Adverse effects of perinatal nicotine exposure on reproductive outcomes

Michael K Wong, Nicole G Barra, Nadia Alfaidy¹, Daniel B Hardy and Alison C Holloway²

Departments of Obstetrics and Gynecology, Physiology and Pharmacology, Children's Health Research Institute, University of Western Ontario, London, Ontario, Canada, ¹University of Grenoble-Alpes, 38000; INSERM U 1036, Grenoble, France; ²iRTSV-Biology of Cancer and Infection, Grenoble, France and ²Department of Obstetrics and Gynecology, McMaster University, RM HSC-3N52, 1280 Main Street West, Hamilton, Ontario, Canada L8S 4K1

Correspondence should be addressed to A C Holloway; Email: hollow@mcmaster.ca

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.


Introduction

Despite increased awareness of its detrimental effects, ~10–23% of pregnant women continue to smoke worldwide (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). Alarmingely, 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...
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 has 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.

<table>
<thead>
<tr>
<th>Main effects</th>
<th>Organism (dose; length of exposure; method)</th>
<th>Involvement of oxidative stress, inflammation, and/or ER stress</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>General pregnancy outcomes</td>
<td></td>
<td></td>
<td>Coleman et al. (2012a,b)</td>
</tr>
<tr>
<td>No significant differences in rates</td>
<td>Human (various NRT doses; randomized control trials)</td>
<td>–</td>
<td>Lassen et al. (2010)</td>
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<tr>
<td>of miscarriage, stillbirth, preterm</td>
<td></td>
<td></td>
<td>Holloway et al. (2005), Gruslin et al. (2009), Wang et al. (2009)</td>
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<tr>
<td>labor, or low birthweight in mothers</td>
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<tr>
<td>exposed to NRTs</td>
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<tr>
<td>No significant differences in birthweight between different NRT</td>
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<tr>
<td>types/duration of use. Simultaneous</td>
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<tr>
<td>use of more than one NRT product</td>
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<tr>
<td>associated with low birthweight</td>
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<tr>
<td>(nonsignificant)</td>
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<tr>
<td>Low birthweight.</td>
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<td>Placental outcomes</td>
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<tr>
<td>↓ interstitial trophoblast invasion</td>
<td>Rat (1 mg/kg per day; 2 weeks pre-pregnancy until weaning; s.c. inj)</td>
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<tr>
<td>↑ placenta hyoxia, and ↓</td>
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<tr>
<td>labyrinth vascularization in E15 placentas</td>
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<tr>
<td>↓ Trophoblast migration, invasion, and differentiation</td>
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<tr>
<td>↓ placental volume blood flow at E155</td>
<td>Macauces (2 mg/kg per day; E6 until E160; osmotic minipump)</td>
<td>Oxidative stress (antioxidant vitamin C ameliorated placental blood flow)</td>
<td>Lo et al. (2015)</td>
</tr>
<tr>
<td>NA</td>
<td></td>
<td>Inflammation (Anti-inflammatory; ↓ LPS-induced TNF production, IL1b, IL8, and IL6 expression, and NFkB activation)</td>
<td>Dowling et al. (2007)</td>
</tr>
<tr>
<td>↑ placental hyoxia and amino acid</td>
<td>Rat (1 mg/kg per day; 2 weeks pre-pregnancy until E15; s.c. inj)</td>
<td>ER stress (↑ PERK and eIF2a phosphorylation, and ATF4, CHOP, and GRP78 expression)</td>
<td>Wong et al. (2015)</td>
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<tr>
<td>starvation. Impaired disulfide bond</td>
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<td>formation in E15 placenta</td>
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<td>↓ cell proliferation.</td>
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<tr>
<td>Male gonadal outcomes</td>
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<tr>
<td>Spermatid retention and degeneration, tubular vacuolation, germ cell depletion, and hyposperma in</td>
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<tr>
<td>7-week-olds</td>
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<tr>
<td>Low birthweight. Leydig hypertrophy</td>
<td>Rat (2 mg/kg per day; E1 until weaning; osmotic minipump)</td>
<td>–</td>
<td></td>
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<tr>
<td>and ↑ testosterone levels in 90-day-olds (7.5-week-olds)</td>
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<tr>
<td>↓ testicular enzyme activity, plasma and intratesticular testosterone levels, plasma gonadotropin levels, sperm count, and spermatogenesis in 7-month-olds</td>
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<tr>
<td>↓ testosterone, weights of testes, epididymis, seminal vesicles, Leydig cell number, disrupted spermatogenesis, and ↑ interstitial spaces</td>
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<tr>
<td>Female gonadal</td>
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<td>↑ time to pregnancy, altered</td>
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<tr>
<td>steroidogenesis (↑ progesterone and ↓</td>
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<tr>
<td>estrogen:progesterone) in 6-month-olds</td>
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<tr>
<td>↓ granulosa cell proliferation and ovarian vascularization and</td>
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<tr>
<td>↑ ovarian cell apoptosis in 26-week-olds</td>
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<tr>
<td>↓ cell survival with 6 mM nicotine. Morphological damage with 10 mM nicotine</td>
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<tr>
<td>↑ cell death with 10 mM smokeless</td>
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<tr>
<td>tobacco nicotine</td>
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<tr>
<td>↓ ovarian weight and number of active corpora lutea. ↑ Number of atretic follicles and endometrial degeneration</td>
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<tr>
<td>Chinese hamster ovary cell (0.1-10 mM; 24 h)</td>
<td></td>
<td>Oxidative stress (↑ glutathione levels and ↑ malondialdehyde and lactate dehydrogenase)</td>
<td>Yildiz et al. (1998)</td>
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<tr>
<td>Chinese hamster ovary cell (1-10 mM; 24 h)</td>
<td></td>
<td>Oxidative stress (↑ 8-OH-dG levels)</td>
<td>Yildiz (2004)</td>
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<tr>
<td>Rat (2 mg/kg per day; 30 days starting in 70-day-olds; s.c. inj)</td>
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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 (O$_2^-$), and hydrogen peroxide (H$_2$O$_2$), 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 (EGF-VEGF) in vivo and in vitro, a key placental angiogenic factor (Brouillet et al. 2012, Holloway et al. 2014). Disruption in the establishment of feto-maternal 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 (TNFα), interleukin 1beta (IL1β) 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 IL1β 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., IL1β, IL6, and TNFα) throughout early development and adulthood (Mohsenzadeh et al. 2014, Orellana et al. 2014). Similarly, embryos exposed to nicotine had increased gene expression of TNFα and IL1β (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.
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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