ASSESSING THE IMPACT OF PRENATAL ELECTRONIC CIGARETTE EXPOSURE ON EMBRYOS AND FETUSES: A COMPREHENSIVE REVIEW COMPARING HUMAN AND ANIMAL STUDIES

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ABSTRACT

The use of electronic nicotinic delivery systems (ENDS) by pregnant women and women of reproductive age is a growing concern. Due to the perception that electronic cigarettes (ECs) are safe or less harmful than smoking traditional tobacco cigarettes, there has been an uptake in EC use among all demographics. In pregnant women who use ECs, the most commonly reported reasons are out of curiosity, their attempts to quit smoking, and general perceptions of reduced harm. Recent studies involving Zebrafish, rats, and mouse animal models have shown that prenatal exposure to EC can cause significant health defects in dams. However, comprehensive research is needed to investigate EC's short- and long-term effects on human maternal, fetal, and child health and development. This review aims to understand how the use of ECs by women affects embryonic and fetal development by determining the effect of ECs and dual-use (ECs + tobacco cigarettes) on pregnancy outcomes. This systematic review completed a search of databases including Google Scholar, Pubmed, and independent journals relating to electronic nicotine delivery systems and pregnancy outcomes. Articles were limited by language and date as later research provided a more comprehensive standing. Articles without full or open access were not included. A total of 31 studies were included in the review showing ECs cause low birth weights (LBW), oxidative stress, increased disease susceptibility, impaired brain development, impaired memory, or non-significant findings. This review provides insights into the emerging trends and challenges associated with EC use during pregnancy, emphasizing the need for further research to inform public health policies and enhance our understanding of the risks posed to public health.

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Introduction

Every day people using common cigarettes get ill from toxins which result in an array of preventable illnesses, disabilities, and over 400,000 annual U.S. deaths (Breland et al. 2017). Minimizing the health risks associated with tobacco cigarette use has been the central focus for endeavors geared towards reducing its consumption thus giving rise to electronic nicotine delivery systems (ENDS). As stated by Wagner et al., (2017) In a test sample, 64.27% believed that e-cigarettes were safer than tobacco cigarettes. Advertising exposure to e-cigarettes (ECs) increases the probability of perceiving ECs to be less harmful than tobacco cigarettes.

While the substitution of traditional tobacco cigarettes with ECs can reduce excess exposure to toxicants (Goniewicz et al. 2014) many individuals are beginning to use Electronic Nicotine Delivery System (ENDS) devices without the gateway of traditional tobacco cigarettes. The acknowledgment that EC vaping is a contributor to various health issues is supported by data that chemicals in EC aerosols contain potentially toxic compounds (Goniewicz et al. 2014). Notably, adverse health effects on gestational development have been under-addressed in scientific literature. The increasing popularity of ECs, especially during pregnancy, has left uncertainties regarding their impact on embryonic and fetal health (Al-Sawalha et al. 2020).

Individuals are turning to vapes or ECs driven by the belief that these alternatives are less harmful than traditional tobacco cigarettes (McCubbin et al. 2017). ECs are sometimes marketed as healthier alternatives to tobacco products which increase their appeal as a replacement for smoking for women who are pregnant (Wagner et al. 2017).

The United States has witnessed a rapid growth of EC sales since making its way into the American market in 2007 (McCubbin et al. 2017). Their perception that e-cigarettes could render them less harmful than conventional cigarettes has contributed to their rise in popularity (Wagner

et al. 2017). Despite numerous studies regarding toxicants in ECs, few have focused on humans and/ or expectant mothers. Data on the varied use of ECs during pregnancy alone or with the use of tobacco cigarettes is in its infancy (Lin et al. 2023).

While many animal studies exist, the effects of ECs in animals may not translate to humans (Van der Worp et al. 2010). Therefore, pregnant mothers should avoid using ENDS devices until more data are available to further report potential risks. Most studies regarding toxicants in ECs and their effect on maternal, embryonic, and fetal health have found significant inverse relationships between active maternal smoking during pregnancy and fetal health. The observed effects include increased risks for low birth weight (LBW) babies, preterm birth, problems with the heart and lungs, decreased head size, developmental disparities, and/ or small-for-gestational-age (SGA) (Miyake et al. 2013).

There are no conclusive results about the health effects of vaping because research on EC exposure during pregnancy has not reached any consensus yet. Despite the increasing acceptance of ENDS, there is still a worry over whether they are safe for use by expectant women. A study by Cardenas et al. 2019 revealed that the use and prevalence of ECs and other Electronic Nicotine Delivery Systems (ENDS) among expectant mothers was 6.8%. Of those 6.8%, 75% had reported to use both ECs and traditional tobacco cigarettes. The increased use of ECs, especially during pregnancy and in addition to traditional tobacco cigarettes, highlights the urgent need to assess the dangers of EC use, alone and concurrently, on public health (Breland et al. 2017) especially the health of pregnant mothers and their unborn children.

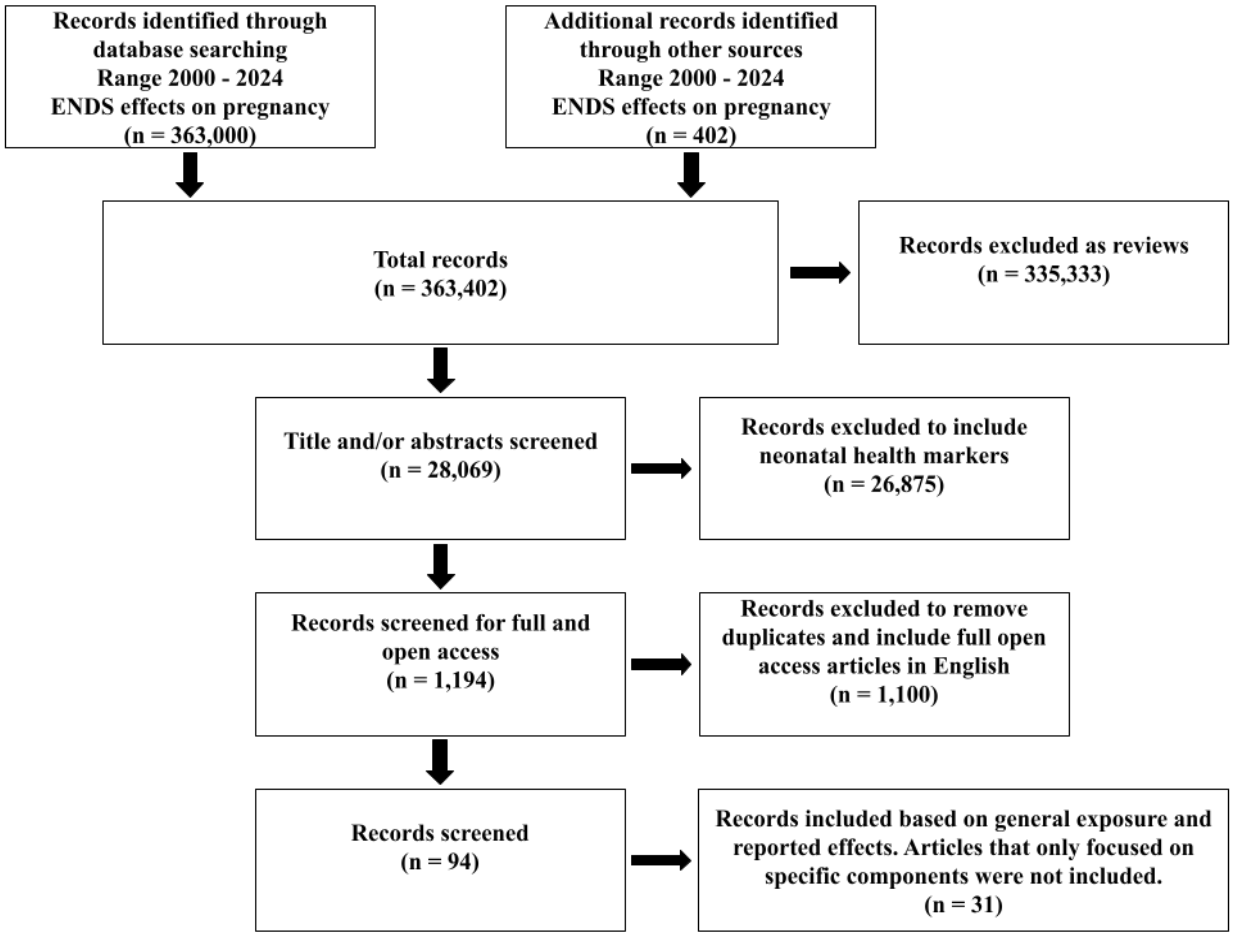
Challenges faced by the switch from or dual use of traditional tobacco cigarettes to Vapes, ECs, or Electronic nicotine delivery systems (ENDS) indicate a negative effect of using both tobacco cigarettes and ECs on fetal development (Palpant et al. 2015). This review provides

insight into the public uptake of electronic nicotine delivery systems (ENDS) among pregnant women and highlights current knowledge gaps regarding the use and effects of ENDS on maternal and fetal health.

Methods

This systematic review followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Figure 1 depicts a flowchart outlining the methodology used in this systematic review based on article search, retrieval, inclusion, and exclusion numbers.

Figure 1: Systematic Review Flowchart



Search Strategy

A search using PUBMED and Google Scholar or similar search engines was used to find peer-reviewed work based on several keywords, phrases, and relative information. The list is as follows: “E-cigarettes”, “electronic cigarettes”, “electronic nicotine delivery systems”, “ENDS”, “vape”, “vaping”, “pregnancy”, “fetus”, “embryo”, “fetal development”, “prenatal”, “reproduction”, “uterus”, “human embryonic stem cells”, “birth weight”, “preterm”, “neurology”, “nicotine”, “toxicity”, “cognition”, “development.” References in case reports and peer-reviewed literature also contributed to gathering literature and data.

Inclusion Criteria and Exclusion Criteria

Case reports and papers relating to prenatal ECs and Vape use reporting results on human or animal embryonic development, fetal development, or similar tests to embryonic stem cells were included. Review papers were included for collection. Title and abstracts needed to review the general effects of ENDS aerosol exposure. The scholarly articles at a minimum needed to: (1) report the testing or level of exposure of e-cigarette aerosol to the subject and (2) report the effects on embryonic or fetal development.

Case reports and other comprehensive review literature that did not report Maternal Electronic Nicotinic Delivery Systems (ENDS) and their effects on embryonic or fetal development were excluded from the study. ENDS devices were defined as including but not limited to Electronic Cigarettes, Vapes, Vape pens, Sticks, Rags, Juuls, Pod mods, Mods, Tanks, Hookah sticks, E-Hookah, and dual use. Articles that only focused on specific components such as menthol or nicotine were not included, articles that mentioned specific components but still reported effects of general exposure were included. Articles were limited by language and date as

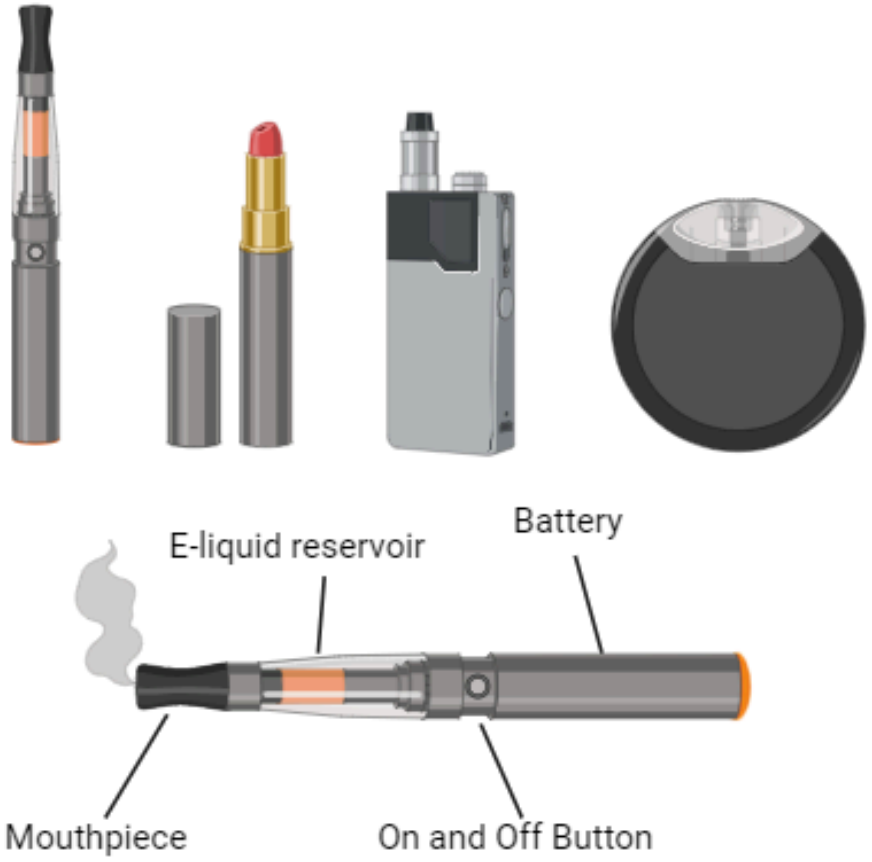
later research provided a more comprehensive standing. Dates ranged from 2000 - 2024, papers outside that range were not included. Most informative data collected came from papers that ranged from 2015 - 2024. Articles without free full or free open access were not included.

What are Electronic Cigarettes?

ECs are also known as vapes, vape pens, sticks, rigs, juuls, pod mods, mods, tanks, hookah sticks, electronic vape products (EVPs), and e-hookah (Breland et al. 2017). These terms describe Electronic Nicotinic Delivery Systems (ENDS) which consist of a battery, a heating element, and a cartridge designed to hold liquids. The liquids used in ENDS often include nicotine, artificial flavorings, propylene glycol (PG), and vegetable glycerin (Margham et al. 2016, Breland et al. 2017). While in use, the liquid is heated into an aerosol that is then inhaled by the consumer.

Of 150 aerosol constituents tested in a single comprehensive study, 46 were detected in EC aerosol while 100 were detected in tobacco cigarettes. Of the 46 compounds, 21 were found due to environmental factors. Of the 25 compounds left, 9 were present but levels could not be quantified and 16 were produced by the use of ECs (Maragham et al. 2016). The toxicants found in ECs included nicotine, propylene glycol, and glycerol but overall the tested toxicants had a lower overall ratio as compared to the traditional tobacco cigarette. Ranging from 82 - 99% lower, ECs may present a potentially healthier alternative than the traditional tobacco cigarette if used as its substitution (Maragham et al. 2016).

Figure 1: Electronic Cigarettes Examples and Parts



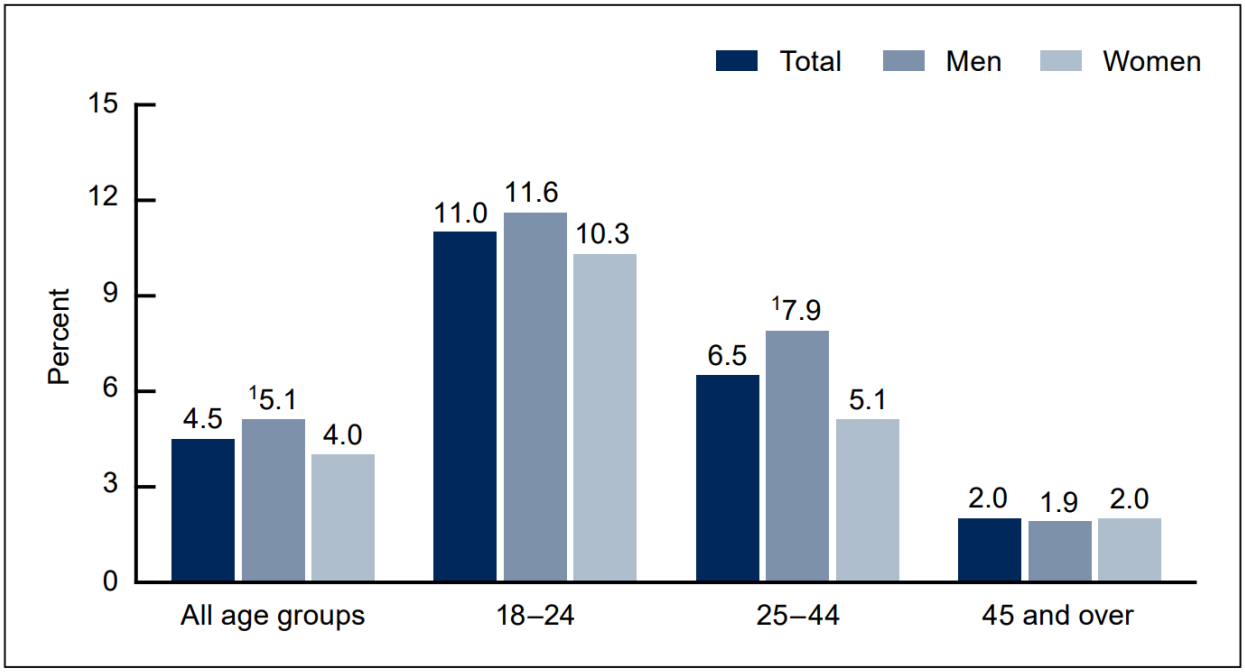
Electronic Cigarette Use

The increasing prevalence of ECs and other Electronic Nicotinic Delivery Systems (ENDS) usage has risen in the U.S. Vaping devices are marketed as less harmful, safer alternatives to traditional tobacco cigarettes (Regan, A.K. et al. 2021). While initially meant to help smoking cessation in non-pregnant individuals, many young individuals and non-smokers have taken to the devices.

Their introduction to the global market in 2004 stemmed from a Chinese pharmacist, Hon Lik. The production and sale of Electronic Nicotinic Delivery Systems (ENDS) has only since increased and is expected to continue on an upward trend (Chang, Y.S. et al. 2021). Due to the

increase in advertisement, production, and popularity of ECs, consumption among younger individuals remains higher than any other age group, as seen in Figure 2 (Kramarow, E. A., & Elgaddal, N. 2023). The trending use of ECs has been attributed to the different flavors available and the aesthetically pleasing vape cloud (Chang, Y.S. et al. 2021).

Figure 2: Percentage of adults aged 18 and over who currently use E-cigarettes, by age group and sex: United States 2021.



Globally, the number of Electronic Nicotinic Delivery Systems (ENDS) users surpasses 10 million, with most individuals coming from the United States, United Kingdom, France, and larger European countries (Margham, J. et al, 2016). After its debut in the global commercial market, the EC has gained widespread popularity, especially among younger generations. A recent study spanning ten years from 2007 to 2017 revealed that approximately 15% of Expecting mothers in the United States had reported using Electronic Nicotinic Delivery Systems (ENDS) and related devices (Walayat, A., et al 2021).

From the time it was introduced in the United States, this country has been said to have experienced the largest and fastest growth of ECs as well as similar ENDS since 2007 (McCubbin et al., 2017). Between 2009 and 2011, in the United States, the overall awareness of the devices had gone up from16% to 58% thereby raising the number of people who had previously used ECs from just 1.8% in 2010 to13% in 2013 (McCubbin et al., 2017).

The increased percentage of ENDS usage, as seen by the data, encroaches on a demographic inclusive of those who are pregnant. Pregnant EC users, compared to individuals who did not use cigarettes or electronic cigarettes, were more likely to be racially white, younger, less educated, be on Medicaid insurance meaning lower income, and have smoked or used electronic cigarettes during previous trimesters (Kim and Oancea, 2020).

Regulatory Challenges and Legal Frameworks for Electronic Cigarettes

For global tobacco control, the World Health Organization has implemented measures to minimize tobacco usage. MPOWER, the measure that stands to monitor, protect, offer, warn, enforce, and raise, has been a stronghold in regulating the tobacco industry. Through comprehensive guidelines that target tobacco control, there has been a remarkable uptake in procedures across the world in hopes of curbing tobacco use (World Health Organization 2019). Ranging from intervention, monitoring practices, preventive policies, and warnings about potential dangers, displays a global commitment to addressing the multifaceted challenges posed by tobacco use. Encompassing Monitor, Protect, Offer, Warn, Enforce, and Raise, MPOWER since its implementation in 2007 has made advancements in low- and middle-income countries (World Health Organization 2019).

Figure 2: WHO REPORT ON THE GLOBAL TOBACCO EPIDEMIC, 2019

The emergence of ENDS may prove a challenge for MPOWER as these policies are specific to tobacco control. The use of ECs has prompted a reevaluation of policies due to their rapid growth and market expansion. By integrating ENDS into tobacco control policymakers can attempt to regulate these products and safeguard public health.

As different countries begin to create legal frameworks to protect public health, the United States Food and Drug Administration (FDA) has struggled to regulate ENDs since their introduction to the economy. Due to the initial lack of regulations, ECs were able to grow unchecked. However, health concerns, especially for the younger demographic, regarding ENDS quickly became apparent leading to stricter rules and regulations (FDA 2019).

In order "To receive marketing authorization of any new tobacco product, manufacturers must follow one of three pathways. FDA anticipates most manufacturers of ENDS are likely to submit their applications through the Premarket Tobacco Product Application (PMTA) pathway." (FDA 2019) The application by the manufacturer must provide the risks and benefits of use for smokers and nonsmokers and the manufacturing process. (FDA 2019)

Similarly in the European Union, manufacturers and imports of ENDS are required to notify the EU market through a "standardized electronic format" (European Union Commission 2014). The design standard format establishes limits on nicotine concentration and volume, child tamper-resistant features, and spill-preventative designs. Furthermore, the ingredients used in the consumable manufacturing process need to follow strict purity standards and consistent nicotinic dose delivery when the product is used with the same strength and duration of exposure (European Union Commission 2014).

Countries like Singapore have completely banned the sale, possession, and import of ENDS and any heated tobacco product in the country. Gateway effects for nonsmokers, the unknown levels of toxicants, and insufficient research on potential long-term health issues remain a concern for the Singaporean government (Singapore Ministry of Health, 2018). A review noted by the Singaporean Ministry of Health, listed as the Cochrane Review, has found little evidence supporting the use of ECs as effective methods for smoking cessation. A review of

38t studies showed that cigarette smoking quit rates were higher among individuals who did not use ENDS in order to quit than those who did. Currently, “Singapore's Health Sciences Authority (HSA) has not received any applications to register ECs as a therapeutic product for smoking cessation” because there is limited evidence on using ENDS for smoking cessation (Singapore Ministry of Health, 2018).

Electronic Cigarette Use During Pregnancy: Demographics

Based on recent literature pregnant EC smokers exhibit specific demographic and socioeconomic characteristics, are predominantly young, white, and non-Hispanic, are younger than age 25, low income, lack adequate education, and face barriers to quality prenatal care (Hawkins et al, 2021. Kim and Oancea, 2020, Wang et al, 2020). In addition, a significant proportion of EC users report abusive experiences and are diagnosed with depression. Another analysis by Church et al. (2020), based on data collected over a period spanning 10 years from 2007 to 2017 indicated that 15 percent of pregnant women had self-reported EC use during pregnancy. Of these data, the highest percentage of EC use were those of childbearing age (18-34 years). A 2021 UK study reported that of a sample of 750 current pregnant smokers and recent ex-smokers who use ENDS, 12.4% used both ECs and traditional tobacco cigarettes, and 3.5% of the sample only vaped (Bowker et al. 2021). Overall 15.9% of the sampled population had reported using ENDS.

The use stems from ECs and similar devices being marketed as healthier alternatives to tobacco products. This increases their appeal to the public including women who smoke when they become pregnant (Wagner et al. 2017). In a 2016 study utilizing data from the Population Assessment of Tobacco and Health (PATH) study, a U.S. national survey, focusing on women of

reproductive age (18-44) revealed that the use of current ENDS among pregnant women was 6.8%, 75% of the reported users were using both ECs and traditional tobacco cigarettes (Cardenas et al. 2019). Others reported over 50% of the surveyed participants had admitted to using ECs and about 14% of the participants had used them while pregnant (Oncken et al. 2017).

Most pregnant users of ECs began due to the association that EC use would reduce the potential adverse health outcomes brought on by smoking traditional tobacco cigarettes (Calder et al. 2021). The process of "vaping" alone or in tandem with traditional tobacco cigarettes raises health concerns especially for expectant mothers as there is a limited understanding of the factors associated with EC use in pregnant women and their birth outcomes (Lin, S. Y et al. 2023). The compounds and toxicity levels from both traditional tobacco cigarettes and ECs found in research done by (Margham et al. 2016) showed that EC use may be a less harmful alternative to tobacco cigarette smoking. While less harmful, the vapor created from ECs contains toxic compounds. Therefore the use of ECs is not risk-free (Goniewicz et al. 2014) (Margham et al. 2016).

While the use of ENDS as a replacement for traditional tobacco cigarettes may lower overall inhaled toxicants, nicotine is also considered a developmental toxicant. Studies by (Walayat, A., et al 2021) have shown that EC usage can be toxic to cardiovascular function and human embryonic stem cells. Similar findings have been noted in a study testing zebrafish exposure to ENDS where "heart rate decreased following the exposure to E-cig solutions' and deformities were later identified in the heart (Chang, Y.S. et al. 2021).

According to a 2016 - 2018 population-based study of 80,000 birth mothers over two years, the use of nicotine-containing ECs in the last 3 months of pregnancy was found to be associated with adverse birth outcomes and the increased incidence is associated The findings

are significant even when adjusted for other variables such as smoking Effects of inhalation (Regan, A.K. et al. 2021). Prenatal nicotine exposure can have adverse effects on fetal and fetal development, including lung, heart, and brain development, increased risk of low birth weight (LBW), preterm birth, stillbirths, and sudden infant death syndrome (Regan, A.K. et al. 2021).

Overall, the data provided supports the view that Electronic Nicotinic Delivery System (ENDS) usage may be less harmful than tobacco cigarette smoking for otherwise healthy individuals, no level of nicotine consumption during pregnancy is deemed safe (McCubbin, A et al. 2017). “The presence of toxicants in e-cigarette aerosols means that their use is [not] risk-free” (Margham, J. et al, 2016), and expecting mothers should be aware of adverse maternal and fetal health implications associated with tobacco and nicotine consumption in any form. Studying the effects of EC toxicants in animals would showcase various aspects of health and development which would contribute insight to the proposed impacts on consumers. While other clinical trials and treatment studies have been attempted, the disparity of treatments between humans and animals highlights the need to continue human-based research.

Animal vs Human Studies

While data found by (Chang, Y.S. et al, 2021) shows developmental toxicities to zebrafish including damage to the dorsal fins and swim bladder zebrafish are used as a model organism for human development. A study by Barbazuk et. al 2000 shows that zebrafish share significant genetic similarities with humans. Of the 80% of genes analyzed in the study, 56% were found to be “homologous segments.” Homologous segments between two organisms correspond to a common evolutionary ancestor and may show similar genetic variants. In

addition to the genetic similarities, zebrafish, and humans have similar embryonic development making zebrafish important models for the analysis of human mutations (Barbazuk et. al 2000).

As much as animal experiments have undeniably contributed to our overall knowledge of biological sciences, their experimental merits in comparison to humans have been highly debated (Van der Worp et al. 2010). Although informative, the findings from "animal studies do not predict with sufficient certainty what will happen in humans" (Van der Worp et al. 2010). It is important to acknowledge the limitations of experimental animal studies and pursue those that more closely mimic human biology.

For example in animal studies, models of acute ischemic stroke, approximately 500 neuroprotective treatments have been documented to improve overall outcomes. However, the translation of the findings has met with difficulty when translating to human patients. In human clinical trials, "neuroprotective" treatment strategies are limited to aspirin and the administration of recombinant tissue plasminogen activator (alteplase) through very early intravenous thrombolysis (Van der Worp HB, et al. 2010).

The Role of Animal Studies in Assessing the Potential Danger of EC Use During Pregnancy to Embryos and Fetuses

Animals play a large role in assessing potential adverse effects of consumer goods, such as testing ENDS aerosols in laboratories instead of human subjects. While experimental human trials on pregnant women are deemed unethical, animal studies can provide useful data that may protect Public Health. According to (Yvan et al. 2006) experiments on animals are done to advance knowledge in terms of healthcare and public wellness. Models such as zebrafish

embryos, mice, and rats have been subjects of ENDS exposure resulting in an array of negative birth outcomes.

According to Table #1, outlining the effects of the EC exposure on animal offspring, many offspring had low birth weights (LBW) (Cahill et al., 2022)(Nguyen et al., 2019)(Chen et al., 2018) (Church, Jamie S. et al. 2020), oxidative stress biomarkers (Cahill et al., 2022)(Al-Sawalha et al, 2020), impaired memory (Al-Sawalha et al, 2020)(Nguyen et al., 2019), increased disease susceptibility, impaired brain development (Church, Jamie S. et al. 2020), and much more.

A study on EC's effects on zebrafish embryos revealed that high concentrations of EC aerosols damaged hair cells and induced developmental toxicities to the dorsal fin, swim bladder, and heart (Chang, Y.S. et al, 2021). These findings highlight the importance of utilizing animal models to uncover potential risks associated with toxicant screenings. It is critical to note that while ENDS may have a reduced toxic exposure profile compared to tobacco cigarettes, risks associated with their use, especially during pregnancy remain a concern. As research is limited, there is little in-depth knowledge about the developmental and long-term effects of exposure to EC toxicants.

However, new findings indicate that exposure to chemicals associated with vape juice and e-liquids before birth, particularly nicotine found in vapes, could potentially harm the developing fetus. Studies have highlighted higher levels of DNA methylation, developmental delays, photosensitivity, motor defects, and brain damage, indicating neurological impairments caused by nicotine in animals Gauthier et al. 2020, Al-Sawalha et al. 2020, Chen et al. 2018, Nguyen et al. 2018, Sifat et al. 2020, Svodoboda et al. 2002).

A recent animal study reported that offspring from mothers exposed to ECs and similar ENDS devices) have reports of health defects. This includes but is not limited to short-term memory deficits, reduced anxiety, and hyperactivity. Physical markers of the study show increases in global DNA methylation in the brain, impaired lung development, reduced crown-rump length, reduced fetal weight, and increased oxidative stress and inflammation (Regan, A.K. et al. 2021). All show a measure of limited fetal growth and a marker of decreased uterine and fetal umbilical blood flow.

Due to the similarities in the genetics of model animal systems, humans are hypothesized to be affected in similar ways if exposed to the same compounds. The harmful effects found in animal studies suggest a "biologically plausible relationship" between exposure to the toxicants produced by ECs and similar ENDS and adverse birth outcomes in humans (Regan, A.K. et al. 2021).

Due to experimental constraints, data from some literature comes from cell experimentation. Conclusions from a study testing human embryonic stem cells (hESC), mouse neural stem cells (mNSC), and human pulmonary fibroblasts (hPF) reported that stem cells obtained from embryos (hESC) and newborns (mNSC) demonstrated greater sensitivity to refill solutions when compared to differentiated adult lung fibroblasts (Bahl, et al, 2012). Compounds such as "Cinnamon Ceylon were highly potent for the three cell types and would likely present more risk than flavors such as Bubblegum which had low cytotoxicity for all cells" (Bahl, et al, 2012). Although this work is informative, it falls short of showcasing true outcomes in human subjects.

In some studies in Table #2, the association between EC use during pregnancy and perinatal outcomes is evident, with possible adverse outcomes such as preterm delivery, low

birth weight (LBW), and the small-age (SGA) incidence of newborns significantly higher than in non-smokers (Regan et al, 2021. Regan and Pereira, 2021 Froggatt et al, 2020). Other studies did not find significant differences in preterm delivery, low birth weight (LBW), and the small-age (SGA) incidence of newborns (McDonnel et al., 2020. Kim and Oancea, 2020). Of the studies that reported significant differences, daily EC users show the strongest association with adverse outcomes, whereas dual users, who use traditional cigarettes and EC demonstrates a higher prevalence of LBW and SGA births based on baseline characteristics affecting birth outcomes (Regan and Pereira, 2021. McDonnel et al., 2020. Wang et al, 2020).

Despite efforts to match sole EC users with smokers using tobacco cigarettes, adverse outcomes are more common among traditional cigarette users (Kim and Oancea, 2020). Notably, using EC increases the likelihood of side effects in children born from mothers who use them compared to abstainers (Kim and Oancea, 2020). In addition, a study published by BP McDonnell involved a prospective observational cohort of pregnant women undergoing antenatal care examined to measure newborn birth weight. The study concluded that EC users and non-users had comparable infant birth weights. Other studies report that infants born to EC users compared to infants born to nonusers have lower birth weights. Much of the reported data does not factor in the choice of e-cigarette flavors, particularly menthol, peppermint, or candy flavors which have been seen to increase the percentages of fetal death (Lin et al. 2023, Cardenas et al. 2019).

Considering the varied perspectives, an online journal article titled Vaping in Pregnancy: A Systematic Review of 23 Studies came to the conclusion that vaping has fewer adverse effects than traditional tobacco cigarette use. While it is mentioned that EC use was intended for nonpregnant use the paper also states that “pregnant mothers who struggle with smoking

cessation could benefit from using vaping products in attempts to quit smoking". Otherwise, ECs are not intended to be used (Calder, R. et al, 2021). The conflicting literature and complexity between EC use and smoking cessation in pregnant individuals sets a scene for a more nuanced exploration of the subject.

Conclusion and need for future research

The comprehensive review assessing the impact of prenatal EC exposure on embryos and fetuses comparing human and animal studies provides recent data detailing potential risks associated with EC use. Findings from both human and animal studies show evidence of adverse health effects on the offspring of exposed mothers including but not limited to low birth weights, oxidative stress biomarkers, impaired cognitive functions, impaired lung function, and overall reduced fetal health.

While humans and animals differ in biology, current experimental research depends on studying the genetic makeup and mechanistic pathways of model animals. The use of animal models such as zebrafish, rats, and mice for EC testing due to genetic and functional similarities allows for the advancement of theoretical outcomes in humans. While consideration is needed to align the discrepancies between human and animal data, the underlying understanding of the effects on children born to mothers exposed to EC provides the groundwork for future research.

Although animal studies have allowed for the exploration of the subject, the need for human studies remains a vital piece in practical applications. The interdisciplinary literature stands to inform the public but with proper research maternal and fetal health may suffer. Additional research on human subjects is necessary to gain a full understanding of the effects on maternal, embryonic, and fetal health posed by ECs or ENDS usage during pregnancy.

Table #1: Prenatal Electronic Cigarette Exposure in Animal Studies

Author(s) + year	Model Studied	Method of Exposure	Results/Outcomes
Cahill et al., 2022	female BALB/c mice using JUUL, a fourth-generation ENDS device	"JUUL group" mice were exposed to mint-flavored JUUL aerosol for 1 hour per day for 20 consecutive days during gestation. exposures ceased before the birth of offspring on day 21 (PND0). "Air group" mice served as control exposed to HEPA-filtered air for the same duration as the JUUL group.	- Mint-flavored JUUL aerosol exposure causes oxidant/antioxidant imbalances in the uterine and placenta. - Placental 11-beta-hydroxysteroid dehydrogenase-2 (HSD2) enzyme expression was decreased in exposed offspring - Dysregulation of 27 genes related to oxidative stress and hypoxia was observed in exposed dams - Pathway analyses of these dysregulated genes were associated with vasoconstriction of blood vessels, placental morphology, placental diseases, and pregnancy disorders. - Offspring exposed to mint-flavored JUUL aerosol in utero had decreased birth length and weight - the birth weight of in-utero JUUL-exposed offspring was, on average, 10.2% lower than that of air-exposed offspring. - Exposure to JUUL aerosol in utero significantly altered lung tissue-to-airspace fraction in offspring at birth, indicating an effect on lung development. - JUUL aerosol exposure during pregnancy dysregulated expression of 7 inflammatory markers in lungs of dams and offspring at birth. - expression of certain inflammatory markers was up-regulated in both dams and offspring exposed to JUUL aerosol, indicating a pro-inflammatory response. - In utero exposure to mint-flavored JUUL aerosol affected the expression of Wnt signaling and epigenetic chromatin modification genes in the lungs of offspring at birth. - Dysregulated genes were associated with important processes in lung development and gene regulation. - Exposure to mint-flavored JUUL aerosol in utero significantly altered the expression of asthma and allergy-related genes in the lungs of adult 11-week-old offspring. - In offspring exposed to JUUL aerosol in utero and challenged with house dust mites (HDM) as adults, significant up-regulation of asthma-related genes was observed. - Epigenetic chromatin modification genes were affected in the lungs of offspring exposed to mint-flavored JUUL

			aerosol in utero, both at birth and at 11 weeks of age. - One gene, Prmt8, was consistently down-regulated from birth to adulthood in both male and female offspring. - The methylation status of the Il-10ra gene was altered in female offspring exposed to JUUL aerosol in utero and treated with HDM as adults. Overall, the study found that in-utero exposure to mint-flavored JUUL aerosol had various adverse effects on pregnancy, offspring development, lung function, and gene expression, and it exacerbated responses to allergens in adulthood.
Chang et al., 2021	Zebrafish embryos	- Zebrafish embryos housed in 15 mM sodium chloride, 0.5 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium sulfate, 0.15 mM monopotassium phosphate, 0.05 mM ammonium phosphate, and 0.7 mM sodium bicarbonate mix at 28.5 C - E-cigarette (E-cig) solution: tobacco-flavored E-cig liquid (specifically, MAG7 Black label, Rayben) - E-Cig concentrations: 0.1%, 0.2%, 0.4%, 0.8%, and 1.0%.	- Abnormal tail development with higher concentrations of E-cig solution. - Decrease in rate of swim bladder development at higher concentrations of E-cig solution. (Neurological damage may affect swim bladder development) - The mortality rate of zebrafish embryos was significantly increased at higher concentrations of E-cig solution. - LD50 (lethal dose for 50% of organisms) of E-cig solution was determined to be 0.4%
Gauthier et al., 2020	Zebrafish embryos	- Adult Zebrafish (mothers) were kept in 10-liter polypropylene tanks with a specific light cycle and were fed a specific diet - Beginning at 31.5 hpf, embryos were exposed to various dilutions of VAEs (ranging from 0.01% to 10%) - Vape aerosol extracts generated from third-generation E-cigs. - 3ml of 6 vape e-liquids, including unflavored, cinnamon, and blue raspberry, each with and without nicotine up to 12 mg/ml	- Embryo photosensitive startle responses (PMRs) were recorded. PMR trials were 30 seconds long and were conducted in total darkness, except for a brief light pulse at 10 seconds. - Zebrafish embryos exposed to dilutions of flavorless nicotine VAPE: 1% and 5% dilutions increased basal activity, while 10% dilution resulted in severe hypoactivity. These effects were not observed in flavorless nicotine-free VAPE, indicating that nicotine was responsible for these neurobehavioral effects. - Photosensitivity decreased with increasing VAE concentration, suggesting impaired sensory perceptions and that higher concentrations of nicotine in VAEs could lead to neuromuscular dysfunction - Both the blue raspberry and cinnamon VAEs decreased photosensitivity similarly to nicotine. - Nicotine-induced hypoactivity was partly or completely abolished by the hyperactive effects of blue raspberry and cinnamon flavors - Combining nicotine with flavorings generally produced additive effects on both activity and photosensitivity.

			- Pure cinnamaldehyde: Lower concentrations (0.01% v/v) of cinnamaldehyde caused hyperactivity and reduced photosensitivity. Higher concentrations (0.1%, 1%, and 10%) resulted in severe hypoactivity and complete abolishment of photosensitivity. - These findings indicated that pure flavoring at specific concentrations found in vapes may be neurotoxic to developing embryos.
Svoboda et al, 2002	Zebrafish embryos	- Embryos were exposed to nicotine and nicotine receptor antagonists - In experiments involving nicotine concentration (0-33 μm) was added to embryo medium with 0.002% 1-phenyl-2 thiourea (PTU) to inhibit pigment formation - In experiments involving nicotinic receptor antagonists (e.g., MLA and DHβE), the antagonist was applied 2 hours before nicotine exposure - Embryo media with nicotine and/or antagonists was refreshed/ replaced every 24 hours.	- Nicotine exposure during embryonic development had significant effects on zebrafish behavior, motoneuron development, and neuronal marker expression. - exposure led to functional paralysis, delayed motor neuron differentiation, and abnormal persistence of neuronal markers, indicating an impact on neurological development - Embryos exposed to 33 μm nicotine were functionally paralyzed at 42-120 hours post fertilization - At higher concentrations, there were more profound effects in the reduction of the number of GFP-positive motoneurons and delayed axonal development - antibodies zn5 and znS5 were used to label spinal neurons. At 42 hpf: nicotine exposure had no apparent effect At 66 hpf: nicotine exposure led to the persistence of neuronal markers in spinal neurons, indicating a delay in development
Al-Sawalha et al, 2020	Female Wistar rats	- Exposure during gestation and days 4-21 of lactation: (male offspring) - 2 groups: Fresh air (control) and E-cigarette aerosol - E-cigarette aerosol composed of 70:30 propylene glycol (PG) to vegetable glycerol (VG) with 18 mg/ml nicotine to mimic commonly available commercial liquids - At whole body exposure device was programmed to produce one 4-sec duration puff of volume 116.7 ml every 10 seconds, for one hour each day from day 4-21	Brain: oxidative stress biomarkers Learning and spatial memory (Radial arm water maze) - ECIG aerosol exposure during gestation and lactation did not significantly affect the learning phase in adult male offspring rats - Exposure to E-CIG aerosol increases the activity of superoxide dismutase (SOD) in the hippocampus of adult male offspring. (SOD: antioxidant enzyme that combats oxidative stress) - No significant effects were observed in catalase and glutathione peroxidase (GPx) activities (antioxidant enzymes) and thiobarbituric acid reactive substances levels (TBARS). - EC exposure did not affect levels of Brain-derived neurotrophic factor (BDNF) in the hippocampus - Impaired long-term memory in adult male offspring: Associated with increased activity of SOD
Chen et al., 2018	BALB/C female mice	- Female mice were exposed to sham (room) air, and e-cigarette aerosols with or	Nicotine-exposed groups had significant increases in mRNA levels of Neuropeptide Y and inducible nitric oxide synthase in the brain.

		without nicotine (18 mg/ml) for six weeks before and during gestation and lactation - Exposure conducted in a chamber filled with e-cigarette fluid aerosols generated e-cigarette device of two 15-minute exposures per day (equivalent to nicotine exposure of two tobacco cigarettes) - Cotinine levels were measured in the blood of offspring to assess nicotine exposure.	E-cig 0 mothers had significantly lower weight gain than controls. E-cig 18 mothers had similar weight gain to the control group. No significant differences in liver weight between the three groups. Retroperitoneal fat mass was significantly reduced in both E-cig 18 and E-cig 0 mothers Proinflammatory cytokine IL-1β increased in E-cig 18 mothers. IL-6 increased in E-cig 0 mothers. TNF-α levels more than tripled in both E-cig 18 and E-cig 0 mothers. E-cig 0 exposure upregulated total Erk1/2 and total JNK in mothers. E-cig 18 upregulated total JNK. Phosphorylated JNK was increased in E-cig 0-exposed mothers. There are no significant differences in body weight or organ weight at P1. At P20, E-cig 0 offspring were heavier than both control and E-cig 18 offspring. E-cig 18 offspring had reduced body weight at P20. Liver weight as percentage of body weight was increased in E-cig 18 offspring at P20. Retroperitoneal fat mass was increased in both E-cig 18 and E-cig 0 offspring at P20. Epididymal fat mass was increased in E-cig 0 offspring compared to both control and E-cig 18 offspring at P20. PDGF mRNA levels were significantly upregulated in E-cig 18 and E-cig 0 offspring at P20. IL-1β protein levels were suppressed in both E-cig 18 and E-cig 0 offspring at 13 weeks. TNF-α protein levels were significantly increased in both E-cig 18 and E-cig 0 offspring at 13 weeks. IL-6 levels were increased in the E-cig 0 group at 13 weeks. Total Erk1/2 and total JNK protein levels were differentially affected by E-cig0 and E-cig 18 exposure. Phosphorylated forms of JNK and Erk1/2 were altered by exposure to E-cig 0 and E-cig 18. Global DNA methylation was increased in both E-cig 0 and E-cig 18 offspring's lungs. Increased expression of inflammatory cytokines, including IL-5, IL-13, and TNF-α, in E-cig 0 offspring at P1.
Church et al., 2020	Female CD-1 Mice	During pregnancy - Filtered air - 50/50 Propylene Glycol and Vegetable Glycerine - Propylene Glycol and	+ Nic: Elevated locomotor activity in offspring - Nic: Lower object discrimination score Reduced interleukin (IL)-4 and interferon-gamma (IFNγ) in diencephalon

		Vegetable Glycerine with 16 mg/mL Nicotine -Whole-body exposure	Low levels of hippocampal IFNγ (females only) - Nic: 2-fold increase of IL-6 in cerebellum.
Nguyen et al., 2018	BALB/C female mice	- Exposure to females before pregnancy, during pregnancy, and lactation: 3 groups: ambient air, E-cigarette aerosol with nicotine (+Nic), and E-cigarette aerosol w/out nicotine (-Nic) - 24 female Balb/C mice were used, with a 12-hour light-dark cycle, and were divided into three experimental groups: Sham, Ecig(+nic), and Ecig(−nic). - Short-term memory was evaluated using NOR test, while anxiety and exploratory behaviors were assessed using the EPM test. - Offspring were euthanized at different time points: D1, D20, and week 13. - Brain tissues were collected and analyzed for genomic DNA and total RNA. - Global DNA methylation was measured with an ELISA kit to detect 5-methylcytosine (5-mC). - Epigenetic PCR array and gene expression analysis were performed using RNA samples, with GAPDH as the reference gene. - Statistical analysis included unpaired two-tailed t-tests for NOR test data and one-way ANOVA with Bonferroni's post-hoc test for EPM, DNA methylation, and gene expression data. - The study followed ethical guidelines and aimed to explore the effects of maternal exposure to e-cigarette aerosols with and without nicotine on offspring behavior and epigenetic	- EC exposed groups with nicotine showed short-term memory deficits. - EC exposed groups with or without nicotine showed reduced anxiety levels in the Elevated Plus Maze (EPM) test. - EC exposed groups without nicotine exhibited higher global DNA methylation at postnatal day 1 (D1) and day 20 (D20) - Significant differences observed in genes related to DNA methylation, histone-lysine demethylation, histone acetylation, and histone phosphorylation exposed brains - behavioral and epigenetic changes including short-term memory deficits and increased anxiety

		changes, conducting multiple assessments and analyses to draw conclusions regarding these exposures.	
Nguyen et al., 2019	BALB/C female mice	Before pregnancy, during pregnancy, and lactation: - ambient air - Tobacco cigarettes - Tobacco cigarettes Switched to e-cigarette aerosol (during gestation) Maternal exposure to e-cigarette aerosols after prior smoke exposure had no significant impact on litter size. Both previous smoke exposure and current e-cigarette aerosol exposure resulted in consistent cotinine levels in mothers and offspring. Offspring born to mothers who switched to e-cigarette aerosol or continued cigarette smoke exposure during pregnancy had lower birth weights. Switching to e-cigarette aerosol exposure led to memory changes and increased hyperactivity in offspring. Switching to e-cigarette aerosol exposure reduced global DNA methylation in offspring. Offspring from mothers who switched to e-cigarette aerosol exposure showed altered mRNA expression of chromatin-modifying genes. Tobacco smoke exposure during pregnancy reduced neuronal counts in the hippocampus of adult offspring, but this effect was not observed with e-cigarette exposure, suggesting potential differences in neurodevelopmental impacts.	- EC exposed groups did not impact on the size of litters - Previous and current smoke exposure to EC aerosols showed similar cotinine levels in mothers and offspring - Offspring born to mothers who switched to EC exposure or were only exposed to cigarette smoke during pregnancy had lower birth weights - When mothers switched to EC exposure offspring displayed changes in memory and increased hyperactivity - When mothers switched to EC exposure offspring showed reduction in global DNA methylation - When mothers switched to EC exposure offspring exhibited alterations in mRNA expression of key chromatin-modifying genes - Adult offspring exposed to tobacco smoke as fetuses had reduced neuronal counts in the hippocampus (not observed in those exposed to e-cigarettes)
Sifat et al, 2020	CD1 female mice	- 3 groups of mothers were exposed to GD5 to PD7:	- Neuron viability, glucose utilization - Neurologic outcome (negative geotaxis reflex test:

		Room air, Vaping e-cigarettes with nicotine, and Vaping e-cigarettes without nicotine	motion of an organism in response to gravitational force.) - maternal exposure to e-cigarette vapor containing nicotine can heighten the susceptibility of offspring to neonatal brain damage from hypoxia-ischemia (HI) and negatively affect their motor and cognitive abilities during adolescence. Additionally, it is the first study to reveal that prenatal e-cigarette exposure can reduce offspring brain glucose utilization and expression of glucose transporters after HI brain injury. These findings suggest that nicotine and e-cigarette exposure may contribute to worsened short- and long-term outcomes in this context.
Walayat et al., 2021	Time-dated pregnant Sprague-Dawley rats	- System delivery: Puff duration 4 seconds, 3 puffs in 30-second intervals per episode 1 episode per hour in a dark phase of 12 hours each day - Chronic intermittent e-cigarette (CIEC) exposure: E-cig exposure mimicked human vaping patterns with puff duration, inter puff interval, and frequency. - Two groups: one exposed to e-cig aerosol (2.4% nicotine) and the other to fresh air (control). - Exposure from gestational day 4 (E4) to gestational day 20 (E20) - Neonatal offspring at postnatal day 9 (P9) anesthetized and performed neck incision, carotid artery ligation, and hypoxia. - P7 pups received ATG5 siRNA or siRNA scramble via intracerebroventricular injection into the right lateral ventricle. Burr hole sealed with bone wax, and wound closed with sutures.	- Growth restriction: reduced brain and body weight - Programs Brain Hypoxic-Ischemic Sensitive Phenotype in Neonates - Increased ROS - Enhanced DNA methylation in neonatal brain - E-cigarette exposure reduced both body weight and brain weight in male and female neonatal pups - E-cigarette exposure caused significant increase in HI-induced brain infarction size in male and female neonatal pups although it was not statistically significant in females - Maternal EC exposure significantly increased ROS production and upregulated protein levels of ROS-associated enzyme NADPH oxidase 2 (NOX2) in neonatal offspring brains. - E-cigarette exposure - E-cig exposure affects DNA methylation profiles in the neonatal brain, with differential effects on DNMT1, DNMT3β, global DNA methylation, and CpG islands methylation at the ATG5 gene promoter region. - E-cigarette exposure significantly suppressed protein levels of ATG5 and LC3β-1/LC3β-2, indicating suppression of autophagic flux in both male and female neonatal brains. - Protein levels of sirtuin 1 (Sirt 1) were also significantly attenuated in both male and female neonatal brains in the e-cigarette-exposed group. - Administration of ATG5 siRNA significantly reduced ATG5 protein levels in neonatal rat brains. Downregulation of ATG5 protein exacerbated HI-induced brain injury in neonates.

Table #2: Prenatal Electronic Cigarette Exposure in Human studies

Author (year)	Study Region	Study Material	Groups	Outcomes
Bahl et al. 2012	United States	Human embryonic stem cells (hESC), mouse neural stem cells (NSC), and human pulmonary fibroblasts (hPF) were exposed to e-cigarette refill liquid		Cytotoxicity was observed excluding hPF cells
Hawkins et al, 2021 Journal of Maternal-Fetal & Neonatal Medicine	United States	2016 - 2017 PRAMS Cross-sectional analysis of 57,046 respondents from 32 US states. Data collected from the 2016-2017 Pregnancy Risk Assessment Monitoring System. Respondents reported their use of electronic nicotine delivery systems (ENDS) and cigarettes during the last 3 months of pregnancy. study linked this self-reported data with birth outcomes recorded on birth certificates. Key birth outcomes examined included birth weight, gestational age, whether baby was small-for-gestational age, and whether the birth was preterm.	- None (153) - ENDS only (301) - Dual use (529) - Cigarettes only (5063)	- Pregnant E-cigarette users were more likely to be young (36.2% under 25 y/o), White (85.9%), and Non-Hispanic (93%). - Often low income (71.8%), uneducated (38.6%), no adequate prenatal care (20.2%), victims of abuse(19.4%), and diagnosed with depression (38.1%). - unfavorable birth outcomes increased by 62% among pregnant e-cigarette users - Other characteristics associated with significant odds of unfavorable birth outcomes included ages under 19, being African-American or Asian, receiving adequate prenatal care, and reporting high blood pressure during pregnancy. - Conversely, the odds of unfavorable birth outcomes decreased by 12% among women who received some level of higher education
Regan et al, 2021	United States	2016 - 2018 PRAMS Study used 2016-2018 PRAMS data. Investigated e-cigarette use during pre-pregnancy and pregnancy. Included 79,176 recent births, assessing preterm birth, small for gestational age, and LBW. Calculated adjusted prevalence ratios with regression models.	Among smokers (during pregnancy): - E-cigarette use before pregnancy (132) -dual-use (132) -nonuse of e-cigarettes (1203) Among nonsmokers (during	Birth outcomes: preterm birth, LBW, SGA neonates 2.7% used e-cigarettes before pregnancy; 1.1% during the last 3 months of pregnancy. No adverse effects relating to EC use before pregnancy. E-cigarette use during pregnancy is associated with increased LBW and preterm birth Daily e-cigarette users showed strongest associations with adverse outcomes.

		Stratified models by prenatal smoking and e-cigarette use frequency.	pregnancy): - E-cigarettes use before pregnancy (241) - E-cigarette use during pregnancy (73) -nonuse of e-cigarettes (9795)	
Regan and Pereira, 2021	United States	2016 - 2018 PRAMS study analyzed 2016-2018 PRAMS data on pregnancy and birth outcomes. Investigated associations between e-cigarette use before and during pregnancy and birth outcomes. Focused on women who smoked combustible cigarettes before pregnancy, had complete data. Defined exposure based on self-reported combustible and e-cigarette use. Examined birth outcomes: preterm birth, small-for-gestational-age, low birthweight. Considered covariates like maternal age, education, and pregnancy intention. Analyzed data from 38 PRAMS sites, weighted for nonresponse and complex sampling. Used SUDAAN software to calculate adjusted prevalences and prevalence ratios. Funding source had no involvement in study.	- Former smokes (8938) - E-cigarette only users (189) -Dual users (585) -Current smokers (6310)	16,022 pregnancies were included out of 20,547 responses During pregnancy: Of those who smoked cigarettes before pregnancy, 14.8% also used e-cigarettes, 44.4% quit smoking but used e-cigarettes. 42.8% of dual users continued using e-cigarettes 60.4% of CC smokers quit smoking during pregnancy. Of the birthing data collected 8.9% were preterm, 13.7% were small-for-gestational-age, and 8.4% were low birthweight. Dual users had higher prevalence of low birthweight and small-for-gestational-age births E-cigarette only users had higher prevalence of low birthweight births and dual users didn't show significant differences in adverse birth outcomes compared to current smokers.
Froggatt et al, 2020	United Kingdom	A cohort assessing fetal and infant behavioral development	- Nonexposed (44) - Cigarette-exposed (29)	- Birth outcomes: birthweight, head circumference, and Apgar score - Neurobehavioral outcomes: orientation, motor maturity, range states, regulation,

		The study included 83 infants divided into three groups: prenatal exposure to cigarettes, prenatal exposure to e-cigarettes, and no prenatal exposure. Birth outcomes and Neonatal Behavioural Assessment Scale (NBAS) scores at one month of age among groups.	- E-cigarette exposure (10)	and automatic stability (NBAS) Cigarette-exposed had lower birth weights and smaller head sizes. Significant differences were found in neurobehavioral outcomes (reflexes, motor maturity, and regulation) Correlations were noted between years of maternal smoking prior to conception and neurobehavioral outcomes. Pairwise comparisons revealed differences in reflexes and motor maturity between non-exposed and cigarette-exposed infants. After adjusting for maternal depression, significant differences persisted in reflexes Pairwise comparisons showed differences in regulation between non-exposed and cigarette-exposed infants but no significant differences between e-cigarette-exposed and cigarette-exposed infants. Controlling for maternal age and maternal depression led to marginal effects on motor maturity.
Kim and Oancea, 2020 NIH PubMed	United States	2016 - 2018 PRAMS - The initial study sample had 55,251 women who met study criteria. - Most participants were complete abstainers (94.80%), followed by exclusive CC smokers (4.62%), and exclusive EC users (0.58%).	- First hypothesis: Exclusive EC use during the third trimester affects birth outcomes (SGA, LBW, preterm birth). - Second hypothesis: Risks of using ECs during pregnancy are not significantly lower than smoking CCs. - Complete abstainers (51430) - Exclusive e-cigarette users (337) - Exclusive smokers (3484)	- Compared to complete abstainers, EC users were more likely to be White, younger, less educated, have lower incomes, and have smoked during previous trimesters - Prenatal care adequacy did not significantly differ between EC users and complete abstainers - Compared to CC smokers, EC users were younger, more educated, had higher incomes, received appropriate prenatal care, and did not smoke during previous trimesters - Adverse outcomes were generally higher among tobacco users. - However, rates of pregnancies of EC users resulting in SGA, LBW, or preterm birth were not significantly higher than complete abstainers - Rates of neonates being born SGA and preterm were not significantly different among EC users - rate of infants with LBW was significantly lower among EC users - Adverse outcomes were more common among non-abstainers.

				- Even after matching EC users and complete abstainers based on baseline characteristics affecting birth outcomes, adverse outcomes remained more common among EC users. - odds of adverse outcomes were significantly higher among EC users compared to abstainers: SGA, LBW, and preterm birth. - Using ECs during the third trimester did not show significantly lower odds of adverse outcomes compared to smoking CCs when comparing EC users and CC smokers. No significant differences were observed in SGA, LBW, or preterm birth between CC smokers and EC users.
McDonnel et al., 2020 BJOG: An International Journal of Obstetrics & Gynaecology	Ireland	- cohort assessing fetal and infant behavioral development - This is a prospective cohort study conducted at a large urban maternity hospital that delivers approximately 8,500 infants annually.	- Exclusive EC users were compared with two groups: smokers (defined as those currently smoking at least one cigarette per day) and non-smokers (defined as those who have never smoked). - Exclusive e-cigarette users (218) -Dual users (195) -Smokers (99) -Nonsmokers (108)	- Infants born to EC users had a mean birth weight of 3470 g, similar to non-smokers (3471 g) and significantly greater than smokers (3166 g). - Mean customized birth centile of EC users was equal to non-smokers (47th centile) and significantly greater than smokers (27th centile). - EC users had significantly lower incidence of low birth weight than smokers (11% versus 28%). - There was no significant impact of age, ethnicity, parity, and socio-economic status on birthweight comparisons between EC users and smokers or EC users and non-smokers. - Mean gestation at delivery was similar among EC users, dual users, smokers, and non-smokers. - Mean Apgar scores in neonates and admission rates to neonatal intensive care units were similar across three groups. - EC users had significantly higher breastfeeding rates at discharge than smokers (48.6% versus 27.2%), but lower than non-smokers (61.1%). - Dual users had obstetric outcomes similar to smokers, including mean birthweight and breastfeeding rates at discharge.
Wang et al, 2020 NIH PubMed	United States	2016 PRAMS Pregnancy Risk Assessment Monitoring System	-Nonsmokers (28770) -Sole smokers	- In 3 months before pregnancy, 6005 mothers smoked cigarettes, with 5029 (84% of smokers, 14% of all mothers) exclusively smoking tobacco cigarettes

		- Participants were asked about their use of e-cigarettes or other electronic nicotine products during 3 months before pregnancy and the last 3 months of pregnancy. - Participants were also asked about cigarette smoking during these two time periods.	(2632) -Sole vapers (126) -Dual users (265)	("sole smokers"), and 976 mothers (16% of smokers, 3% of all mothers) both smoking and using e-cigarettes ("dual-users"). - 267 mothers (1% of all mothers) exclusively vaped in 3 months before pregnancy. -Pre-pregnancy sole smokers: 55% stopped using tobacco products, 43.6% continued to smoke, 0.3% switched toECs, and 1.0% became dual-users - Pre-pregnancy dual-users: 49% quit, 25.9% switched to smoking, 6.8% switched to vaping, and 18.4% did not change. - Dual-users had a higher percentage of young, low-educated, non-Hispanic White, and unmarried mothers. They were more likely to have unhealthy BMIs and consume alcohol - Prenatal care varied: users were less likely to receive adequate prenatal care. - A similar comparison was made for pre-pregnancy dual-users by their behavior in late pregnancy. Those who switched to only vaping had higher education levels and were more likely to receive adequate prenatal care. - Late-pregnancy sole smokers had higher odds of preterm birth and SGA - Mothers who solely vaped in late pregnancy had risk of preterm birth that was not significantly different from non-users but they exhibited an elevated risk of SGA - Late-pregnancy dual-users had similar risk of preterm birth but an elevated risk of SGA
Cardenas et al., 2019 NIH PubMed	United States	- study utilized data from Population Assessment of Tobacco and Health (PATH) study, U.S. national survey. - study focused on women of reproductive age (18 to 44 years old) who were pregnant - The final sample included 1,130 women to examine factors affecting changes in e-cigarette use before and	- Any current ENDS use (23) - Current ENDS dual users (17) - Current ENDS (6) - Current cigarette smokers (56)	- Those who did not smoke before were less likely to use e-cigarettes while pregnant - Those who smoked during pregnancy were more likely to use e-cigarettes while pregnant - Perception was a predictor of EC use during pregnancy. - history of e-cigarette use was associated with higher risk of high-risk birth

		during pregnancy. - Among this group, 597 women had birth information available to evaluate association between e-cigarette use and birth outcomes, including 488 with normal births, 75 with high-risk births, and 34 with fetal deaths. - Patients treated at prenatal clinical service serving low-risk pregnant women	- Secondhand smoke/aerosol (45) - Use other tobacco products (11) - Unexposed (97)	- African American women were less likely to initiate vaping compared to White women but were more likely to experience fetal death - use of menthol, mint, or candy e-cigarette flavors before and during pregnancy, compared to other flavors, was associated with higher odds of fetal death

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