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Effects of cigarette smoking on reproduction

C. Dechanet[1,*], T. Anahory[1], J.C. Mathieu Daude[2], X. Quantin[3], L. Reyftmann[1], S. Hamamah[1], B. Hedon[1], and H. Dechaud[1]

[1]Department of Medicine and Biology of Reproduction, Hôpital Arnaud de Villeneuve, 371 Avenue du Doyen Gaston Giraud, 34 295 Montpellier Cedex 5, France [2]Department of Toxicology, Hôpital Lapeyronie, 371 Avenue du Doyen Gaston Giraud, 34 295 Montpellier Cedex 5, France [3]Department of Thoracic Oncology, Hôpital Arnaud de Villeneuve, 371 Avenue du Doyen Gaston Giraud, 34 295 Montpellier Cedex 5, France

*Correspondence address. Tel: +33 467336481; Fax: +33 467336290; E-mail: c-dechanet@chu-montpellier.fr

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BACKGROUND: Cigarette smoking is associated with lower fecundity rates, adverse reproductive outcomes and a higher risk of IVF failures. Over the last few decades, prevalence of smoking among women of reproductive age has increased. This review focuses on current knowledge of the potential effects of smoke toxicants on all reproductive stages and the consequences of smoke exposure on reproductive functions.

METHODS: We conducted a systematic review of the scientific literature on the impact of cigarette smoking and smoke constituents on the different stages of reproductive function, including epidemiological, clinical and experimental studies. We attempted to create hypotheses and find explanations for the deleterious effects of cigarette smoke observed in experimental studies.

RESULTS: Cigarette smoke contains several thousand components (e.g. nicotine, polycyclic aromatic hydrocarbons and cadmium) with diverse effects. Each stage of reproductive function, folliculogenesis, steroidogenesis, embryo transport, endometrial receptivity, endometrial angiogenesis, uterine blood flow and uterine myometrium is a target for cigarette smoke components. The effects of cigarette smoke are dose-dependent and are influenced by the presence of other toxic substances and hormonal status. Individual sensitivity, dose, time and type of exposure also play a role in the impact of smoke constituents on human fertility.

CONCLUSIONS: All stages of reproductive functions are targets of cigarette smoke toxicants. Further studies are necessary to better understand the deleterious effects of cigarette smoke compounds on the reproductive system in order to improve health care, help to reduce cigarette smoking and provide a better knowledge of the molecular mechanisms involved in reproductive toxicology.

Key words: cigarette smoke / reproductive functions / fecundity / IVF

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Introduction

In Europe, smoking prevalence among women of reproductive age has increased over the last decades and reached 33% in 2006 (Huisman *et al*., 2005). In the USA, during the same period, the prevalence rate was 28% (CDC, 2008).

The relationship between decreased fertility and smoking is not well known. In a study involving infertile and pregnant smokers, Hughes *et al*. (2000) observed that only 47% of infertile patients and 14% of pregnant patients believed that smoking significantly impaired fertility. Moreover, only 30% of infertile patients were informed by their physicians about the risks of smoking. Poor understanding of the deleterious effects of smoking on fertility highlights the necessity for physicians to encourage patients of childbearing age to quit smoking.

Cigarette smoking is associated with reproductive life impairment such as an earlier onset of menopause (Jick and Porter, 1977), higher infertility risk (Augood *et al*., 1998; de Mouzon and Belaisch-Allart, 2005), lower fecundity rate (Baird and Wilcox, 1985; Tzonou *et al*., 1993; Bolumar *et al*., 1996; Hull *et al*., 2000) and lower IVF success rates (Hughes and Brennan, 1996; Feichtinger *et al*., 1997; Augood *et al*., 1998; Klonoff-Cohen *et al*., 2001; Neal *et al*., 2005; Wright *et al*., 2006). In a recent meta-analysis involving 21 studies that investigated the effects of smoking on IVF results, smoking was associated with a lower chance of clinical pregnancy [odds ratio (OR) = 0.56, 95 confidence interval (CI) 0.43–0.73], higher risk of miscarriage and ectopic pregnancy, and a lower chance of live birth per cycle (OR = 0.54, 95 CI 0.30–0.99) (Waylen *et al*., 2009). Despite controversial results, studies involving IVF procedures demonstrated that cigarette smoke had deleterious effects on all steps: ovarian sensitivity (Elenbogen *et al*., 1991; Hughes *et al*., 1994; El-Nemr *et al*., 1998), number of oocytes (Van Voorhis *et al*., 1996; El-Nemr *et al*., 1998; Klonoff-Cohen *et al*., 2001; Wright *et al*., 2006; Fuentes *et al*., 2010), fertilization (Elenbogen *et al*., 1991; Gruber *et al*., 2008), implantation and early placentation (Winter *et al*., 2002; Soares *et al*., 2007).

Cigarette smoke contains about 4000 compounds belonging to a variety of chemical classes known to be toxic, including polycyclic aromatic hydrocarbons (PAH) [e.g. benzo(a)pyrene (BaP), acenapthelene, phenanthrene, pyrene and chrysene], nitrosamines, heavy metals [e.g. cadmium (Cd), lead and cobalt], alkaloids (nicotine), aromatic amines and so forth (Kaiserman and Rickert, 1992; Ding *et al*., 2005). These compounds have different properties and probably different targets on the human reproductive system. The aim of this review was to focus on current knowledge of tobacco smoke effects on the reproduction process and analyse for each reproductive stage the deleterious effects of smoke components.

Methods

For this systematic review, Pubmed, EMBASE and Web of Science databases were used to collect all human epidemiological and clinical studies, as well as experimental studies with animal or cell culture models, by means of the following keywords: 'smoke', 'cigarettes', 'tobacco', 'fertility', 'fecundity', 'assisted reproductive techniques', '*in vitro* fertilization', 'folliculogenesis', 'oocyte', 'steroidogenesis', 'Fallopian tubes', 'embryo', 'embryo implantation', 'endometrium', 'trophoblast', 'myometrium', 'uterine Doppler', 'uterine blood flow', 'passive smoking', 'active smoking', 'mainstream smoke', 'sidestream smoke', 'environmental tobacco exposure', 'antenatal exposure' and 'childhood exposure'. In addition, references cited in the selected articles and reviews were searched. Four hundred and forty-eight publications were found. Only clinical and experimental studies were included. We excluded studies analysing cigarette smoke effects on male fertility and publications about other types of smoke (i.e. Marijuana). As we focused on reproductive functions from folliculogenesis to implantation, we excluded publications about the effects of cigarette smoke on pregnancy, the fetus and placenta. Only publications written in English and French were considered. One hundred and eighty-one publications were selected and analysed. Our review was conducted according to different reproductive functions which were classified as follows: folliculogenesis, steroidogenesis, preimplantation embryo development, Fallopian tube function, embryo implantation, uterine flow velocity and myometrial activity. For each reproductive function, we collected observations from human epidemiological or clinical studies about cigarette smoke effects. Then, we attempted to find hypotheses and explanations for the deleterious effects of cigarette smoke observed in experimental studies. Thereafter, factors influencing the negative effects of cigarette smoke on reproductive function were studied.

Results

Cigarette smoking and folliculogenesis

Effects of cigarette smoke on folliculogenesis

Cigarette smoking is associated with a risk of an earlier onset of menopause, which is advanced by 2 years (Jick and Porter, 1977). Cooper *et al*. (1995) demonstrated a higher FSH level in smokers. Ovarian reserve seems to be lower in smokers: Freour *et al*. (2008) evaluated anti-Mullerian hormone (AMH) in patients with comparable FSH and estradiol (E_2) levels on Day 3 of the menstrual cycle and found that AMH was significantly lower in smokers (3.06 versus 3.81 μg/l).

Experimental studies confirmed the deleterious effect of cigarette smoke (Table I). In a mouse model exposed to BaP, Mattison *et al*. (1989) found ovarian weight to be decreased. When different types of animal models were exposed to cigarette smoke metabolites, such as Cd, nicotine or BaP, regardless of the administration route (i.p., intra-ovarian or oral), follicle loss was reported at all stages of folliculogenesis (Shiromizu and Mattison, 1984; Mattison *et al*., 1989; Miller *et al*., 1992; Lienesch *et al*., 2000; Barbieri *et al*., 2005). Primordial follicles appeared to be especially sensitive to cigarette smoke (Mulligan Tuttle *et al*., 2009). Moreover, follicle growth was also shown to be inhibited, with smaller-sized follicles after nicotine (Bordel *et al*., 2006) or BaP exposure (Neal *et al*., 2007). Follicle growth in an isolated rat follicle culture decreased by 35% when exposed to 1.5 ng/ml of BaP, a concentration representative of levels found in the follicular fluid of women who smoked an average of 15 cigarettes/day (Neal *et al*., 2007).

Impairment in follicle growth could be explained by morphological alterations of the cumulus–oocyte complex (COC). When cultures of porcine COC were exposed to cigarette smoke compounds, such as cotinine, anabasine, nicotine and Cd, Vrsanska *et al*. found an inhibitory effect on cumulus expansion, with abnormal extracellular matrix. Hyaluronic acid synthesis was diminished in the presence of Cd and nicotine (Vrsanska *et al*., 2003). Liu *et al*. (2008a) demonstrated a dose-dependent negative effect of nicotine on bovine COC expansion as well as an impairment of perivitelline space formation, suggesting

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Table I Effects of cigarette smoke compounds on folliculogenesis.

Reference	Model	Exposure	Toxicants	Dose	Effects
Neal *et al.* (2007)	Rat follicle	Culture medium	BaP	1.5, 5, 45 and 135 ng/ml	Inhibition of follicle growth
					Inhibition by 35% at 1.5 ng/ml (equivalent follicular concentration of 15 daily cigarettes)
					Dose-dependent decreased growth
Bordel *et al.* (2006)	Hamster dorsal skin chamber with transplanted follicles	Daily s.c. injection	Nicotine	0.2 and 1 mg/kg	Inhibition of follicle growth
					Increased cells apoptosis with increased caspase-3 levels
					No effect on follicular angiogenesis
Vrsanska *et al.* (2003)	Porcine COC	Culture medium	Nicotine	2×10^{-4} to 10^{-6} M	Decreased COC expansion
			Anabasine	10^{-4} to 10^{-6} M	Decreased hyaluronic acid synthesis
			Cotinine	10^{-4} to 10^{-6} M	Decreased progesterone synthesis
Neal *et al.* (2007)	Human COC	Mainstream smoke	BaP	Smokers follicular fluid BaP = 1.32 ng/ml	Inhibition of follicle growth
					Decreased E_2 synthesis
Lienesch *et al.* (2000)	*Xenopus laevis*	Dorsal lymph injection	Cadmium	3.0 and 5.0 mg/kg	Decreased follicle growth
					Increased number of atretic oocytes
Barbieri *et al.* (2005)	Human COC	Cigarette smoke	Cigarette smoke	Not mentioned	Decreased number of retrieved oocytes
Miller *et al.* (1992)	Mouse	i.p. injection	BaP	0–500 mg/kg	Decreased ovarian volume
					Decreased *corpus luteum* volume
					Decreased *corpus luteum* number
Mattison *et al.* (1989)	Mouse	Intraovarian injection	BaP and metabolites:	Not mentioned	Decreased ovary weight and volume
			7,8-oxide (7,8-O)		Decreased number of follicles at all stages of development
			7,8-dihydrodiol		
			7,8-dihydrodiol-9,10-epoxide		
Mulligan Tuttle *et al.* (2009)	Mouse	Exposure chambers	Mainstream smoke	1 puff/52 s	Decreased ovarian volume
		Culture medium	BaP	$1-1 \times 10^{-5}$ g/ml	Decreased number of follicles
					Decreased Bcl-2 expression
Liu *et al.* (2008a, b)	Bovine COC	Culture medium	Nicotine	0.05, 1.0, 2.5, 5.0 and 10.0 mmol	Decreased COC expansion
					Decreased perivitelline space formation
Paksy *et al.* (1997)	Human granulosa cells	Culture medium	Cadmium	$6-16-32-64 \times 10^{-6}$ M	Cytoplasmic retractions
					Cells detachment
Sanders *et al.* (2002)	Bovine granulosa and thecal cells	Culture medium	Nicotine	0.3, 3, 30 and 10^{-6} M	Decreased cell viability

Gieseke and Talbot (2005)	Hamster COC	Culture medium	Smoke solution from 60 puffs of cigarette	Not mentioned	Decreased COC size Loss of cumulus cell Increased matrix degradation
Nampoothiri *et al.* (2007)	Rats	*In vivo*	Cadmium	i.p. injection of cadmium 0.05 mg/kg	Inhibition of SOD activity Increased catalase activity
		In vitro with granulosa cells		Culture medium	

COC, cumulus–oocyte complex; BaP, benzo(a)pyrene; E_2, estradiol; SOD, superoxide dismutase.

that smoke components induced impairment of the mucification process. Paksy *et al.* (1997) studied the effects of smoke metabolites on human granulosa cell culture: at high doses of Cd or low doses with longer exposure times, granulosa cells began to separate, cellular extensions retracted and nuclear abnormalities were observed. In addition, high doses of Cd led to granulosa cell necrosis (Leoni *et al.*, 2002).

Zenzes *et al.* investigated the effect of cigarette smoking on oocyte maturation in IVF patients: in patients younger than 35 years, a positive correlation between the number of cigarettes smoked and follicular cotinine was observed. Surprisingly, a positive correlation was also seen between follicular cotinine level and the rate of oocyte maturation (Zenzes *et al.*, 1997b). In contrast, in a frog model exposed to Cd, Lienesch *et al.* (2000) observed an accumulation of Cd in ovaries as well as delayed oocyte development and maturation. Different results regarding oocyte maturation in these two studies could be accounted for by differences in the toxicants studied and models used. In a mouse model exposed to nicotine, Mailhes *et al.* studied the rate of chromosomal abnormalities in metaphase II oocytes. In non-exposed mice, the rates of premature chromatid separation and premature anaphase were, respectively, 4.6 and 0.3%, whereas in the group exposed to high levels of nicotine, the rates were 9.2 and 5.4%, respectively (Mailhes *et al.*, 2000). Higher rates of morphological oocyte abnormalities and aneuploidies were observed after nicotine exposure, suggestive of deleterious effects of smoke metabolites on COC and nuclear maturation.

Presence of cigarette smoke metabolites in ovarian tissue

Many cigarette smoke compounds have thus far been identified in ovarian tissue (Table II). Nicotine and cotinine were found in the follicular fluid (Weiss and Eckert, 1989; Zenzes *et al.*, 1996) (mean cotinine levels of 710.4, 76.3 and 4.2 ng/ml, respectively, in active, passive and non-smokers), with a positive correlation between follicular cotinine levels and the rate of cigarette consumption (Zenzes *et al.*, 1996). Cotinine was also detected in both the nucleus and the cytoplasm of the granulosa cells (Zenzes *et al.*, 1997a). BaP was also identified in granulosa cells (Zenzes *et al.*, 1998). Neal *et al.* (2007, 2008) investigated

Table II Cigarette smoke metabolite concentrations (ng/ml) in human serum and follicular fluid in smokers and non-smokers.

	Serum		Follicular fluid		Reference
	NS	S	NS	S	
Cotinine			3.8	340	Zenzes *et al.* (1998)
PAH					
BaP	0.22	0.40	0.03	1.32	Neal *et al.* (2007)
Acenaphtelene	0.44	0.99	1.44	1.71	Neal *et al.* (2008)
Phenantrene	5.9	5.45	3.20	3.56	Neal *et al.* (2008)
Pyrene	0.27	0.30	0.25	0.22	Neal *et al.* (2008)
Chrysene	0.40	0.20	0.15	0.15	Neal *et al.* (2008)
Cadmium	0.85	0.97	7.93	6.73	Shaham *et al.* (1996)

NS, non-smokers; S, smokers; PAH, polycyclic aromatic hydrocarbons.

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follicular PAH levels in IVF patients and found that BaP levels were positively correlated with female cigarette consumption (mean BaP levels of 1.32, 0.05 and 0.03 ng/ml, respectively, in active, passive and non-smokers). This may suggest that the follicular fluid that bathes the growing follicle acts as a sink for toxicants such as BaP. Thus, they established that 1.5 ng/ml of BaP corresponded to a human follicular fluid BaP concentration resulting from consuming 15 cigarettes/day. Cd was also detected in human ovarian tissue and the follicular fluid, with higher levels in smokers than non-smokers (Zenzes *et al.*, 1995a). All these studies allow us to conclude that follicular fluid and ovarian cells retain toxic compounds and create a toxic environment for follicle growth and oocyte maturation, to differing degrees depending on the number of cigarettes smoked per day.

Mechanisms involved in folliculogenesis impairment

Some mechanisms explaining folliculogenesis impairment have been described: abnormal oxidative stress, increased cellular apoptosis, abnormal cross-talk between oocyte and granulosa cells, and impairment of oocyte nuclear function.

Paszkowski *et al.* measured follicular oxidative activity in smokers: lipid peroxidation product was 0.49, 0.50 and 1.07 μmol/l and the total antioxidative capacity was 440.0, 385.4 and 362.3 μmol/l, respectively, in non-, passive and active smokers. Moreover, they found a positive correlation between the rate of lipid peroxidation and the level of patient exposure to cigarette smoke (Paszkowski *et al.*, 2002). The effects of cigarette smoke on oxidative stress are well known as are the effects of smoke on cellular apoptosis and aneuploidy (Lee *et al.*, 1989; Van der Vaart *et al.*, 2004; Kim *et al.*, 2008). Cd was shown to increase ovarian oxidative stress: Nampoothiri *et al.* evaluated the effects of Cd on mouse ovarian oxidative stress by using granulosa cells exposed *in vitro* to Cd and granulosa cells isolated from mice exposed for 15-day periods. Increased lipid peroxidation, reduced glutathione contents, increased catalase activity and decreased superoxide dismutase activity were observed in ovaries exposed to Cd (Nampoothiri *et al.*, 2007).

Cigarette smoking was shown to be associated with follicle loss, involving complex mechanisms and cell death pathways. Higher expression and synthesis of Bax, a pro-apoptotic molecule, were observed in mouse ovaries after exposure to BaP (Matikainen *et al.*, 2001). The action of BaP is mediated through the aryl hydrocarbon receptor (AhR), a cytoplasmic receptor identified in granulosa cells (Bussmann and Baranao, 2006) and implicated in follicle growth (Benedict *et al.*, 2000; Pocar *et al.*, 2005). The identification of an AhR-response element in Bax promoters suggested that AhR and Bax were implicated in cell death signalling pathways of granulosa cells exposed to smoke components (Matikainen *et al.*, 2001). Mulligan Tuttle *et al.* (2009) studied apoptosis markers in ovaries of mice exposed to mainstream smoke (MS) and found lower levels of Bcl-2, an anti-apoptotic protein. Using human ovarian tissue transplanted subcutaneously in mice exposed to PAH, Jurisicova *et al.* (2007) observed an up-regulation of harakiri, a Bcl-2 interacting protein involved in cell death pathways, in the granulosa and stromal cells.

Paksy *et al.* (1997) demonstrated that human granulosa cells exposed to Cd were characterized by cytoplasmic retractions and fewer intercellular junctions. *In vitro*, BaP was shown to inhibit gap junction formation (Sharovskaya *et al.*, 2006), junctions being indispensable for oocyte–granulosa cell cross-talk. In Sertoli cells exposed to Cd, lower levels of connexin 43, a molecule involved in gap junction structure were observed (Fiorini *et al.*, 2004; Gershon *et al.*, 2008). Furthermore, smoke components are associated with damage to DNA. Using comet assay, Sinko *et al.* (2005) studied nuclear consequences in granulosa cells from IVF patients: higher rates of DNA strand breaks in smokers were observed. Moreover, high levels of BaP–DNA adducts in human luteal cells were also detected (Shamsuddin and Gan, 1988).

Cigarette smoking was associated with an increased risk of oocyte aneuploidy (Zenzes *et al.*, 1995b). In mouse models exposed to nicotine, higher rates of both chromosomal abnormalities and premature separation of sister chromatids during meiosis were observed (Mailhes *et al.*, 2000). In rat germinal cells exposed to increasing BaP doses, inhibition and blockage of meiosis were shown (Georgellis *et al.*, 1990), implying that smoke components may induce meiotic spindle disturbances. With bovine oocytes exposed to nicotine, Liu *et al.* (2007, 2008a) observed a dose-dependent increased rate of aneuploidy during meiosis with irregular, malformed and multipolar spindles, abnormal chromosomal alignment and disorganized microfilaments. It was suggested that actin filaments were targets for nicotine, resulting in disorganized microfilaments and chromosomal segregation (Liu *et al.*, 2007). Liu *et al.* (2008b) studied the effects of nicotine on meiotic spindles in bovine oocytes at different meiotic stages and found that the second meiotic spindles were far more sensitive to nicotine. Most constituents of cigarette smoke, such as PAH, have carcinogenic properties with the ability to link and intercalate within the DNA helix, inducing mutation, DNA adduct formation and carcinogenesis (Baird *et al.*, 2005). All these mechanisms could also explain abnormal oocyte nuclear maturation.

Cigarette smoke is associated with impairment of folliculogenesis. Ovaries retain smoke compounds, resulting in a toxic follicle environment, inducing increased oxidative stress, abnormal intercellular cross-talk, meiosis impairment and activation of cell death pathways. Consequences are follicle loss, abnormal follicle growth, and impairment of morphology and oocytes maturation.

Cigarette smoking and steroidogenesis

Effects of cigarette smoking on steroidogenesis

Among cigarette smoke compounds, some display properties of endocrine disruptors (Mlynarcikova *et al.*, 2005). Smokers present an abnormal endocrine profile characterized by higher testosterone level (Barbieri *et al.*, 2005), higher level of FSH (Cooper *et al.*, 1995) and lower E_2 level during ovarian stimulation in IVF (Van Voorhis *et al.*, 1992, 1996). Several authors have observed that smoke compounds disrupt steroidogenesis, leading to impairment of E_2 synthesis (Barbieri *et al.*, 1986; Osawa *et al.*, 1990; Piasek and Laskey, 1994; Bodis *et al.*, 1997; Gocze *et al.*, 1999; Sanders *et al.*, 2002; Vidal *et al.*, 2006) and progesterone synthesis deficiency (Paksy *et al.*, 1989, 1997; Piasek and Laskey, 1994). The analysis of follicular fluid components in smokers treated with IVF revealed a decreased estrogenic concentration with an increased androgen/estrogen ratio, indicative of an androgenic follicular environment (Gustafson *et al.*, 1996; Van Voorhis *et al.*, 1996).

Cigarette smoke compounds and endocrine disruptors

Cadmium. Cd is an endocrine disruptor which is involved in the impairment of steroidogenesis (Paksy *et al.*, 1989, 1997; Piasek and Laskey,

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1994; Henson and Chedrese, 2004). Cd decreases expression of the low-density lipoprotein receptor implicated in cholesterol internalization, the first step in steroidogenesis (Jolibois *et al.*, 1999). In porcine granulosa cell lines exposed to low doses of Cd, an increased genomic expression of P450 side-chain cleavage (SCC) enzyme, involved in the conversion of cholesterol to pregnenolone, was observed. At high doses, Cd was shown to inhibit $P450_{scc}$ expression, resulting in a decreased E_2 synthesis (Smida *et al.*, 2004). Cd was reported to have an inhibitory effect on 3-β-hydroxysteroid-dehydrogenase gene expression (Smida *et al.*, 2004). The chemical structure of Cd is close to that of calcium: this property facilitates interaction with intra-cellular calcium signalling (Lacroix and Hontela, 2006; Costa and Varanda, 2007) and Cd is probably also involved in FSH and LH intra-cellular signalling mechanisms.

Nevertheless, Cd was also found to act as an estrogen-like factor, particularly in endocrine tissues (Stoica *et al.*, 2000). This property is related to its ability to link with estrogen receptors (Nesatyy *et al.*, 2005), resulting in an enhanced expression of estrogen-dependent genes (Darbre, 2006; Alonso-Gonzalez *et al.*, 2007).

Benzo(a)pyrene. BaP was described as an endocrine disruptor (Inyang *et al.*, 2003). In experimental studies, BaP was shown to inhibit P450 aromatase expression and activity (Dong *et al.*, 2008) and to decrease 17-β-hydroxysteroid-dehydrogenase and 17–20 lyase activities, which are all involved in steroidogenesis (Rocha Monteiro *et al.*, 2000).

Similar to Cd, BaP presents estrogen-like properties (Charles *et al.*, 2000; Gozgit *et al.*, 2004), owing to the steric resemblance of PAH to sex steroids. Thus, PAH might act on the same sites as steroid hormones (Charles *et al.*, 2000). DNA binding was observed *in vitro* with high doses of BaP (Charles *et al.*, 2000; Fertuck *et al.*, 2001). In human tissue, and particularly in ovarian tissue, BaP levels and biodisponibility were lower, and an estrogen-like effect still needs to be demonstrated (Fertuck *et al.*, 2001).

Compounds in cigarette smoke can act as endocrine disruptors in a number of different ways, and opposite consequences have been observed, such as estrogenic and anti-estrogenic effects. These opposite effects could be explained by actions on the different stages and various targets of the steroidogenesis. The complexity of the effects of smoke compounds must be investigated to elucidate the consequences of cigarette smoke on steroidogenesis.

Cigarette smoking and preimplantation embryo development

Embryos and smoke metabolites

Several metabolites of cigarette smoke have been identified in the embryo and its environment. BaP was detectable in the embryo, at three and eight blastomere stages, in the cytoplasm and nucleus (Fabro and Sieber 1969; Zenzes *et al.*, 1999). Nicotine was also identified in the endometrium (Fabro and Sieber, 1969) and uterine fluid (Poppe *et al.*, 1995), suggesting that embryo development started in a 'toxic' environment.

Mechanisms and effects of cigarette smoke compounds on embryo development

Current knowledge of the potential effects of smoking on embryo development remains poor. Shiloh *et al.* (2004) evaluated the zona pellucida thickness in women who did, and did not, smoke: a thicker zona pellucida was observed in female smokers (20.1 μm in smokers versus 15.3 μm in non-smokers). Gruber *et al.* (2008) evaluated the effect of female smoking on IVF embryo quality; they found that the smoking status had no influence on embryo morphology score, the rate of fragmentation and arrested embryos. However, a lower fertilization rate was observed in smokers than non-smokers (78.2 versus 85.7%). Using female mice exposed to cigarette smoke, Hassa *et al.* (2007) found that the rate of growing and not arrested embryos on Day 2 was lower in exposed mice as compared with controls (32 versus 75%); however, on Day 3, the rate of arrested embryos was identical in the two groups. Liu *et al.* (2008b) evaluated bovine embryo development after exposure to cigarette smoke and reported a higher rate of multinucleated blastomeres.

Zenzes *et al.* investigated preimplantation embryo development using 1682 embryos from couples who underwent IVF. Surprisingly, they found the fertilization rate and the proportion of good-quality embryos to be increased with increasing follicular cotinine levels. According to the authors, these results may be explained by a cotinine-mediated inhibition of apoptosis in developing embryos of smokers, resulting in an increased ability to survive (Zenzes *et al.*, 1999).

The effects of Cd were also studied in mouse embryos: although no effect was observed at low levels of exposure, high doses led to embryo degeneration with a necrotic appearance (Yu *et al.*, 1985). At the blastocyst stage, Cd induced inner cell mass cells necrosis with appearance of cytoplasmic vacuoles and residual bodies (Abraham *et al.*, 1984).

The effects of PAH were studied on murine embryos: s.c. PAH exposure led to fewer morula and blastocyst stage embryos and fewer cells per embryo, resulting in a 20% loss of total cell number in embryos exposed to PAH (Detmar *et al.*, 2006). BaP effects are mediated via the AhR. In rabbit embryos, AhR expression was confirmed in blastomeres at the morula stage, trophoblast cells and inner cell mass at the blastocyst stage (Tscheudschilsuren *et al.*, 1999). There seems to be a gradual appearance of AhR during embryonic development and this time-dependent expression could account for the late effects of smoke components on embryonic development. Detmar *et al.* (2006) observed, in mice embryos, that exposure to PAH for 24 h significantly increased the level of Bax transcript by a factor of two and the level of caspase activity by 35%. In mice blastocysts exposed to BaP, Pedersen *et al.* (1985) observed an increase in sister chromatid exchanges, correlated with increasing BaP exposure.

Different molecules contained in cigarette smoke have different pro- or/and anti-apoptosis properties, leading to a probable impairment of embryo development. The increased apoptosis phenomenon observed in experimental studies could be accounted for by high levels of exposure: these levels were probably higher than those observed *in vivo*, explaining the controversial results observed in IVF studies. Mechanisms involved in the effects of smoke on embryo apoptosis or survival remain unclear and must be elucidated.

Cigarette smoking and Fallopian tubes

Effects of cigarette smoke on embryo transport through Fallopian tubes

The hypothesis that the oviduct could be considered as a target of cigarette smoke was raised after observation of an increased rate of ectopic pregnancies following exposure to tobacco smoke (Chow *et al.*, 1988; Saraiya *et al.*, 1998; Stergachis *et al.*, 1991; Bouyer

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et al., 2003; Karaer et al., 2006), with an increased risk with increasing number of cigarettes smoked (Saraiya et al., 1998; Bouyer et al., 2003; Karaer et al., 2006) and when cigarette consumption was active (Stergachis et al., 1991; Bouyer et al., 2003; Karaer et al., 2006). These observations suggest that cigarette smoke could have deleterious consequences on tubal functions. Smoking cessation seems to be beneficial to tubal function, although a risk remains, suggesting chronic and irreversible tubal lesions. Even if multivariate analysis with adjustment for confounding variables has often revealed associations between smoke and ectopic pregnancy, categorizing smoking as a strong risk factor should be done with caution. In fact, smoking is also associated with risk behaviours (Jonsson et al., 1997), such as alcohol intake, with pelvic inflammatory diseases and also multiplicity of sexual partners, which are individual risk factors for ectopic pregnancy.

Cigarette smoke and tubal dysfunction

Migration of the COC and embryo through the Fallopian tubes involves adhesion between the COC or embryo and tubal epithelium, ciliary activity and tubal muscular contraction (Table III). All these steps could represent targets of smoke toxicants. In hamster oviducts exposed to smoke solutions and gas phase extracted from MS and sidestream smoke (SS), decreased ciliary beat frequency (CBF), inhibition of oocyte retrieval and infundibular smooth muscle contractions (ISMC) were observed (Knoll et al., 1995; Magers et al., 1995; Knoll and Talbot, 1998; Talbot et al., 1998; Riveles et al., 2003, 2004, 2005, 2007; Gieseke and Talbot, 2005), which could explain abnormal embryo transport and ectopic implantation (Knoll and Talbot, 1998; DiCarlantonio and Talbot, 1999; Riveles et al., 2003, 2005). All negative effects were observed in a dose-dependent manner (Knoll et al., 1995; Knoll and Talbot, 1998; Riveles et al., 2003). Moreover, Riveles et al. (2007) suggested that SS had more inhibitory effects than MS. While studying the effects of MS and SS compounds from traditional commercial cigarettes, Riveles et al. found that all of them inhibited CBF, oocyte retrieval rate and ISMC. Using *ex vivo* hamster oviducts, they demonstrated that smoke solutions extracted from MS of Marlboro red cigarettes decreased oocyte retrieval rate by 20%, CBF by 70% and ISMC by 99.4% (Riveles et al., 2007). When studying effects on the oviduct, Riveles et al. assessed the levels of many compounds contained in MS and SS, establishing for each one the lowest observable adverse effect levels (LOAEL). The LOAEL for nicotine and cotinine was high, with inhibitory effects on oocyte retrieval rate at 10^{-2} M for nicotine and 10^{-5} M for cotinine, suggesting that both nicotine and cotinine were not the major compounds involved in tubal dysfunction. However, for many other compounds, such as cyanide, pyridine and pyridine derivatives, and pyrazine and pyrazine derivatives, the LOAEL was lower than the concentration contained in MS and SS (Riveles et al., 2004). Cyanide is present in both MS and SS at concentrations of 167 and 67 μM, respectively, and had inhibitory effects on CBF at concentrations ranging from 50 to 100 μM (Talbot et al., 1998), suggesting involvement of cyanide in tubal dysfunction.

Mechanisms involved in alteration of tubal function

The mechanisms involved in impairment of ciliary beating remain poorly understood. Normal ciliary activity is related to ciliary cell quantity (Paltieli et al., 1995). Magers et al. (1995) investigated ciliated

Table III Effects of cigarette smoke on tubal functions.

Reference	Model	Exposure	Dose of toxicants	Effects
Magers et al. (1995)	Female hamster	Exposure chambers to mainstream and sidestream smoke	Serum cotinine levels:	Blebs on the surface of epithelial cells
	Histologic analysis of oviducts		72.8 ± 40.9 ng/ml under mainstream smoke exposure 14.45 ± 8.9 ng/ml under sidestream smoke exposure	Decreased ciliary cell quantity
Knoll et al. (1995)	Female hamster oviducts *ex vivo*	Smoke solution and gas phase from 60 puffs of mainstream and sidestream smoke	Nicotine levels in mainstream smoke solution: 129 ± 48 μg/ml mainstream gas: 0.7 ± 0.2 μg/ml sidestream smoke solution: 279 ± 57 μg/ml sidestream smoke gas: 54 ± 7 μg/ml	Dose-dependent decreased ciliary beat frequency after exposure to smoke solutions and gas phase
Knoll and Talbot (1998)	Female hamster oviducts *ex vivo*	Smoke solution and gas phase from 60 puffs of mainstream and sidestream smoke	Nicotine levels in mainstream smoke solution: 129 ± 48 μg/ml mainstream gas: 0.7 ± 0.2 μg/ml sidestream smoke solution: 279 ± 57 μg/ml sidestream smoke gas: 54 ± 7 μg/ml	Dose-dependant decreased oocyte retrieval rate Persistence of decreased oocyte retrieval after washing Dose-dependent decreased infundibular ciliary beat frequency Reversible ciliary beat frequency after washing

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Talbot *et al.* (1998)	Female hamster oviducts *ex vivo*	Smoke solution and gas phase from 60 puffs of mainstream and sidestream smoke	Concentration of ciliotoxic agents in mainstream smoke solution	Dose that inhibits ciliary beat frequency
			Acrolein: 50 ± 9 μM	Acrolein: 1.78 mM
			Formaldehyde: 166 ± 47 μM	Formaldehyde: 1.66 mM
			Phenol: 447 ± 16 μM	Phenol: 10 mM
			Cyanide: 167 ± 43 μM	Cyanide: 50 μM
Riveles *et al.* (2003)	Female hamster oviducts	Smoke solution and gas phase from 60 puffs of mainstream and sidestream smoke	Pyridine compounds isolated in smoke solutions and tested *ex vivo*: 2-methylpyridine, 3-methylpyridine, 4-methylpyridine, 2,3-dimethylpyridine, 2,5-dimethylpyridine, 2,6-dimethylpyridine, 3,4-dimethylpyridine, 2-ethylpyridine, 3-ethylpyridine, 3-vinylpyridine, 4,4-bipyridine, nicotine, cotinine, nornicotine, β-nicotyrine	Mainstream cigarette smoke solutions: oocyte retrieval rate decreased by 60% ciliary beat frequency decreased by 35% infundibular smooth muscle contraction decreased by 57%
			Consecutive doses in the range of 10^{-13}–10^{-1} M was used to determine the dose that caused inhibition of oocyte retrieval rate, ciliary beat frequency and infundibular smooth muscle contraction	Inhibitory effects are observed at picomolar dose for 2-ethylpyridine, 4-methylpyridine, 2-methylpyridine, 3-vinylpyridine and 3-ethylpyridine Inhibitory effect on oocyte retrieval rate was observed at 10^{-2} M for nicotine and 10^{-5} M for cotinine
Riveles *et al.* (2004)	Female hamster oviducts *ex vivo*	Smoke solution and gas phase from 60 puffs of mainstream and sidestream smoke	Pyrazines were identified in smoke solutions and gas phase and were tested to define the LOAEL: 2-methylpyrazine, 2,5-dimethylpyrazine, 2,6-dimethylpyrazine, 2,3,5-trimethylpyrazine, 2-ethylpyrazine, 2-methoxy-3-methylpyrazine	Pyrizine inhibited ciliary beat frequency and oocyte retrieval rate at picomolar dose and infundibular smooth muscle contraction at nanomolar dose Pyrazine derivatives also inhibited ciliary beat frequency, oocyte retrieval rate and infundibular smooth muscle contraction at picomolar dose
Gieseke and Talbot (2005)	Female hamster oviducts *ex vivo*	Smoke solution and gas phase from 60 smoke puffs of mainstream and sidestream smoke	Nicotine levels in mainstream smoke solution: 129 ± 48 μg/ml mainstream gas: 0.7 ± 0.2 μg/ml sidestream smoke solution: 279 ± 57 μg/ml sidestream smoke gas: 54 ± 7 μg/ml	Decreased COC adhesion to infundibulum Decreased oocyte retrieval More inhibitory effect with sidestream solutions Decreased size of COC Loss of cumulus cells Extracellular matrix COC disruption Increased adhesion between oocyte and infundibulum

Continued

Table III *Continued*

Reference	Model	Exposure	Dose of toxicants	Effects
Riveles *et al.* (2005)	Female hamster oviducts *ex vivo* Establishment of the LOAEL on oocyte retrieval rate, ciliary beat frequency, and infundibular smooth muscle contraction	Smoke solution from 10 puffs Mainstream and sidestream	Compounds isolated in solid phase extraction of mainstream smoke solution: 2-methylphenol, 4-methylphenol, 2,4-dimethylphenol, 2,5-dimethylphenol, 2-methoxyphenol, 4-methoxyphenol, 2,6-dimethoxyphenol, 2-ethylphenol, 4-ethylphenol, hydroquinone, indole, 5-methylindole, quinoline, isoquinoline, benzene, 2-cyclopenten-1-one and 3-methyl-2-cyclopenten-1-one	Decreased ciliary beat frequency LOAELs from 10^{-12} to 10^{-1} M for phenolic compounds Decreased oocyte retrieval LOAELs from 10^{-12} to 10^{-2} M for phenolic compounds Decreased muscle contraction LOAELs from 10^{-12} to 10^{-2} M for phenolic compounds
Riveles *et al.* (2007)	Female hamster oviducts *ex vivo*	Solution and gas from 10 smoke puffs of traditional commercial cigarettes (Malboro red and light, Camel filtered and unfiltered, Advance, Omni and Omni light) Mainstream and sidestream smoke	Identification of compounds in smoke solutions and gas phase of traditional commercial cigarettes For Marlboro red, composition of smoke solution: 4-methylpyridine, 106.34 mg/ml; 2-ethylpyridine, 1.1 pg/ml; 3-ethylpyridine, 9.20 mg/ml; 2-methylpyrazine, 19.19 mg/ml; 2-ethylpyrazine, 0.239 mg/ml; 4-methylphenol, 5.32 mg/ml; 4-ethylphenol, 6.23 mg/ml; quinoline, 0.61 mg/ml; indole, 1.82 mg/ml Establishment of the LOAEL for all these compounds on oocyte retrieval rate, ciliary beat frequency and infundibular smooth muscle contraction	Mainstream and sidestream smoke solutions of all commercial cigarettes tested inhibited oocyte retrieval rate, ciliary beat frequency and infundibular smooth muscle contraction Sidestream smoke solutions were more inhibitory than mainstream smoke solutions Mainstream smoke solutions from Marlboro red decreased oocyte retrieval rate by 20%, ciliary beat frequency by 70% and infundibular smooth muscle contraction by 99.4% LOAEL for oocyte retrieval rate was 9×10^{-9} mg/ml for 4-methylpyridine, 1×10^{-9} mg/ml for 2-ethylpyridine, 1×10^{-7} mfg/ml for 3-ethylpyridine, 9×10^{-10} mg/ml for 2-methylpyrazine, 1×10^{-9} mg/ml for 2-ethylpyrazine, 1.08×10^{-9} mg/ml for 4-methylphenol, 1×10^{-10} mg/ml for 4-ethylphenol, 1×10^{-9} mg/ml for quinoline and 1×10^{-12} mg/ml for indole

LOAEL, lowest observable adverse effect level.

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cells in the oviductal ampulla of hamsters exposed to smoke and found a lower rate of ciliated cells versus controls (69.2, 62.2 and 65.8%, respectively, in control, MS and SS exposed). A defective quality of ciliary beats was observed after exposure of animal oviducts to smoke (Riveles *et al.*, 2005). This ciliary dyskinesia observed after exposure to cigarette smoke was also described in other epithelia, such as the bronchial epithelium (Wyatt *et al.*, 2000; Elliott *et al.*, 2006). Some components of cigarette smoke interfere with proteic complexes involved in ciliary mobility, such as axoneme and dynein (Sisson *et al.*, 1991) or calcium signalling and protein kinase-mediated pathways (Villalon *et al.*, 1989; Wyatt *et al.*, 2000), which could all contribute to impairment of ciliary activity. In animal models, it was also demonstrated that CBF was influenced and dependent on sex steroids, acting through steroid receptors which were identified in ciliary epithelial cells (Paltieli *et al.*, 2000; Shao *et al.*, 2007). As previously described, smoke exposure, acting through impairment of steroidogenesis, could also disturb ciliary activity. Decreased oocyte retrieval could be explained by abnormal and increased adhesion between COC and tubal epithelium, leading to a slow migration of COC. Decreased CBF could obviously contribute to slow COC migration. A quantitative and qualitative impairment of ciliated cells resulting from smoke exposure could account for excessive adhesion between COC and tubal epithelium (Magers *et al.*, 1995), whereas an abnormal COC extracellular matrix (Vrsanska *et al.*, 2003; Gieseke and Talbot, 2005) was thought to be implicated in the abnormal relationship between COC and tubal epithelium, abnormal oocyte retrieval and abnormal migration through Fallopian tubes.

Fallopian tubes seem to be targets of cigarette smoke with deleterious consequences on ciliary cell quantity and quality, oocyte retrieval deficiency, CBF impairment and COC–epithelial cell excessive adhesion. These findings could easily explain abnormal tubal function and the higher rates of ectopic pregnancy observed in patients who smoke.

Cigarette smoking and embryo implantation

Embryo implantation requires a properly prepared endometrium. Site and quality of implantation play a major role in determining the risk of morbidity and mortality during pregnancy.

Impairment of embryo implantation was suspected in cigarette smokers: lower implantation rates were observed in smokers who underwent IVF, even if the results were controversial (Winter *et al.*, 2002; Freour *et al.*, 2008). Using human oocyte donation models, Soares *et al.* (2007) studied implantation rates in recipients according to their smoking status: implantation rates were lower in heavy smokers (>10 cigarettes/day) than in non-smokers (25.8 and 32.3%, respectively).

Effects of cigarette smoke on the endometrium

The potential effects of cigarette smoke compounds on the endometrium are not well known (Table IV). Using female rats exposed to nicotine, Card and Mitchell investigated the potential effects of nicotine on endometrial decidualization by assessing the weight of the uterus after mechanically induced decidualization. They found a lower uterus weight after nicotine administration and concluded that there was an adverse effect on the decidualization process (Card and Mitchell, 1978). Using primary endometrial cells from hysterectomy specimens and human endometrial epithelial cell lines, Khorram *et al.* studied the effects of an aqueous cigarette smoke solution. They observed a significant dose-dependent decrease in endometrial proliferation, involving nitric oxide (NO)-mediated pathways (Khorram *et al.*, 2010).

BaP acts through AhR, a receptor located in the endometrial stroma and epithelial cells. The AhR levels were shown to vary during the entire cycle and peri-implantation period (Kuchenhoff *et al.*, 1999; Kitajima *et al.*, 2004). A potential implication of this receptor was demonstrated using a mouse model: AhR knockout mice were characterized by early pregnancy loss and intrauterine fetal death (Abbott *et al.*, 1999), suggesting that AhR plays a role in the mechanism of implantation and trophoblast invasion.

By interfering with cytochromes involved in estrogen metabolism, BaP and PAH derivatives could act as an anti-estrogenic factor, thereby compromising endometrial maturation (Fertuck *et al.*, 2001; Bao *et al.*, 2002). Using immortalized human endometrial cells, Bao *et al.* (2002) investigated the effects of BaP on CYPA1, a cytochrome involved in estrogen catabolism and demonstrated that incubation with BaP increased CYPA1 expression and activity (12-fold at 1 μM). These observations could explain abnormal endometrial maturation. Cd could also disturb endometrial maturation. Zhang *et al.* (2007) demonstrated that animal models exposed to i.p. Cd had a thicker endometrial epithelial layer and stromal inflammation. Tsutsumi *et al.* investigated the effects of Cd on endometrial maturation using human endometrial stromal cell cultures, with prolactin as a marker of decidualization; when exposed to low doses of Cd (10 and 100 nmol/l), no change in prolactin expression was observed. At 1 μmol/l, prolactin concentration showed a significant 2.4-fold increase, indicating a $CdCl_2$-induced decidualization process: the authors concluded that an earlier $CdCl_2$-induced decidualization process could have been the cause of the lower implantation rates seen in heavy smokers (Tsutsumi *et al.*, 2009).

Effects on endometrial angiogenesis

The hypothesis that smoke compounds, particularly BaP, influence angiogenesis is strongly supported by (i) the presence of AhR, in endometrial vessels walls (Kitajima *et al.*, 2004) and (ii) observation of hypertrophic vessel walls in AhR knockout mice (Fernandez-Salguero *et al.*, 1997). Thus, a BaP-induced inhibitory effect on endothelial cell proliferation is strongly suspected. Soghomonians *et al.* investigated the *in vitro* effects of cigarette smoke on human uterine endothelial cells incubated with smoke-conditioned medium as well as on PECAM-1, a molecule involved in endothelial cell adhesion. They found that cigarette smoke compounds (i) influenced human endothelial cell mobility and morphology, (ii) increased PECAM-1 surface expression and (iii) induced aberrant localization of PECAM-1 (Soghomonians *et al.*, 2004), suggesting an aberrant regulation of the angiogenic process caused by smoke compounds. The effects of nicotine on angiogenesis have been studied more comprehensively using placenta, in the later stages of pregnancy: nicotine was implicated in the activation of endothelial cell migration and proliferation, and presented pro-angiogenic properties (Cooke and Bitterman, 2004; Dasgupta and Chellappan, 2006), resulting in increased placental capillary development (Pfarrer *et al.*, 1999).

Smoke compounds seem to present pro- and anti-angiogenic properties, probably involving complex mechanisms. Further studies are

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Table IV Effects of cigarette smoke on implantation.

Reference	Model	Dose of toxicants	Effects
Smoke effects on endometrium			
Card and Mitchell (1978)	Rat uterus	s.c. nicotine injection 0.5–5.0 mg/kg	Decreased uterus weight Nicotine suppressed uterine responsivity to decidualization
Soghomonians *et al.* (2004)	Human uterine endothelial cell culture in a smoking chamber	Nicotine levels 1.25–10 mg/m^3	Increased PECAM-1 synthesis Abnormal endothelial cell PECAM-1 distribution Decreased endothelial cell mobility and migration
Zhang *et al.* (2007)	Rat uterus and endometrium	i.p. cadmium injection 0.12–1.20 mg/kg	Thicker luminal epithelial cell layer, endometrium and myometrium Stromal inflammation Cellular oedema Decreased PCNA expression
Tsutsumi *et al.* (2009)	Human endometrial stromal cells	Cadmium 10–100–1000 nmol/l	Increased prolactin gene expression Earlier decidualization and disrupted timed decidualization
Khorram *et al.* (2010)	Human endometrial surface epithelial cell line and human endometrial cells	Aqueous cigarette smoke-saturated solution Nicotine: 10^{-5} mol/l BaP: 10^{-5} mol/l	Smoke solution inhibited cell proliferation in a dose-dependent manner No effect on cell viability by smoke solution Increased proliferation via NO pathway BaP and nicotine activated NO synthase expression
Smoke effects on implantation and placentation			
Zhang *et al.* (1995)	Human choriocarcinoma cell lines BeWo	BaP in culture medium: 1 nM–50 μM	Decreased binding of EGF to BeWo Decreased EGF receptor protein levels but not EGF mRNA levels Inhibition of cell proliferation Decreased EGF-stimulated hCG secretion
Zhang and Shiverick (1997)	Human placental trophoblastic choriocarcinoma cell line JEG-3	BaP 10 μM for 1, 3, 5 and 7 days	Decreased cell proliferation Decreased EGF receptor level Decreased TGF-β1 mRNA level
Genbacev *et al.* (2000)	Placenta from 6–8, 8–10 and 10–12 gestational weeks for *in situ* study	0 cig/day <10 cig/day 11–20 cig/day >20 cig/day	Thin syncytiotrophoblast Reduced number of villous cytotrophoblast Areas of discontinuity in cytotrophoblast layer Highly circonvoluted fetal blood vessels Increasing number of blindly ended cytotrophoblast columns Amorphous matrix in cytotrophoblast columns Increased number of cell islands Decreased Ki67 reactivity of villous and columns cytotrophoblasts
	Placenta from first trimester termination of non-smokers leading to anchoring villi culture	Nicotine in culture medium: 0.23, 2.3 or 6.0 μM	Increased rate of apoptosis Decreased expression of fibronectin and fibronectin receptor integrin α5/β1 Decreased trophoblast proliferation and invasion
Zdravkovic *et al.* (2006)	Placenta from first trimester termination at 6–8 weeks of gestation (smoker and non-smokers)	0 cig/day	Increased number of cell islands

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Table IV *Continued*

Reference	Model	Dose of toxicants	Effects
		<10 cig/day	Increased number of nonadherent cell columns
		11–20 cig/day	Decreased cytotrophoblast L-selectin expression
		>20 cig/day	
	Organ culture of placental anchoring villus explants	Nicotine in culture medium: 0.23, 2.3, 4.6, or 6.0 μM	Decreased L-selectin expression Lowest effective dose of nicotine on L-selectin expression 4.2 μM
			Decreased development of cell columns
Genbacev *et al.* (1995)	Placenta from first trimester termination at 6–8 weeks of gestation (smoker and non-smokers)	0 cig/day >20 cig/day	Decreased anchoring villi Less prominent cytotrophoblast columns
	Culture of human cytotrophoblasts	Nicotine in culture medium: 0.23, 1.15 or 2.3 μM	Decreased cytotrophoblast proliferation and differentiation
			Decreased cytotrophoblast invasion
			Dose-dependent effect
			Decreased MMP-9 production and activation
Thirkill *et al.* (2006)	Trophoblast cells from term macaque placentas	Cigarette smoke-conditioned medium	Decreased trophoblast migration
	Human uterine microvascular endothelial cells	Nicotine 1.25–10 mg/m^3	Reduced chemokine RANTES expression
Jolibois *et al.* (1999)	Culture of human trophoblast cells	Cadmium in culture medium 0, 5, 10 and 20 μM	Inhibition of syncytial maturation No effect on DNA fragmentation and cell viability

BaP, benzo(a)pyrene; PECAM, platelet endothelial cell adhesion molecule 1; PCNA, proliferating cell nuclear antigen; NO, nitric oxide; EGF, epidermal growth factor; mRNA, messenger ribonucleic acid; TGF-β1, transforming growth factor beta-1; MMP-9, matrix metallopeptidase-9; DNA, deoxyribonucleic acid; RANTES, regulated upon activation normal T-cells expressed and secreted.

necessary to understand the consequences of, and to clarify the mechanisms involved in, the effects of smoke on angiogenesis, impairment of embryo implantation and early placental development.

Effects of cigarette smoking on trophoblastic adhesion and invasion

Effects of cigarette smoking on the implantation process were demonstrated using mouse models: Esposito *et al.* (2008) studied fetal outcomes in pregnant mice exposed to cigarette smoke only during the peri-implantation period and found a lower fetal weight (1.10 g) than in the control group (1.18 g).

Histological studies of first trimester placenta demonstrated that smoking was associated with abnormal placental morphology such as a thinner syncytiotrophoblast, fewer villous cytotrophoblasts, a discontinuous cytotrophoblast layer, presence of highly circonvoluted fetal blood vessels, an increased number of blindly ending cytotrophoblast columns and fewer anchoring villi (Genbacev *et al.*, 1995; Zhang *et al.*, 1995; Genbacev *et al.*, 2000; Zdravkovic *et al.*, 2006).

Implantation and early placentation require adhesion between blastocyst and endometrium, trophoblastic proliferation, differentiation, migration and invasion. Using human trophoblastic cells, it was demonstrated that cigarette compounds decreased the likelihood of normal placental formation, trophoblastic migration (Genbacev *et al.*, 2000; Thirkill *et al.*, 2006; Zdravkovic *et al.*, 2006), invasion and differentiation (Genbacev *et al.*, 1995, 2000) (Table IV). Using human trophoblast cells, Genbacev *et al.* (2000) investigated cytotrophoblast mitotic ability and observed a dose-dependent decrease in mitotic and proliferative ability after smoke exposure. They also studied the migration ability by *in vitro* analysis of cytotrophoblast outgrowth of cultured villous tissue after the addition of increasing doses of nicotine and found a dose-dependent decrease in migration and invasion ability (Genbacev *et al.*, 1995).

Migration and invasion require an interaction between trophoblast and endometrium and involves molecules located on the endometrium layer and the trophoblast surface. The L-selectin receptor and its oligosaccharide ligand are implicated in the trophoblast–endometrium adhesion process (Genbacev *et al.*, 2003) as well as in the interaction between the extra-villous cytotrophoblast and the endometrium (Prakobphol *et al.*, 2006). In smokers, Zdravkovic *et al.* (2006) described lower levels of L-selectin in trophoblast and cytotrophoblast cells, explaining adhesion impairment and the deleterious interaction between the endometrium and the cytotrophoblast cells.

Trophoblastic invasion is controlled by molecules such as matrix metalloproteases (MMP), epidermal growth factor (EGF) and hCG (Cameron, 1998; Bischof and Campana, 2000; Isaka *et al.*, 2003; Lala and Chakraborty, 2003; Staun-Ram *et al.*, 2004).

In the placental tissue of smokers, lower levels of MMP-9 were observed in cytotrophoblastic cells and MMP-9 activity was decreased by 90% when high doses of nicotine were added to the culture medium (Genbacev *et al.*, 1995). On the promoter of the MMP-1 gene, a response element was identified as a target of smoke

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compounds, which suggested that smoke compounds had a direct influence on MMP gene expression (Mercer *et al.*, 2009). Zhang *et al*. demonstrated that human placental trophoblastic cell lines exposed to BaP showed an altered ability to proliferate owing to lower EGF and EGF receptor expression (Zhang *et al.*, 1995; Zhang and Shiverick, 1997). hCG is a key regulator implicated in endometrial receptivity and trophoblastic invasion through MMP regulation (Fluhr *et al.*, 2008). In floating villi, the fusion of cytotrophoblast is regulated by hCG. Using human placental explants cultured *in vitro*, hCG secretion by trophoblast cells was shown to be influenced by cigarette smoke compounds: when exposed to low doses of Cd or BaP, hCG pulse amplitude and secretion were increased and, in contrast, in the case of high doses of Cd, hCG pulse amplitude was inhibited (Barnea and Shurtz-Swirski, 1992; Boadi *et al.*, 1992). A modification of hCG secretion profile, depending on the smoke compounds and the level of exposure, could explain different degrees of implantation impairment as well as the complexity of abnormalities described.

Cigarette smoking and uterine flow velocity

During the menstrual cycle, changes in blood flow velocity occur in the uterine artery. During the implantation window, a low uterine pulsatility index and high uterine flow velocity were observed (Sladkevicius *et al.*, 1993, 1994; Tan *et al.*, 1996).

Goswamy *et al.* (1988) introduced the concept of infertility related to vascular impairment. Even if the relationship between abnormal uterine or endometrial blood flow velocity and IVF failure remains controversial (Ng *et al.*, 2007b; Hoozemans *et al.*, 2008), several authors have demonstrated that uterine arterial ultrasound abnormalities were associated with a lower implantation rate in IVF (Ng *et al.*, 2007a; Dechaud *et al.*, 2008; Merce *et al.*, 2008).

Effect of cigarette smoking on uterine and endometrial blood flow

Cigarette smoking was shown to induce vascular flow changes with increasing blood pressure and vasoconstriction, immediately following cigarette consumption (Moliterno *et al.*, 1994). Increased levels of vasoactive molecules, such as epinephrine, norepinephrine (Zhu and Parmley, 1995) or endothelin (Haak *et al.*, 1994), were observed immediately after cigarette consumption. Inhibition of NO-induced endothelial relaxation after nicotine exposure was also observed in animal uterine arteries (Xiao *et al.*, 2007) and could participate in haemodynamic changes.

The hypothesis that cigarette smoking could influence uterine artery velocity is controversial (Morrow *et al.*, 1988; Newnham *et al.*, 1990; Muller *et al.*, 2002; Albuquerque *et al.*, 2004). Ng *et al.* (2006) analysed the effects of cigarette smoking on uterine and endometrial velocity in IVF: no effects were found during Doppler examination of smokers. Lymperopoulou *et al*. studied uterine blood flow in smoking and non-smoking pregnant women according to cotinine levels ($<$ and $\geq$20 ng/ml): the mean diastolic index was lower in the group with higher cotinine levels (38.7 versus 44.3%). They also found a negative correlation between the uterine artery resistance index (RI) and cotinine levels (Lymperopoulou *et al.*, 1996). Albuquerque *et al.* (2004) studied the effects of maternal smoking on uterine and umbilical blood flows, taking into account the interval between the last cigarette and the ultrasound scan. They found a higher incidence of Notch in smokers but failed to find any difference between smokers and non-smokers with respect to the uterine artery RI (0.54 and 0.52, respectively, in the non-smoking and smoking groups). However, RI declined as time after the last cigarette elapsed (Albuquerque *et al.*, 2004). Evaluating uterine artery RI in pregnant women who smoke, before and after smoking 2 cigarettes, Castro *et al.* (1993) found a significant decrease of uterine RI within 5 min after cigarette consumption (from 0.55 to 0.49) with a return to normal levels within 30 min. These findings indicate a short-lived but substantial effect of smoke compounds on uterine arteries. More studies are necessary to confirm the effects of cigarette smoke on uterine blood flow and to investigate a potential effect on spiral arteries and on implantation.

Cigarette smoking and myometrial activity

During the menstrual cycle, the uterus is characterized by myometrial contractions with variations depending on the phase of the cycle, mainly influenced by hormonal status (Lyons *et al.*, 1991; Shafik, 1997; Bulletti *et al.*, 2000; Kunz and Leyendecker, 2002).

Fanchin *et al.* (1998) demonstrated that a high myometrial contraction frequency on the day of embryo transfer in IVF was associated with lower plasma progesterone levels and implantation rates, suggesting the important role of myometrial quiescence in the implantation process and the role of progesterone in myometrial quiescence.

The potential effect of cigarette smoking on myometrial activity remains poorly understood. However, a negative effect of smoke compounds on myometrial activity was suspected based on the higher rate of premature labour observed in pregnant women who smoke (Cnattingius *et al.*, 1999; Jaddoe *et al.*, 2008).

Effects of cigarette smoke on myometrial activity

The synthesis of progesterone, a regulator of myometrial quiescence, appeared to be reduced after smoke exposure (Paksy *et al.*, 1989; Piasek and Laskey, 1994). Using rat models, Bojanowska *et al.* (1985) observed that smoke exposure increased the release of neurohypophysial oxytocin. In rat models and human myometrial cells exposed to cigarette smoke extracts, a higher sensitivity to oxytocin as well as a higher frequency of oxytocin-induced contractions was observed (12.2/10 versus 6.4/10 min in controls). Furthermore, higher oxytocin receptor transcript levels (3- to 4-fold) were found in the myometrium of smokers than non-smokers (Egawa *et al.*, 2003). Likewise, Nakamoto *et al.* (2006) confirmed higher myometrial sensitivity to oxytocin after smoke exposure, but observed increased levels of oxytocin receptor transcripts in preterm myometrium only. These observations suggest that exposure to smoke led to both an earlier and an overexpression of oxytocin receptors resulting in an increased sensitivity to the ligand, along with an aberrant regulation of myometrial contraction and quiescence.

Mechanisms involved in smoke-induced contractions have not been sufficiently investigated. Cd, whose structure is close to that of calcium, was shown to interact with calcium and oxytocin and, as such, affected myometrial activity. At lower Cd concentrations, spontaneous contractions of *ex vivo* human myometrial samples were enhanced (Sipowicz *et al.*, 1995).

Steroidogenesis impairment, higher secretion of oxytocin and its receptors, increased oxytocin sensitivity, and interactions with calcium signalling have all been observed after smoke exposure. A

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possible relationship between abnormal myometrial contractility and exposure to smoke, as well as between smoke consumption and the implantation process, could be suspected. More studies are necessary to confirm the consequences of cigarette smoke on myometrial quiescence.

Factors influencing smoke effects on reproductive tract and function

Human and experimental studies demonstrated deleterious effects of smoke on reproductive functions. However, conclusions remain heterogeneous. Many factors could explain different consequences observed in these different studies: smoking behaviour, individual sensitivity, interaction with other toxicants, presence of environmental tobacco smoke (ETS) and time and duration of exposure.

Smoking behaviour and inter-individual sensitivity

In a study involving men smoking the same cigarette brand, blood nicotine levels ranged from 31.3 to 41.0 ng/ml (Armitage *et al.*, 1975). Such a difference could be partially explained by different smoking behaviour, such as volume, duration and length of puffs (Russel *et al.*, 1980; Sutton *et al.*, 1982). Individual differences in blood nicotine levels are attributable for 50–60% to smoking behaviour while cigarette yield of nicotine influenced <25% of blood cotinine levels (Herning *et al.*, 1983). Inter-individual differences in nicotine and cotinine metabolism could also explain differing cotinine and nicotine blood levels. Black smokers were shown to have higher cotinine levels than white smokers, independent of the number of cigarettes smoked (Caraballo *et al.*, 1998; Perez-Stable *et al.*, 1998). In studies with twins, it was demonstrated that the metabolism of nicotine and cotinine was influenced by genetic and environmental effects (Lessov-Schlaggar *et al.*, 2009; Swan *et al.*, 2009). Swan *et al.*, 2009 showed that nicotine metabolism differed depending on individual characteristics, such as sex and BMI. Different smoking behaviours, ethnicity and variation in individual metabolism remain difficult to study but probably contribute to the heterogeneous conclusions derived from human studies.

Interactions and influence of other xenobiotic agents

Interactions with other toxicants could also explain the different effects on reproductive functions. In most animal studies, only the effects of one compound were analysed, but cigarette smoke contains more than 4000 compounds. Using cells in culture, Hewitt *et al.* demonstrated different levels of Bax and Bcl-2 following exposure to BaP, and depending on the presence or not of other xenobiotic substances, and particularly depending on the presence of E_2 (Hewitt *et al.*, 2007). Moreover, Swan *et al.* (2009) observed a higher nicotine metabolism in women who used oral contraceptives than those who did not. These observations suggest that environmental toxicants could act in a synergystic, inhibitory or antagonist manner, depending on the presence of other substances.

Doses and duration of exposure

A negative association between the number of daily cigarettes and fecundability was observed (Baird and Wilcox, 1985; Howe *et al.*, 1985; Bolumar *et al.*, 1996), in a dose-dependent manner (Curtis *et al.*, 1997). A positive correlation between follicular fluid smoke compounds levels and the number of daily cigarettes smoked was also shown (Zenzes *et al.*, 1996; Neal *et al.*, 2008). In experimental studies, a dose–response relationship was also often observed, confirming that deleterious effects of cigarettes are correlated to the extent of exposure. However, animals were often exposed to acute doses of smoke, different from the level of human exposure, and without taking into consideration, the duration of exposure. In couples undergoing IVF, Klonoff-Cohen *et al.*, (2001) demonstrated that long duration of smoke exposure (>5 years) was associated with IVF failure [RR of not achieving a pregnancy = 4.27 (1.53–11.97)]. In mouse models exposed to a repeated low dose of PAH, a greater ovotoxicity than a single high dose was observed (Borman *et al.*, 2000). These conclusions highlight the importance of taking doses and exposure duration into account for a better understanding of the heterogeneous effects of smoke on human reproductive functions.

MS, SS and environmental smoke exposure

In many human studies, only active smoking has been recorded, without taking ETS into account. The effects of SS smoke are not well investigated and controversial. Pattinson *et al.* (1991) evaluated IVF outcomes in active, passive and non-smokers; patients were considered as passive smokers if their husbands smoked at least 1 cigarette a day: similar pregnancy rates were observed among non-smokers and passive smokers. Neal *et al.*, (2005) observed a decreased and similar pregnancy rates per transfer in passive and active smoking patients after IVF. Klonoff-Cohen *et al.* (2001) evaluated the effects of passive smoking on IVF outcomes and found fewer retrieved oocytes in couples in which only the husband smoked. The compositions of MS and SS are different: PAH levels were found to be higher in SS than MS (about 10-fold) (Lodovici *et al.*, 2004; Moir *et al.*, 2008). Follicular fluid analysis of passive smokers revealed the presence of smoke compounds at a higher level when compared with non-smokers (Zenzes *et al.*, 1996; Neal *et al.*, 2008). These observations led to a better understanding of the effects of SS, and that passive smoking should be taken into consideration.

Time of exposure

The hypothesis of deleterious effects of antenatal and childhood exposure to cigarette smoke on adult fertility was raised (Baird and Wilcox, 1986; Weinberg *et al.*, 1989; Wilcox *et al.*, 1989; Jensen *et al.*, 1998; Laurent *et al.*, 1992; Joffe *et al.*, 2000). An association of prenatal exposure and active adult smoking was also demonstrated, being more deleterious on fecundability than adult smoking without prenatal exposure (Jensen *et al.*, 2006). In animal experiments, early deleterious effects on folliculogenesis were demonstrated: using pregnant mice exposed to cigarette smoke, analysis of the ovaries in offspring demonstrated fewer follicles in mice that were exposed to smoke prenatally (Vähäkangas *et al.*, 1985). Using mice models exposed to BaP, Mackenzie and Angevine (1981) studied reproductive function and ovarian histology: fewer litters and hypoplastic ovaries with fewer follicles were observed in mice prenatally exposed. Only one human study has analysed the effects of prenatal exposure on follicle count. Lutterodt *et al.* investigated the effects of maternal cigarette smoke exposure during the first trimester on human embryonic ovaries obtained from legal abortions. They found fewer

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oogonia and somatic cells in the exposed group (Lutterodt et al., 2009), suggesting an early, irreversible and deleterious effect of maternal smoke. Moreover, using ovarian cell cultures from mice fetuses, Matikainen et al. (2002) demonstrated that addition of BaP to the culture medium led to fetal oocyte apoptosis and increased Bax expression. Deleterious effects of prenatal exposure have raised questions about the irreversible effects and decreased ovarian reserve at birth. Moreover, prenatal exposure could interact with, or increase, the negative effects arising from active and passive exposure to smoke in both childhood and adulthood. Different effects at different times of exposure explain the difficulties in analysing the consequences of exposure to smoke, as well as the additive and complex effects of different cumulative exposures.

The effects of past smoking on reproductive functions are also not well known. In many studies, past smokers are considered as non-smokers. Few studies have categorized patients into active, past and non-smokers. Curtis et al. (1997) did not find a decreased fecundability ratio in past smokers. Jensen et al. (2006) observed that past smokers showed the same time period necessary for conceiving as non-smokers. As few studies have analysed the effects of past smoking, and because in many studies, past smoking was not categorized, conclusions are difficult to establish. However, given the absence of, or only minor, effects of past smoking on fertility, and the negative effects observed when exposure occurred during prenatal life and childhood, this suggest a critical time of exposure, with a high sensitivity to cigarette smoke during fetal development. However, regardless of the observed effects of past smoking, teenagers, women in reproductive life and pregnant women should all be encouraged to stop smoking.

Limitations of experimental and human studies

Experimental studies showed deleterious effects of cigarette smoke on reproductive function. Doses used in experimental studies likely do not correspond to blood and tissue toxicant levels. Moreover, durations and routes of administration are also different. Only one compound was examined in experimental studies, but humans are exposed to more than 4000 compounds. Owing to the limitations of animal studies, extrapolation to human observations should be carried out with great care. However, experimental studies confirm the deleterious effects observed in human studies, allowing us to better understand the negative effects of cigarette smoking on reproductive function and the mechanisms involved.

Conclusion

Exposure to cigarette smoke impairs every stage of the reproductive process and each part of the reproductive system such as folliculogenesis, steroidogenesis, embryonic development and transport, endometrial maturation, implantation and early placentation, uterine vascular velocity and myometrial activity. Cigarette smoke compounds interact with different reproductive targets, depending on individual sensitivities, the presence of other toxic substances and according to time, dose, type and duration of exposure. Because infertile women are known to be motivated to stop smoking, particularly when they are attending for assisted reproduction treatments (Hughes et al., 2000), physicians should encourage these patients to stop smoking.

Further studies are necessary to understand the deleterious effects of smoke compounds on the reproductive system and to provide better knowledge of the molecular mechanisms involved in reproductive toxicology.

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