light polypeptide 6 (MYL6) [30].

Orzabal et al. evaluated the effects of vaping E-cigarettes during gestation on offspring growth and maternal and fetal vascular hemodynamics [31]. Sprague-Dawley dams were assigned to Pair-Fed Control, Pair-Fed Juice, or Juice + Nicotine groups and then underwent either a prenatal or prenatal + postnatal exposure paradigm in a custom-engineered vaping system [31]. The Juice+ Nicotine group exhibited significantly decreased fetal weight and crown-rump length. Pre- and postnatal exposure to Juice+ Nicotine resulted in decreased pup weight and crown-rump length. Blood flow in the Juice+ Nicotine group was decreased in the maternal uterine and fetal umbilical circuits by 49.50% and 65.33%, respectively [31]. Bellow in the Table 2 are summarized all available data about E-cigarettes and its health hazard during pregnancy and intrauterine fetus.



Author	Year of publication	Human/Animal study	Results of using e-cigarettes during pregnancy
Cardenas et al. [20]	2019	Human	Small-for-gestational-age babies
Froggatt et al. [21]	2020	Human	Decreased self-regulation and motor maturity, abnormal reflexes on Neonatal Behavioral Assessment Scale (NBAS)
Kim and Oancea [22]	2020	Human	Neonates were small-for-gestational-age, have low birthweight, or born preterm
Lauterstein et al. [23]	2016	Animal	Decreases in memory, cognition, and learning due to greater frontal cortex gene expression changes
Church et al. [24]	2020	Animal	Elevated locomotor activity in the elevated plus-maze and altered stress-coping strategies in the forced swim task, low object discrimination score in the novel object recognition task. Maternal E-cigarette exposure with nicotine showed a reduction in interleukin-4 and interferon-gamma in the diencephalon and a low level of hippocampal IFN $\gamma$ (females only). E-cigarette exposure without nicotine revealed a 2-fold increase of IL-6 in the cerebellum.
Al-Sawalha et al. [25]	2020	Animal	Increased activity of superoxide dismutase in the hippocampus impairing long-term memory
Wetendorf et al. [26]	2019	Animal	A significantly impaired embryo implantation, despite high levels of progesterone. A change in the integrin, chemokine, and Janus Kinase (JAK) signaling pathways were observed. Female offspring exposed in utero to e-cigarettes showed a significantly low weight, whereas males exhibited a slight deficiency in fertility.
Noël et al. [27]	2020	Animal	Decreased the offspring's birth weight and body length, altered fetal lung structure, and

			dysregulating of the Wnt signaling, which is essential to lung organogenesis, also was detected.
Wang et al. [28]	2020	Animal	Female exposed to e-cigarette's aerosols, with or without nicotine, demonstrated increased lung protein abundance of LEF-1 (lymphoid enhancer-binding factor 1), fibronectin, and E-cadherin; however, altered E-cadherin and PPAR $\gamma$ (peroxisome proliferator-activated receptor $\gamma$ ) levels were observed only in males exposed to e-cigarette's aerosols with nicotine. Lipogenic and myogenic messenger ribonucleic acid (mRNAs) were dysregulated, PAI-1 (plasminogen activator inhibitor-1) was increased in females and males exposed prenatally to e-cigarette aerosols with nicotine, while MMP9 (matrix metalloproteinase 9) was downregulated in both sexes.
McGrath-Morrow et al. [29]	2015	Animal	Study showed a decrease in total body weight, modestly impaired lung growth and elevated plasma cotinine.
Palpant et al. [30]	2015	Animal and human embryonic stem cells	Heart malformation, reduced heart function, pericardial edema, and decreased expression of cardiac transcription factors suggesting a persistent delay in differentiation was observed. In human cardiomyocytes samples, a reduced expression of sarcomeric genes such as ventricular myosin light chain-2 (MLC2v) and myosin light polypeptide 6 (MYL6) was observed.
Orzabal et al. [31]	2019	Animal	Decreased fetal weight and crown-rump length. Blood flow was decreased in the maternal uterine and fetal umbilical circuits.

**Table 2:** Summary of data about E-cigarettes effects on pregnancy and intrauterine baby.

### Further research

Although E-cigarettes are safer than conventional cigarettes, there are several areas of concern about E-cigarette safety. Considerations include the potential for a lifetime addiction to nicotine, eventual transition to traditional tobacco use, and the health effects of nicotine or other chemicals found in E-cigarettes.

The safety of E-cigarettes must be compared with the use of tobacco-derived products and non-nicotine-containing products. However, they do not contain carbon monoxide or any other harmful toxins in tobacco-containing cigarettes; women should be warned of the dangers of nicotine, heavy metals, and other chemicals, which are the main components of E-cigarettes and their harmful effects on their intrauterine baby. E-cigarettes' substances are dangerous, and there are so many different combinations of chemicals in E-cigarettes that studying them is very difficult. The lack of evidence studies regarding E-cigarettes has raised significant concern for public health. The effects of E-cigarettes on pregnancy and fetal development are currently unexplored due to the novelty of this product; thus, more deep research on E-cigarette products is demanded.

It is well known that smoking is hazardous during pregnancy for women and intrauterine babies. Smoking during pregnancy is associated with risk for hypertension, abruption of placenta, intrauterine growth restriction of baby, intrauterine death, stillbirth, premature rupture of membrane, premature delivery, and low birth weight. Additionally, the

intrauterine baby is at the risk of congenital defects of the mouth and lip, neurobehavioral defects, and respiratory dysfunction. Thus, further research should be done to know better and understand the effects of E-cigarettes products on pregnant women and intrauterine babies. E-cigarettes are new products, but the health effects of electronic cigarettes remain uncertain. An E-cigarette contains toxic chemicals in lower concentrations than cigarette smoke; however, it contains harmful chemicals not found in tobacco smoke.

In this review, we found several studies done on pregnant animals; however, only a few data were found about E-cigarettes' effects on pregnant women and intrauterine fetuses.

### Conclusion

Data on the effects of E-cigarettes on pregnant women and intrauterine fetuses are very scarce. Most research used an animal model, with these studies clearly indicating that the use of E-cigarettes may negatively affect intrauterine fetuses and the health of pregnant women. However, more large studies should be done in the future to better understand the effect of E-cigarettes on human health.

Thus, in summary, the data presented here strongly support that E-cigarette usage during pregnancy is harmful to fetal lung, heart, and central nervous system development. The data are strong enough to raise major concerns, and it is hoped that education and regulation will prevent pregnant women from using E-cigarettes.

**Conflict of interest:** All authors declare no conflict of interest.

**Funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### References:

1. Chiang SC, Abrams LC, Cleary SD, et al. E-cigarettes and Smoking Cessation: A Prospective Study of a National Sample of Pregnant Smokers. *BMC Public Health* 19 (2019): 964.
2. Electronic Cigarettes, CDC. Page last reviewed: September 9, 2020. [https://www.cdc.gov/tobacco/basic\\_information/e-cigarettes/index.htm](https://www.cdc.gov/tobacco/basic_information/e-cigarettes/index.htm) (2021).
3. Rahman MA, Hann N, Wilson A, et al. Electronic cigarettes: patterns of use, health effects, use in smoking cessation and regulatory issues. *Tobacco Induced Diseases* 12 (2014): 1-9.
4. What's in an E-Cigarette? American Lung Association. Page last updated: July 13, 2020. <https://www.lung.org/quit-smoking/e-cigarettes-vaping/whats-in-an-e-cigarette> (2021).
5. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems; Eaton DL, Kwan LY, Stratton K, editors. *Public Health Consequences of E-Cigarettes*. Washington (DC): National Academies Press (US) (2018).
6. Blood-Siegfried J, Rende EK. The long-term effects of prenatal nicotine exposure on neurologic development. *Journal of Midwifery & Women's Health* 55 (2010): 143-152.
7. Wickstrom R. Effects of nicotine during pregnancy: human and experimental evidence. *Current Neuropharmacology* 5 (2007): 213-222.
8. What's the deal with Propylene Glycol? Nala Care. Published April 05, 2020. <https://nalacare.com/blogs/journal/whats-the-deal-with-propylene-glycol#:~:text=Propylene%20glycol%20is%20unsafe%20for,associated%20with%20propylene%20glycol%20exposure> (2021).
9. Duong A, Steinmaus C, McHale CM, et al. Reproductive and developmental toxicity of formaldehyde: a systematic review. *Mutation Research/Reviews in Mutation Research* 728 (2011): 118-138.
10. Yang Y, Zhang Z, Zhang H, et al. Effects of maternal acrolein exposure during pregnancy on testicular testosterone production in fetal rats. *Molecular Medicine Reports* 16 (2017): 491-498.
11. Zhang N, Chen M, Li J, et al. Metal Nickel Exposure Increase the Risk of Congenital Heart Defects Occurrence in Offspring: A Case-Control Study in China. *Medicine* 98 (2019): e15352.
12. Lead Screening During Pregnancy and Lactation. ACOG. Number 533 (Reaffirmed 2019), accessed March

- 27,2021.<https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2012/08/lead-screening-during-pregnancy-and-lactation#:~:text=Elevated%20lead%20levels%20in%20pregnancy%20have%20been%20associated%20with%20gestational,of%20maternal%20blood%20lead%20levels>.
13. Kippler M, Tofail F, Gardner R, et al. Maternal cadmium exposure during pregnancy and size at birth: a prospective cohort study. *Environmental Health Perspectives* 120 (2012): 284-289.
  14. Espart A, Artime S, Tort-Nasarre G, et al. Cadmium exposure during pregnancy and lactation: materno-fetal and newborn repercussions of Cd (II), and Cd–metallothionein complexes. *Metallomics* 10 (2018): 1359-1367.
  15. Nishijo M, Nakagawa H, Honda R, et al. Effects of maternal exposure to cadmium on pregnancy outcome and breast milk. *Occupational and Environmental Medicine* 59 (2002): 394-397.
  16. Exposure to benzene during pregnancy: a pilot study raises concerns in British Columbia. *ScienceDaily*. November 13, 2017.  
<https://www.sciencedaily.com/releases/2017/11/171113095435.htm#:~:text=Health%20hazards%20of%20benzene%20include%20birth%20defects&text=The%20health%20impacts%20of%20benzene,%2C%22%20said%20Caron%2DBeaudoin> (2021).
  17. Morales-Rubio RA, Alvarado-Cruz I, Manzano-León N, et al. In utero exposure to ultrafine particles promotes placental stress-induced programming of renin-angiotensin system-related elements in the offspring results in altered blood pressure in adult mice. *Particle and Fibre Toxicology* 16 (2019): 1-6.
  18. Kahr MK, Padgett S, Shope CD, et al. A qualitative assessment of the perceived risks of electronic cigarette and hookah use in pregnancy. *BMC PublicHealth* 15 (2015): 1-8.
  19. Hawkins SS, Wylie BJ, Hacker MR. Use of ENDS and cigarettes during pregnancy. *American Journal of Preventive Medicine* 58 (2020): 122-128.
  20. Cardenas VM, Cen R, Clemens MM, et al. Use of Electronic Nicotine Delivery Systems (ENDS) by pregnant women I: Risk of small-for-gestational-age birth. *Tobacco Induced Diseases* 17 (2019).
  21. Froggatt S, Reissland N, Covey J. The effects of prenatal cigarette and e-cigarette exposure on infant neurobehaviour: A comparison to a control group. *EClinicalMedicine* 28 (2020): 100602.
  22. Kim S, Oancea SC. Electronic cigarettes may not be a "safer alternative" of conventional cigarettes during pregnancy: evidence from the nationally representative PRAMS data. *BMC Pregnancy and Childbirth* 20 (2020): 557.
  23. Lauterstein DE, Tijerina PB, Corbett K, et al. Frontal cortex transcriptome analysis of mice exposed to electronic cigarettes during early life stages. *International Journal of*

- Environmental Research and Public Health 13 (2016): 417.
24. Church JS, Chace-Donahue F, Blum JL, et al. Neuroinflammatory and behavioral outcomes measured in adult offspring of mice exposed prenatally to e-cigarette aerosols. *Environmental Health Perspectives* 128 (2020): 047006.
25. Al-Sawalha N, Alzoubi K, Khabour O, et al. Effect of electronic cigarette aerosol exposure during gestation and lactation on learning and memory of adult male offspring rats. *Physiology & Behavior* 221 (2020): 112911.
26. Wetendorf M, Randall LT, Lemma MT, et al. E-cigarette exposure delays implantation and causes reduced weight gain in female offspring exposed in utero. *Journal of the Endocrine Society* 3 (2019): 1907-1916.
27. Noël A, Hansen S, Zaman A, et al. In utero exposures to electronic-cigarette aerosols impair the Wnt signaling during mouse lung development. *American Journal of Physiology-Lung Cellular and Molecular Physiology* 318 (2020): L705-L722.
28. Wang Q, Sundar IK, Blum JL, et al. Prenatal exposure to electronic-cigarette aerosols leads to sex-dependent pulmonary extracellular-matrix remodeling and myogenesis in offspring mice. *American Journal of Respiratory Cell and Molecular Biology* 63 (2020): 794-805.
29. McGrath-Morrow SA, Hayashi M, Aherrera A, et al. The effects of electronic cigarette emissions on systemic cotinine levels, weight and postnatal lung growth in neonatal mice. *PloS One* 10 (2015): e0118344.
30. Palpant NJ, Hofsteen P, Pabon L, et al. Cardiac development in zebrafish and human embryonic stem cells is inhibited by exposure to tobacco cigarettes and e-cigarettes. *PloS One* 10 (2015): e0126259.
31. Orzabal MR, Lunde-Young ER, Ramirez JI, et al. Chronic exposure to e-cig aerosols during early development causes vascular dysfunction and offspring growth deficits. *Translational Research* 207 (2019): 70-82.



This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC-BY\) license 4.0](https://creativecommons.org/licenses/by/4.0/)