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Adverse effects of perinatal nicotine exposure on reproductive outcomes

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Abstract

Nicotine exposure during pregnancy through cigarette smoking, nicotine replacement therapies or e-cigarette use continues to be a widespread public health problem, impacting both fetal and postnatal health. Yet, at this time, there remains limited data regarding the safety and efficacy in using these nicotine products during pregnancy. Notably, reports assessing the effect of nicotine exposure on postnatal health outcomes in humans, including reproductive health, are severely lacking. Our current understanding regarding the consequences of nicotine exposure during pregnancy is limited to a few animal studies, which do not comprehensively address the underlying cellular mechanisms involved. This paper aims to critically review the current knowledge from human and animal studies regarding the direct and indirect effects (e.g. obesity) of maternal nicotine exposure, regardless of its source, on reproductive outcomes in pregnancy and postnatal life. Furthermore, this review highlights several key cellular mechanisms involved in these adverse reproductive deficits including oxidative stress, inflammation, and endoplasmic reticulum (ER) stress. By understanding the interplay of the cellular mechanisms involved, further strategies could be developed to prevent the reproductive abnormalities resulting from exposure to nicotine *in utero* and influence informed clinical guidelines for pregnant women.

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Introduction

Despite increased awareness of its detrimental effects, ~10–23% of pregnant women continue to smoke worldwide, with rates higher than 50% in some communities (i.e., Northern Territories in Canada) (Tong *et al.* 2013, Cui *et al.* 2014). Among women who attempt to quit smoking during pregnancy, it is reported that only half will successfully abstain; the steep rates of relapse are partly attributable to the highly addictive nature of nicotine in cigarettes (Tong *et al.* 2013, Orton *et al.* 2014). However, maternal exposure to nicotine during pregnancy is not only restricted to cigarette smoking. Various nicotine-based pharmacotherapies for smoking cessation have been developed (i.e., nicotine replacement therapy (NRT)) and their usage have been considered beneficial for those struggling with heavy dependence (Myung *et al.* 2012). Non-combustible smoking alternatives containing nicotine (i.e., e-cigarettes) have also increased in popularity within recent years, especially among adults of reproductive age (Carroll Chapman & Wu 2014). The effects of maternal nicotine exposure alone have been long

overlooked in comparison to the health risks of tobacco smoking; however, there is currently insufficient evidence to verify the safety and efficacy of using these nicotine-containing products during pregnancy (Coleman *et al.* 2011, Coleman *et al.* 2012a, De Long *et al.* 2014). In fact, there is increasing evidence suggesting that maternal exposure to nicotine alone can lead to many deleterious consequences in the fetus, necessitating a more comprehensive evaluation of the long-term health effects on the offspring (Bruin *et al.* 2010). Alarmingly, a recent survey reported that 47% of obstetricians/gynecologists inconsistently screen their pregnant patients for exposure to these non-combustible tobacco products, and only 5% felt fully informed of the potential side effects (England *et al.* 2014). Therefore, this paper aims to critically review the current knowledge available on the effects of maternal nicotine exposure from recent human and animal studies. We are specifically interested in investigating the long-term reproductive health outcomes of offspring exposed to nicotine *in utero*. Furthermore, we will review some of the major cellular mechanisms involved, including oxidative stress, inflammation, and endoplasmic

reticulum (ER) stress, which are suggested to underlie nicotine-induced impairments in pregnancy and reproductive organ function.

Pharmacology of nicotine

The use of nicotine during pregnancy is especially concerning because it may directly impact fetal organ development. Nicotine can easily traverse membrane barriers due to its lipophilic nature and activate nicotinic acetylcholine receptors (nAChRs) (Langley 1905, Henderson & Lester 2015). Endogenous agonists such as acetylcholine normally bind nAChRs to regulate downstream cellular and physiological responses; however, exogenous agents like nicotine can compete for the binding sites and exert alternative, and potentially pathological, effects (Albuquerque *et al.* 2009).

Whole body nicotine distribution is rapid, occurring within seconds to minutes from exposure, with the highest affinities in the brain, lung, liver, kidney, spleen, and skeletal muscle (Breese *et al.* 1997, Benowitz *et al.* 2009). Nicotine also accumulates in breast milk, placental tissue, amniotic fluid, and fetal blood (Luck & Nau 1984, Dahlstrom *et al.* 1990), leading to significant fetal and neonatal exposure. Research in animal models have clearly demonstrated that fetal and neonatal exposure to nicotine results in a wide range of short- and long-term health consequences for the offspring, including deficits in postnatal reproductive function (Bruin *et al.* 2010, Behl *et al.* 2013).

Adverse effects of nicotine exposure during pregnancy on reproductive outcomes

Pregnancy

There is no doubt that maternal smoking is associated with numerous adverse pregnancy outcomes, including an increased risk of spontaneous abortion, preterm birth, stillbirth, fetal growth restriction, and low birthweight (U.S. Department of Health and Human Services 2014). Studies on the effects of NRT use in human pregnancies, however, have generally reported fewer effects. A 2012 Cochrane review analyzing six randomized controlled trials of NRT use during pregnancy did not report any significant differences in rates of stillbirth, preterm labor, or low birthweight, although adherence in these studies were admittedly low (Coleman *et al.* 2012b). However, it is important to note that NRT use did not improve prolonged abstinence from smoking in mothers compared to placebo groups (Coleman *et al.* 2012a), suggesting that the doses provided may not have been sufficient to aid with smoking cessation and/or induce any changes in pregnancy or neonatal outcomes. Interestingly, another study found that the simultaneous use of more than one NRT product during pregnancy, which resulted in a higher dose of nicotine, was

associated with a mild decrease in birthweight in human offspring; this indicates that higher nicotine doses may indeed carry some risks for the offspring (Lassen *et al.* 2010). This finding was consistent with animal studies demonstrating that nicotine exposure during pregnancy leads to significant reductions in birthweight (Holloway *et al.* 2005, Gruslin *et al.* 2009, Wang *et al.* 2009). Because e-cigarette use can lead to comparable nicotine levels as tobacco smoking (Dawkins & Corcoran 2014, Etter 2014), it is possible that exposure to nicotine alone, via the use of e-cigarettes, may also lead to adverse pregnancy outcomes (Table 1).

Postnatal health outcomes

In general, fewer studies have examined the postnatal reproductive outcomes in maternal smoke-exposed offspring. In humans, prenatal exposure to cigarette smoke is associated with various reproductive health impairments in both male and female offspring (Hakonsen *et al.* 2014). Specifically, maternal cigarette smoking was found to lead to impaired semen quality in men and decreased fecundability in women (Hakonsen *et al.* 2014). These reproductive impairments may be attributed to aberrant fetal gonadal development (Mamsen *et al.* 2010) and/or impaired postnatal gonadal function, such as deficits in gonadal steroidogenesis (Hakonsen *et al.* 2014). To date, there are no human studies examining the reproductive outcomes in children exposed to NRTs *in utero*. Studies in animal models have identified that prenatal exposure to nicotine alone can result in increased germ cell depletion and altered steroidogenesis in male offspring (Lagunov *et al.* 2011, Paccola *et al.* 2014) and increased ovarian cell apoptosis, altered steroidogenesis, and impaired fertility in female offspring (Holloway *et al.* 2006, Petrik *et al.* 2009).

Although these impairments in postnatal reproductive health following nicotine exposure may be due to direct effects on gonad development and/or function, the possibility exists that nicotine may also indirectly affect reproductive health via changes in metabolic homeostasis. For example, obesity and type 2 diabetes mellitus (DM) have been strongly associated with detrimental reproductive outcomes, including decreased fertility, impaired sex hormone levels, and reduced sperm quality in human and animal studies (Jangir & Jain 2014, Kawwass *et al.* 2015). Interestingly, prenatal nicotine exposure leads to an increased risk of postnatal obesity and DM in animal studies (Behl *et al.* 2013), raising the possibility that nicotine-induced obesity and/or DM may contribute to the reproductive health deficits in nicotine-exposed offspring. However, it is important to note that currently none of the randomized controlled trials of NRT use during pregnancy have investigated the effects of nicotine exposure during fetal life on either metabolic or reproductive outcomes in the offspring. Given that the

Table 1 Summary of studies investigating the adverse effects of nicotine exposure on general pregnancy and reproductive health outcomes.

Main effects	Organism (dose; length of exposure; method)	Involvement of oxidative stress, inflammation, and/or ER stress	Reference
General pregnancy outcomes			
No significant differences in rates of miscarriage, stillbirth, preterm labor, or low birthweight in mothers exposed to NRTs	Human (various NRT doses; randomized control trials)	–	Coleman <i>et al.</i> (2012a,b)
No significant differences in birthweight between different NRT types/duration of use. Simultaneous use of more than one NRT product associated with low birthweight (nonsignificant)	Human (various NRT doses; self-reported telephone interviews)	–	Lassen <i>et al.</i> (2010)
Low birthweight.	Rat (1 mg/kg per day; 2 weeks pre-preg until weaning; s.c. inj) Rat (1 mg/kg per day; E8 until E15, E18, or E21; s.c. inj)	–	Holloway <i>et al.</i> (2005), Gruslin <i>et al.</i> (2009), Wang <i>et al.</i> (2009)
Placental outcomes			
↓ interstitial trophoblast invasion, ↑ placenta hypoxia, and ↓ labyrinth vascularization in E15 placentas	Rat (1 mg/kg per day; 2 weeks pre-preg until E15; s.c. inj) Rcho-1 cells (1 nM–1 mM)	–	Holloway <i>et al.</i> (2014)
↓ Trophoblast migration, invasion, and differentiation			
↓ placental volume blood flow at E155. ↑ syncytiotrophoblast sprouting and villous cytotrophoblast islands at E160	Macaques (2 mg/kg per day; E26 until E160; osmotic minipump)	Oxidative stress (antioxidant vitamin C ameliorated placental blood flow)	Lo <i>et al.</i> (2015)
NA	Primary placental cells (1–100 μM; 30 min pre-treatment)	Inflammation (Anti-inflammatory: ↓ LPS-induced TNF production, IL1b, IL8, and IL6 expression, and NFκB activation)	Dowling <i>et al.</i> (2007)
↑ placental hypoxia and amino acid starvation. Impaired disulfide bond formation in E15 placentas	Rat (1 mg/kg per day; 2 weeks pre-preg until E15; s.c. inj)	ER stress (↑ PERK and eIF2a phosphorylation, and ATF4, CHOP, and GRP78 expression)	Wong <i>et al.</i> (2015)
↓ cell proliferation.	BeWo cells (15 μM; 24–72 h)	ER stress (↑ GRP78 expression)	Repo <i>et al.</i> (2014)
Male gonadal outcomes			
Spermatid retention and degeneration, tubular vacuolation, germ cell depletion, and hypospermia in 7-week-olds	Rat (1 mg/kg per day; 2 weeks pre-preg until weaning; s.c. inj)	–	Lagunov <i>et al.</i> (2011)
Low birthweight. Leydig hypertrophy and ↑ testosterone levels in 90-day-olds (7.5-week-olds)	Rat (2 mg/kg per day; E1 until weaning; osmotic minipump)	–	Paccola <i>et al.</i> (2014)
↓ testicular enzyme activity, plasma and intratesticular testosterone levels, plasma gonadotropin levels, sperm count, and spermatogenesis in 7-month-olds	Rat (0.6 mg/kg per day; 12 weeks starting in 4-month-olds; ip inj)	Oxidative stress (↑ lipid peroxidation, hydrogen peroxide, and hydroxyl radical generation. ↓ glutathione, antioxidants, and mitochondrial membrane potential)	Jana <i>et al.</i> (2010)
↓ testosterone, weights of testes, epididymis, seminal vesicles, Leydig cell number, disrupted spermatogenesis, and ↑ interstitial spaces	Rat (1 mg/kg per day; 8 weeks starting in 8- to 12-week-olds; ip inj)	Oxidative stress (↓ antioxidant activity and ↑ TBARS levels. Green tea extract ameliorated nicotine-induced damage)	Mosbah <i>et al.</i> (2015)
Female gonadal			
↑ time to pregnancy, altered steroidogenesis (↑ progesterone and ↓ estrogen:progesterone) in 6-month-olds	Rat (1 mg/kg per day; 2 weeks pre-preg until weaning; s.c. inj)	–	Holloway <i>et al.</i> (2006)
↓ granulosa cell proliferation and ovarian vascularization and ↑ ovarian cell apoptosis in 26-week-olds	Rat (1 mg/kg per day; 2 weeks pre-preg until weaning; s.c. inj)	Oxidative stress (Rosiglitazone ameliorated nicotine-induced damage)	Petrik <i>et al.</i> (2009)
↓ cell survival with 6 mM nicotine. Morphological damage with 10 mM nicotine	Chinese hamster ovary cell (0.1–10 mM; 24 h)	Oxidative stress (↓ glutathione levels and ↑ malondialdehyde and lactate dehydrogenase)	Yildiz <i>et al.</i> (1998)
↑ cell death with 10 mM smokeless tobacco nicotine	Chinese hamster ovary cell (1–10 mM; 24 h)	Oxidative stress (↑ 8-OH-dG levels)	Yildiz (2004)
↓ ovarian weight and number of active corpora lutea. ↑ Number of atretic follicles and endometrial degeneration	Rat (2 mg/kg per day; 30 days starting in 70-day-olds; s.c. inj)	–	Camargo <i>et al.</i> (2014)

Table 1 Continued.

Main effects	Organism (dose; length of exposure; method)	Involvement of oxidative stress, inflammation, and/or ER stress	Reference
Morphological anomalies in ER of mouse oocytes	Mice (5 mg/kg per day; 30 days starting in 4- to -5-week-olds; s.c. inj)	ER stress (Proposed due to altered ER morphology) Oxidative stress (↑ serum MDA levels)	Rajikin <i>et al.</i> (2009)
Systemic Low birthweight	Rat (2–6 mg/kg per day; E1 until parturition; s.c. inj)	Inflammation (Pro-inflammatory: ↑ serum levels of hs-CRP, IL6, TNF α , TGF β , and nitric oxide)	Mohsenzadeh <i>et al.</i> (2014)
Perinatal nicotine exposure further amplified postnatal high fat diet-induced alterations in neural function	Mice (60 mg/kg per day; E5 until weaning; osmotic minipump)	Inflammation (Pro-inflammatory: ↑ serum IL1 β)	Orellana <i>et al.</i> (2014)
Embryonic Morphological anomalies, ↑ caspase 3 and ↓ BclxL expression	Mouse embryo (1 mM; 48 h exposure)	Inflammation (Pro-inflammatory: ↑ TNF α and IL1 β expression) Oxidative stress (↑ lipid peroxidation and ↓ antioxidant activity)	Lin <i>et al.</i> (2014)

NRT, nicotine replacement therapy; s.c. inj, subcutaneous injection; Ip inj, i.p. injection; pre-preg, Pre-pregnancy; E, embryonic/gestational day; LPS, lipopolysaccharide; ER, endoplasmic reticulum; MDA, malonaldehyde; hs-CRP, high-sensitivity C-reactive protein.

animal literature implicates impairments in offspring fertility following nicotine exposure *in utero*, future clinical studies investigating the long-term reproductive health outcomes of human adults exposed to nicotine alone are warranted.

With the increasing use of e-cigarettes in women of reproductive age (Carroll Chapman & Wu 2014) and continuing uncertainties surrounding the safety of NRT use during pregnancy (De Long *et al.* 2014), there remains a critical need to further understand the long-term health impacts of developmental nicotine exposure. There is emerging evidence from animal studies that prenatal nicotine exposure may compromise reproductive health in the exposed offspring, yet we are only beginning to understand the cellular events that mediate these long-term consequences. The remainder of this review will focus on the underlying roles of oxidative stress, inflammation, and ER stress in nicotine-induced injury with a focus on placental development/function and reproductive outcomes in the exposed offspring.

Cellular mechanisms underlying adverse nicotine-induced reproductive health outcomes

The role of reactive oxygen species and oxidative stress

Free radicals, such as reactive oxygen species (ROS), are generated as a natural by-product of cellular metabolism and oxidative protein folding in the mitochondria and ER. Common forms of ROS include nitric oxide (NO), superoxide (O₂⁻), and hydrogen peroxide (H₂O₂), which carry out important cellular functions under physiologically balanced levels (e.g., signaling/feedback, autophagy, oxygen sensing, immunity/inflammation, and cell differentiation) (Sena & Chandel 2012). Augmented pro-oxidant ROS quantities and/or impaired antioxidant capacity alters oxidative balance and culminates in a

condition known as 'oxidative stress.' Under conditions of prolonged oxidative stress, the unstable reactivity of excessive ROS can lead to free radical damage in DNA, proteins, carbohydrates, and lipids, and eventually, mitochondrial-mediated apoptosis and cell death (Cao & Kaufman 2014, Chaudhari *et al.* 2014). Increased oxidative stress has been demonstrated to impair placental development and function as well as cause damage to oocytes, sperm, and embryos (Agarwal *et al.* 2008, Herrera *et al.* 2014, Holloway *et al.* 2014), thus it is thought to underlie many aspects of impaired reproductive health (Agarwal *et al.* 2012, Agarwal *et al.* 2014, Dai *et al.* 2015).

In animal models, maternal administration of nicotine adversely affects placental development and function (Holloway *et al.* 2014, Lo *et al.* 2015). Although maternal tobacco use has been shown to increase markers of oxidative stress in the placenta (Sbrana *et al.* 2011), *in vivo* and *in vitro* studies have failed to find evidence of oxidative damage or increased ROS production in trophoblast cells following nicotine administration (Holloway *et al.* 2014, Repo *et al.* 2014, Lo *et al.* 2015). Interestingly, placentas from nicotine-treated animals exhibit evidence of hypoxia, which has been demonstrated to increase ROS production (Herrera *et al.* 2014). Consistent with this observation, nicotine treatment decreased local and circulating endocrine gland-derived vascular endothelial growth factor (EG-VEGF) *in vivo* and *in vitro*, a key placental angiogenic factor (Brouillet *et al.* 2012, Holloway *et al.* 2014). Disruption in the establishment of fetomaternal circulation may lead to increased hypoxia and oxidative damage in the placenta (Holloway *et al.* 2014). Moreover, some of the nicotine-induced deficits in placental function can be ameliorated by co-administration with an antioxidant (e.g., vitamin C) (Lo *et al.* 2015). Taken together, these results suggest

that subtle changes in the placental redox balance may underlie nicotine-induced deficits in placental development and function.

There is considerable evidence from animal studies that perinatal exposure to nicotine results in oxidative stress and/or decreased antioxidant potential in the offspring (Bruin *et al.* 2008, Xiao *et al.* 2011, Conceicao *et al.* 2015), suggesting that increased oxidative stress may be a potential mechanism underlying deleterious nicotine-induced reproductive outcomes. Indeed, adult animals exposed to nicotine exhibited increased ROS production and oxidative damage in the testes, which was associated with testicular damage and decreased sperm counts (Jana *et al.* 2010, Mosbah *et al.* 2015). Interestingly, the testicular pathology caused by nicotine exposure in the adult animals (e.g., degeneration of seminiferous tubules, germ cell exfoliation, loss of Leydig cells, and disrupted spermatogenesis) (Jana *et al.* 2010, Mosbah *et al.* 2015) are remarkably similar to the histological results in the testes of male offspring who were exposed to nicotine *in utero* (Lagunov *et al.* 2011, Paccola *et al.* 2014), suggesting a common underlying mechanism. The relationship between nicotine, oxidative stress, and ovarian physiology has been less well studied, although nicotine has been shown to cause oxidative stress in Chinese Hamster Ovary cells (Yildiz *et al.* 1998, Yildiz 2004). Importantly, oxidative stress is associated with increased ovarian cell apoptosis and follicle loss – outcomes that have been similarly observed in rats exposed to nicotine in adulthood (Camargo *et al.* 2014) and fetal life (Petrik *et al.* 2009). Collectively, these findings suggest that nicotine-induced oxidative stress may be an important, and potentially modifiable, pathway leading to impaired reproductive health in the offspring.

The role of inflammation

Inflammation is a complex physiological response involving the influx of activated leukocytes and increased production of pro-inflammatory cytokines (i.e., tumor necrosis factor alpha (TNF α), interleukin 1beta (IL1 β) and interleukin 6 (IL6)), chemokines, and growth factors. Acute inflammatory activation is necessary in responding to infectious or environmental insults, yet, prolonged inflammation may lead to many potential reproductive complications including impaired placental development/function and infertility (Weiss *et al.* 2009, Schmatz *et al.* 2010, Christiansen 2013, Bachir & Jarvi 2014).

Cytokines produced by cells in the feto-maternal interface play a key role in the regulation of placental development (i.e., trophoblast proliferation, migration, and invasion) and function (i.e., placental hormone secretion) (Bowen *et al.* 2002). Nicotine treatment of placental cells *in vitro* reduced lipopolysaccharide (LPS)-induced production of the cytokines IL1 β and IL6 (Dowling *et al.* 2007), which play an important role in

trophoblast invasion and migration (Jovanovic & Vicovac 2009, Prutsch *et al.* 2012). This data suggests that the adverse effects of maternal smoking on pregnancy outcomes might be due in part to the direct effects of nicotine on the main processes of placental development; however, whether inflammatory responses play a critical role in the nicotine-induced deficits in placental development and function have yet to be fully verified.

Although there is considerable evidence that nicotine exposure in adults results in anti-inflammatory responses in a variety of tissues (Gallowitsch-Puerta & Tracey 2005), fetal exposure to nicotine has been associated with increased inflammation in the offspring. Rodents exposed to nicotine *in utero* had significantly increased circulating serum pro-inflammatory cytokines (e.g., IL1 β , IL6, and TNF α) throughout early development and adulthood (Mohsenzadeh *et al.* 2014, Orellana *et al.* 2014). Similarly, embryos exposed to nicotine had increased gene expression of TNF α and IL1 β (Lin *et al.* 2014). Importantly, these cytokines play key roles in germ cell survival and gonadal steroidogenesis (Bornstein *et al.* 2004, Perez *et al.* 2013, Field *et al.* 2014). As fetal exposure to nicotine in rodents has been demonstrated to cause germ cell loss and altered steroidogenesis (Holloway *et al.* 2006, Petrik *et al.* 2009, Lagunov *et al.* 2011, Paccola *et al.* 2014), it is biologically plausible that these effects may be mediated by an altered inflammatory response, although this has yet to be experimentally determined.

The role of ER stress and the unfolded protein response

The ER is the essential organelle responsible for protein synthesis, folding, and secretion, lipid biosynthesis, and calcium homeostasis (Braakman & Bulleid 2011). Any perturbation of ER function and homeostasis resulting in the luminal accumulation of misfolded or unfolded proteins is known as 'ER stress.' The unfolded protein response (UPR) initially seeks to restore ER homeostasis by attenuating the global rate of incoming protein translation, while paradoxically increasing the expression of genes involved in improving protein folding capacity. However, in the presence of prolonged ER stress, apoptosis is initiated (Chambers & Marciniak 2014, Kawakami *et al.* 2014).

The role of ER stress in adverse nicotine-induced reproductive outcomes has not been studied extensively. The placenta is particularly susceptible to ER stress due to its high protein secretory activity, and augmented ER stress has been demonstrated to be associated with adverse placental development and fetal growth restriction (Yung *et al.* 2012, Kawakami *et al.* 2014, Yang *et al.* 2015). Interestingly, similar placental and fetal outcomes were reported in animal models of nicotine exposure during pregnancy (Holloway *et al.* 2005, Holloway *et al.* 2014, Gruslin *et al.* 2009). Indeed, nicotine administration during pregnancy increased placental ER stress

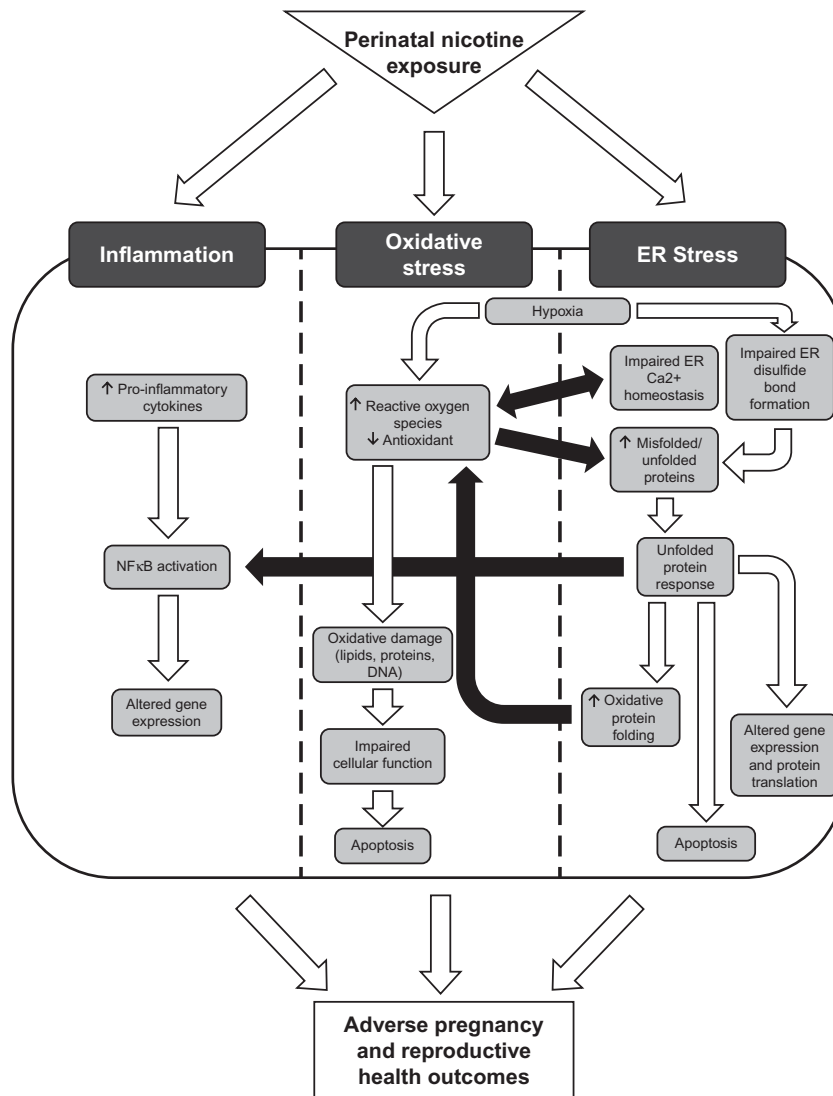


Figure 1 Proposed mechanisms by which prenatal nicotine exposure can adversely influence pregnancy (i.e., effects on placenta) and postnatal reproductive health outcomes (i.e., effects on gonadal development and function). White arrows indicate the normal pathway within a specific mechanism, whereas black arrows indicate interconnected pathways between the mechanisms.

resulting in the activation of the UPR at embryonic day 15 (Wong *et al.* 2015). It is possible that this is due to a direct effect of nicotine on the placenta, as cultured human trophoblast cells treated with nicotine had an increased expression of some ER stress markers (Repo *et al.* 2014). Alternatively, nicotine could be acting indirectly, as maternal nicotine exposure is known to induce vasoconstriction in placental vasculature (Pastrakuljic *et al.* 1999, Machaalani *et al.* 2014), decrease placental blood flow (Lo *et al.* 2015), and decrease trophoblast invasion leading to a delay in the establishment of the fetomaternal circulation (Holloway *et al.* 2014). The ensuing reduction in oxygen supply may cause placental hypoxia, which is also a trigger for ER stress (Koritzinsky *et al.* 2013, Holloway *et al.* 2014, Wong *et al.* 2015).

To date, there is no evidence directly linking prenatal nicotine exposure to ER stress in male or female reproductive organs; however, several indirect lines of evidence suggest that ER stress may be a cellular

mechanism underlying reproductive deficits in nicotine-exposed offspring. Firstly, ER stress has been shown to play a key role in ovarian cell apoptosis and follicular atresia (Yang *et al.* 2015), a phenotype similarly observed in nicotine-exposed offspring (Petrik *et al.* 2009). Secondly, nicotine exposure causes morphological changes in the ER of adult mouse oocytes (Rajikin *et al.* 2009); ultrastructural changes in the ER have also been documented in response to ER stress (Schonthal 2012). Finally, adult male mice exposed to cigarette smoke had altered protein processing in the epididymis (Zhu *et al.* 2013) – an observation consistent with altered sperm maturation seen in nicotine-exposed rat offspring (Lagunov *et al.* 2011). Taken together, these findings suggest the possibility that fetal exposure to nicotine may increase ER stress in the ovary and testes potentially leading to reproductive deficits in postnatal life. For more detail on general pregnancy outcomes and cellular mechanisms involved, please refer to Table 1.

Conclusion

In summary, we have presented evidence from a wide collection of animal and cell culture studies proposing the deleterious impact of prenatal nicotine exposure on pregnancy outcomes and the reproductive health of both male and female offspring. The deleterious effects of nicotine in the placenta and reproductive organs may be mediated through, but not limited to, the augmentation of oxidative stress, inflammation, and ER stress. Importantly, current research suggests that the functional involvement of these three mechanisms are very often inseparable (Fig. 1) (Chaudhari *et al.* 2014). For example, oxidative stress and ER stress are often tightly linked, and the activation of ER stress has been shown to trigger inflammatory pathways (Chaudhari *et al.* 2014). However, the degree to which each mechanism may differentially contribute to adverse pregnancy and reproductive outcomes is currently not well understood. Therefore, future research investigating the mechanistic underpinnings of maternal nicotine exposure must take an integrative approach to understand the relative involvements of oxidative stress, inflammation, and ER stress. Moreover, despite how evidence from both *in vitro* and animal studies have demonstrated that early life exposure to nicotine may cause impaired reproductive health of the offspring, these outcomes have not been well studied in humans. Given that there is still considerable controversy surrounding the long-term effects of NRT use during pregnancy as it relates to both conventional NRT (i.e. gum, patches, and spray) and emerging forms of nicotine delivery (i.e. e-cigarettes) (De Long *et al.* 2014), further studies of the long-term health outcomes of nicotine exposure, including reproductive outcomes, are urgently needed.

Declaration of Interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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