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Placental Hypoxia and Foetal Development Versus Alcohol Exposure in Pregnancy

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Abstract — Aims: To examine the causes of variability in the effect of maternal drinking on the foetus, with particular reference to the pattern, frequency and duration of the period of drinking, differences in maternal, foetal and placental metabolism of ethanol/acetaldehyde, and genetic factors. Methods: Narrative review of published studies of the pathogenesis of foetal alcohol syndrome (FAS) with emphasis in the development of the central nervous system. Results: Animal models suggest that acetaldehyde, the primary hepatic oxidative metabolite of ethanol, reaches the foetus either by placental production or by placental transference, which in turn could affect foetal growth and development. The most likely hypothesis regarding the decrease of foetal growth is via hypoxia and increased oxidative/nitrative stress, which interfere with cellular processes that require oxygen in order to function adequately, such as placental transport. Conclusion: There seems to be an association between the teratogenic effect, hypoxia and oxidative stress, the molecular mechanism involved (e.g. apoptosis) and the range of effects. The review sums ups the evidence that could explain some of the abnormalities in the brain development that could be related to behavioural problems observed in individuals with FAS/foetal alcohol spectrum disorder. This suggests that alcohol consumption produces failures in the normal migration of radial cells, from which the rest of the brain cells would eventually develop.

INTRODUCTION

Upon recognition of pregnancy, most women spontaneously reduce their alcohol intake. However, the recognition of the pregnancy does not occur until 4–6 weeks of gestation (Floyd et al., 1999) and thus, many women may drink alcohol prior to realizing they are pregnant.

Alcohol is one of the commonest teratogenic agents and its uncontrolled consumption by pregnant women can give rise to an irreversible condition in the child, foetal alcohol syndrome (FAS). This syndrome, described by Jones and Smith (1973), is characterized by intrauterine growth retardation (IUGR), craniofacial malformations, physical and mental retardation, and cardiac septal defects. However, FAS represents only a part of the spectrum of foetal alcohol effects. The term foetal alcohol spectrum disorders (FASDs), is currently used to describe a lesser degree of deformities associated to FAS, sometimes unnoticeable except by close examination, as well as a variable degree of mental retardation (Rossett, 1980; Chaudhuri, 2000). While some offspring of mothers who drink heavily during pregnancy develop FAS and evidence all the symptoms described earlier, some others show no symptoms at all, a condition known as ethanol resilience (Gemma et al., 2006, 2007). Also, a considerable number show only partial FAS-related phenotypes.

It has been proposed that maternal ethanol ingestion may cause foetal injury, particularly the impairment of somatic and brain growth, by at least two mechanisms: (a) directly, by fetotoxicity from ethanol and/or acetaldehyde; (b) indirectly, by ethanol-induced placental injury and selective foetal malnutrition (Fisher and Karl, 1988; Bosco, 2005). The wide variety of cellular/biochemical effects of alcohol on foetal tissues is in itself a puzzle, and this fact strongly suggests that the fetotoxic responses to alcohol may reflect a multifactorial setting.

This review will focus on recent insights into normal process of placental and human development that are susceptible to the mother’s alcohol consumption.

Embryonic developmental processes

After fertilization, the nuclei of the sperm and the oocyte fuse to form the zygote. As this cell travels to the uterus, it divides, forming a cluster of cells, the morula, by about 3 days after fertilization. As the morula enters the uterine cavity, fluid penetrates into it to form the blastocyst. The epithelial outer wall of this structure is the trophoblast, and the inner cell mass is the embryoblast. During implantation, the trophoblast differentiates into two layers: the syncytiotrophoblast and the cytotrophoblast. The former is external and has many nuclei and a continuous cytoplasm forming a syncytiu. The cytotrophoblast consists of a layer of ovoid cells immediately under the syncytiotrophoblast. Both structures contribute to the formation of the villi and ultimately the placenta. Villous cytotrophoblast fuse to form the syncytiotrophoblast layer that contributes to the exchange of gas and nutrient, as well as to the process of waste elimination. In anchoring villi, cytotrophoblast generates a multilayered column of highly invasive extravillous trophoblast (EVT) that later migrates into the decidua and remodels the endometrial spiral arteries to produce the low-resistance vascular system that is essential for foetal growth (Pijnenborg et al., 1981a,b; Aplin, 1991).

Meanwhile, the embryoblast cell mass organizes itself into a flat disc-shaped structure, the bilaminar germ disc, which consists of two layers of cells (the epiblast and the hypoblast), with the primitive streak forming ulterior on the surface of the epiblast. During the gastrulation process, the cells from the epiblast layer migrate towards the primitive streak to form the mesoderm layer between the epiblast and the hypoblast layers—forming thus the trilaminar germ disc, composed by ectoderm, mesoderm and endoderm. These three layers are responsible for the formation of all the body organ systems.

An important but yet unresolved question is when exactly the critical periods for ethanol exposure are manifested during embryogenesis, and which of the molecular
components that are expressed during such periods are ethanol-sensitive (Chudley et al., 2005; Zhou et al., 2011).

**Placental functions**

The passage of nutrients from the maternal blood to the foetus is mediated by the placenta, an organ that establishes critical functional connections for embryonic survival (Cross et al., 1994). The placenta transports oxygen, nutrients and antibodies to the foetus and removes carbon dioxide and metabolic waste; serves as a protective barrier against harmful effects produced by certain drugs and microorganisms; acts as a partial barrier between the mother and foetus in order to prevent foetal and maternal blood from mixing; and produces steroid and peptide hormones essential for maintaining the pregnancy (Bosco, 1995, 2005). It is essential then that for a normal foetal metabolism and growth, an adequate exchange across the placenta must occur.

Epigenetic regulation of the placenta evolves during the preimplantation developmental period and further gestation. Epigenetic modification refers to heritable changes in gene expression that are not mediated by alterations in the DNA sequence (Jaenisch and Bird, 2003). These expression patterns, including the important parent-of-origin-dependent gene expression resulting from genomic imprinting, play a pivotal role in proper foetal and placental development. Imprinted genes are those whose expression depends on their parental origin (Delaval and Feil, 2004). Imprinting is also controlled by epigenetic mechanisms under the control of environmental factors and nutrients (Reik et al., 2003). This may provide a linkage between maternal nutrition and foetal placental growth (Myatt, 2006; Nelissen et al., 2011).

It is known that the number of placental genes altered by moderate ethanol exposure plays critical roles in pattern formation during the development of the nervous system. For example, bone morphogenic proteins coordinate the acquisition of pattern information and the stimulation of proliferation in the embryonic spinal neural tube (Chesnutt et al., 2004). A substantial amount of work remains to be done in order to confirm the utility of placental gene alterations as a biomarker system, both for detecting ethanol consumption and for its potential use as a prognostic indicator of adverse neurobehavioral outcomes in the absence of morphological alterations.

Systematic examination of altered gene expression as a function of different levels and patterns of ethanol consumption, as well as the persistence of gene alterations after the last drinking episode are critical questions that remain to be addressed. Further, how the presence of other common pregnancy risk factors impacts ethanol-induced alterations in placental gene expression patterns needs to be determined. For example, how will concomitant exposure to factors such as nicotine (Aliyu et al., 2009), other drugs of abuse, stress, malnutrition or heavy metals exposure modify a biomarker signature pattern? Data from such studies would be critical for interpreting altered patterns of placental gene expression in clinical studies (Rosenberg et al., 2010).

It is also well known that the placenta generates reactive oxygen species (ROS), which may contribute to the oxidative stress observed even in normal pregnancy, but this is increased in pregnancies complicated by preeclampsia (PE), IUGR and pre-gestational diabetes, where oxidative and nitrative stress are increased (Webster et al., 2008; Myatt, 2010). Recently, it has been demonstrated that identical maternal ethanol exposure levels produced different levels of foetal exposure in a dizygotic human twin pair (Gareri et al., 2009). This was also observed in guinea pig littersmates through concentration of fatty acid ethyl meconium analysis (Chan et al., 2004; Brien et al., 2006).

**Oxidative stress in the placenta**

Placental pathology has long been associated with IUGR and PE in humans. The development of placenta is a highly regulated process and is therefore quite susceptible to perturbation. Foreign compounds may interfere with placental functions at many levels, including signalling, production and release of hormones and enzymes, transport of nutrients and waste products, implantation, cellular growth and maturation, and finally in the delivery. Placental responses may also be due to alcohol/toxicodynamic responses, e.g. hypoxia (Myllynen et al., 2005; Cross, 2006; Salihu et al., 2011). On the other hand, oxidative stress constitutes a unifying mechanism of injury of many types of disease processes. It occurs when there is an imbalance between the production of ROS and the ability of the biological system to readily detoxify these intermediate reactive or easily repair the resulting damage (Rodrigo et al., 2005; Wells et al., 2009).

The mechanism of oxidative stress seems to operate in alcohol ingest pregnancy (Ornay, 2007). It has been demonstrated that ethanol exposure induces oxidative stress in the human placental villi (Kay et al., 2000). This may account for the decreased nitric oxide (NO) release because NO may be shunted towards scavenging free radicals (Dotsch et al., 2001). Decreased NO availability could adversely affect placental blood flow regulation, which could, in turn, account for the restriction of growth observed in ethanol-exposed foetuses.

The defence mechanisms against ROS damage are also enhanced in pregnancy. Thus, a progressive increase in free radical scavengers, such as glutathione and bilirubin, as well as in the activity of antioxidant enzymes in placenta has been reported (Watson et al., 1997; Qanungo and Mukherjea, 2000). In the same line of evidence, Gundogan et al. (2010) have demonstrated the impact of ethanol-mediated oxidative stress on placental trophoblast function and its potential impact on pregnancy loss. They found that rat chronically exposed to ethanol during gestation evidenced placental apoptosis/necrosis. Ethanol mediates its adverse effect on pregnancy maintenance via inhibition of the prolactin family hormones (Soares, 2004).

**Peroxytirnitrte mediates lipid oxidation and nitration**

As the human foetal-placental vasculature lacks autonomic innervation, autocrine and/or paracrine agents such as NO radical play an important role in the regulation of foetal-placental blood flows (Myatt and Cui, 2004). Conversely, the activity of NO is prolonged by the presence of superoxide dismutase, which removes superoxide. Nevertheless, when tissues are induced simultaneously produce both NO and superoxide in a concentrated and localized manner by inflammatory stimuli, sepsis and ischemia/reperfusion, both NO and superoxide react to produce the peroxynitrile anion (ONOO\(^-\)), a powerful oxidant of a variety of biomolecules (Beckman et al., 1994) that has cytotoxic activity and
inhibits mitochondrial electron transport, resulting in the inhibition of cellular respiration (Radi et al., 1994; Szabó, 2003) that cause lipid peroxidation and nitrate tyrosine residues (Brown and Borutaite, 1999; Palacios-Callender, 2004). In addition, Myatt et al. (1996, 2002) observed increased expression of nitrotyrosine residues in the foetal vasculature and villous stroma of preeclamptic and diabetic placentas.

Peroxynitrite has also been shown to disorganize actin polymerization through actin nitration (Kasina et al., 2005). These effects have been associated with disruption of both intestinal (Banan et al., 2001) and endothelial barrier function (Neumann et al., 2006). It is important to note that the placenta plays a function similar to that of the intestine in order to absorb metabolites and it has also been demonstrated that peroxynitrite produce intestinal barrier dysfunction mediate by ethanol-induced microtubule disruption (Banan et al., 2000). Once the level of cellular damage inflicted by peroxynitrite supersedes any possibility of repair, the cell eventually dies via one of the two main pathways of cell demise, necrosis or apoptosis (Bonfoco et al., 1995; Virag et al., 2003).

On the other hand, Olney et al. (2002) reported that a single episode of ethanol intoxication, lasting for several hours, can trigger a massive wave of apoptotic neurodegeneration in the developing rat or mouse brain. The window of vulnerability coincides with the developmental period of synaptogenesis, also known as the brain growth-spurt period, which in rodents is a postnatal event, but in humans extends from the 6 month of gestation to several years after birth (Ikonomidou et al., 2000).

**Placental apoptosis**

The morphological architecture and function of the human placenta depends upon an adequate balance in the process of proliferation, differentiation and apoptosis. An imbalance between them may result in spontaneous abortion, PE, preterm delivery and reduced foetal growth (Myatt, 2002; Crocker et al., 2003). In the last decade Huppertz et al. (2006) have characterized the role of the apoptosis cascade in villous trophoblast turnover and syncytiun formation. Apoptosis has been observed to naturally occur in placentas of normal human pregnancies, but as expected, placentas from women with PE or IUGR show enhanced apoptosis when compared with those from normal pregnancy (Allaire et al., 2000).

**Oxidative stress in the foetal development**

Exposure of the developing placenta, embryo or foetus to environmental agents such as alcohol or acetaldehyde is known to produce anatomical anomalies leading to in utero death or structural birth defects (Gundogan et al., 2008), a process commonly termed teratogenesis (Wells et al., 2009).

The cellular mechanisms underlying ethanol-induced damage in utero are not yet well understood, although induction of oxidative stress is believed to be a putative mechanism due to an imbalance in prooxidant and antioxidant levels (Cohen-Kerem and Koren, 2003). Ethanol can induce oxidative stress both directly and indirectly. The direct effect is achieved by the formation of free radicals, which react with various cellular components. Formation of free radicals in the presence of ethanol has been demonstrated in cell lines such as rat hepatocytes (Henderson et al., 1995) as well as in the rat animal model (Reinke et al., 1987). Another direct oxidative stress effect of ethanol is the formation of ROS (Dong et al., 2010), which probably plays a role in mediating programmed cell death (Jacobson, 1996). Oxidative stress mechanisms seem to operate in teratogenicity caused by hypoxia as well as alcohol abuse (Ornoy, 2007). It has also been reported in rat hepatocytes that ethanol can induce oxidative stress indirectly by reducing the intracellular antioxidant capacity, such as the levels of glutathione peroxidase (Oh et al., 1998; Bailey et al., 2001).

The effects of ROS and oxidative stress on placental, embryonic and foetal development may adversely alter the development by causing oxidative damage on the cellular lipids, proteins and DNA, and/or by altering signal transduction. The latter can adversely alter the cellular function or trigger apoptotic or necrotic cellular death (Wells et al., 2009).

Additionally, the low antioxidant defences in foetal tissues and accumulation of toxic aldehyde products of lipid peroxidation predispose the foetus to oxidative damage. Wentzel et al. (2006) found that vitamin E treatment administered to pregnant chronic ethanol-consuming rats diminishes foetal malformations. This study was in agreement with the study of Heaton et al. (2000), who were able to block the effects of ethanol on Purkinje cells by using a very high dose of vitamin E.

However, some authors have not found a clear effect of antioxidant vitamin E supplementation (Tran et al., 2005), thereby raising the issue of the importance of dosage and variable sensitivity in different tissues towards the deleterious effects of ethanol. Wentzel and Eriksson (2008), using two different rat strains exposed to ethanol for 48 h in early pregnancy (9–11 days of gestation), have proposed a role for genetic predisposition, oxidative stress and apoptosis in ethanol teratogenicity. These authors suggest that the teratogenic predisposition of the more susceptible rat strain may reside, at least in part, in the regulation of the ROS-scavenging enzymes. Folic acid also acts as an antioxidant and can modulate the effects of ethanol on Purkinje cells by using γ-aminobutyric acid receptor B (GABA_B R) and protein kinase A-α (PKA) expression during early rat foetal development.

**Alcohol and pregnancy hypertension**

It has been demonstrated that pregnancy-induced hypertension contribute to low weight at birth and preterm delivery. Although alcohol-associated hypertension is common among women who drink heavily (Ascherio et al., 1996; Seppa et al., 1996), the effect of alcohol abuse on the course of hypertensive pregnancies has not been sufficiently studied. Mankes et al. (1985) showed that alcohol administration during pregnancy increased hypertension, caused multiple birth defects, and increased foetal mortality in both normotensive and spontaneously hypertensive rats.
Neuroactive steroid responses to hypoxic stress

Compromised pregnancies can have serious effects on foetal brain development, the nature of which depends, in large part, on the time of gestation when they occur. Maternal stress, infections or problems with placentalation can affect brain development due to changes in the delivery of oxygen and glucose to the brain, or the cytokine environment, leading to acute cell death (Inder et al., 1999; du Plessis and Volpe, 2002; Hirst et al., 2009). In addition, chronically suboptimal conditions during pregnancy dramatically increase the sensitivity of the foetal brain to further episodes of hypoxia/ischaemia around the time of birth and in the immediate neonatal period. The resulting damage can lead to severe neuropathologies, including intellectual impairment and cerebral palsy (Inder et al., 1999).

Hirst et al. (2009) used the term neuroactive steroids to refer to steroids that influence foetal or maternal nervous system function and may be synthesized in both the nervous system and/or other peripheral organs. Pregnancy is characterized by elevated neuroactive steroid levels both in the maternal circulation and brain, as well as in the foetal brain. The placenta is a source of considerable amounts of progesterone that enter not only into the maternal circulation, but also into the foetal blood and the foetal brain, where it is actively converted into allopregnanolone (Crossley et al., 1997). It has also been reported that severe foetal hypoxia produces greater damage when the synthesis of allopregnanolone is suppressed (Yawno et al., 2007; Hirst et al., 2009). Evidence from animal studies indicates that elevated neuroactive steroid levels in pregnancy suppress excitability and increase lethargy (Puolletti et al., 2006). These alterations are resolved at birth with the removal of the placenta, suggesting that placental progesterone production is mostly responsible for the elevated neuroactive steroid levels. In addition, progesterone has been found to act on gene expression in neural cells to promote myelination by interaction with associated Schwann cells. As progesterone receptors were not detectable in Schwann cells, these observations suggest a possible interaction between neuronal and glial cells in order to promote myelination (Schumacher et al., 2007).

In another line of evidence, it has been demonstrated that human and animals foetus prenatally exposed to alcohol have smaller brain size and thinner cerebral cortex, leading to significant decreases in the total cell number (Miller and Potempa, 1990; Ashwell and Zhang, 1996; Miller, 1996; Archibald et al., 2001). Amino-acid-activated ion channels of excitatory (glutamate) and inhibitory (GABA) neurotransmitters in the prenatal rat brain have been shown to be altered in these fetuses (Lee et al., 1994; Allan et al., 1998; Naseer et al., 2010). Additionally, Ikonomidou (2000) demonstrated that ethanol effects on the developing rat brain trigger a widespread neuronal death by blocking the N-methyl-d-aspartate (NMDA)–glutamate receptor and activating GABA_A receptors. It has also been reported that neuroactive steroids reduce NMDA-induced excitotoxicity both in vitro (Lockhart et al., 2002) and in vivo models of brain injury (Djobali et al., 2005). These excitatory pathways contribute to brain injury in the neonate following acute hypoxic episodes that may occur around the time of birth (Gilbert Evans et al., 2005).

Impaired placentation in rat FAS

IUGR is a key feature of FAS, and recently Gundogan et al. (2008, 2010) have demonstrated in the rat that chronic gestational exposure to ethanol causes increased foetal resorption as well as impairment in placental development, and placentalation. Since ethanol in maternal blood reaches the foetus and/or the placenta, its toxic effects on the foetus can be directly or indirectly mediated. The direct effect of foetal exposure to ethanol was demonstrated by Chu et al. (2007) on rat foetal brain development and the indirect effect is related to placental pathology, especially within the rat placental barrier. The ischemia or infarction observed in ethanol-exposed placentas reduced the thickness of the organ by an increase in cellular necrosis. Since the exchange of nutrients between the mother and the foetus occurs within the placental barrier, ethanol-induced reductions in the mass of this layer could impair the delivery of nutrients to the foetus and thereby resulting in IUGR.

Gundogan et al. (2008, 2010) described that a second major placentation abnormality associated with chronic gestational exposure to ethanol was failure of maternal uterine spiral arteries to remodelling by EVT. This compromises both placental blood flow as well as the nutrients exchange (Pijnenborg et al., 1981b). Therefore, the motile and invasive properties of EVT are critical for the establishment and maintenance of pregnancy, and ensuring adequate blood and nutrient delivery to the foetus in order to support growth and development (Gundogan et al., 2008).

Alcohol-induced apoptosis of neural crest cells

Although it is clear that exposure to alcohol during gestation can have profound consequences, not all the cells within the embryo are equally affected. Studies in mice and chicks models have demonstrated that alcohol exposure at specific stages of early embryonic development results in significant death among cells destined to give rise to facial structures, such as the cranial neural crest cells (cNCC). Alcohol triggers apoptosis in retinoic acid (RA, a type of vitamin A) deficient cells from the neural crest, and also reduces levels of antioxidant compounds such as free radicals scavengers (Smith, 1997). Furthermore, Wentzel and Eriksson (2009) demonstrated on NCC of 10-day rat embryos that ethanol causes a shift towards apoptosis in both neural cells from cNCC as well as trunk (tNCC) portion, which is diminished by treatment with the antioxidant N-acetylcysteine. Oxidative defence genes as well as genes involved in NCC development are differently affected in cNCC compared with tNCC upon ethanol exposure: the cNCC Hox genes are down-regulated, whereas tNCC are up-regulated. Normal craniofacial morphology develops as a consequence of interactions between embryonic tissues such as cNCC, mesoderm and ectoderm and requires precise regulation of cell movement, growth, patterning and differentiation of craniofacial tissue (Sant’Anna and Tosello, 2006). Alcohol exposure during the gastrulation period decrease the rate of cell division in mice embryos (Sulik, 1984), and the process of migration of mesoderma cells towards the primitive streak (Nakatsuji and Johnsson, 1984). Deficiencies in gastrulating mesodermal cells are responsible for inducing and maintaining neuroepithelial differentiation, an adverse effect on the mesoderm that
could result in size reduction in the neural plate, which was particularly noticeable in the forebrain region (Sulik et al., 1984).

Interestingly, alcohol exposure causes cCNN apoptosis only if alcohol is administered before the CNN migrate from their birthplace into the neuroectoderm. Once the cells began the migration towards the site where the face will develop, they become resistant to alcohol-induced apoptosis (Cartwright and Smith, 1995). Studies in animal models have linked the characteristic facial abnormalities in FAS to cell death by apoptosis of cCNN during very well defined periods of vulnerability such as gastrulation or neurulation (Cartwright et al., 1998). One mechanism by which this may occur is thought to be the formation of free radicals (Chen and Sulik, 1996). Others described mechanisms are deficiency in RA, altered expression of homeobox genes, intracellular communication and alterations in the activity of growth factors. Because neural crest cells differentiate into several neuronal lineages, these findings offer novel insights into how ethanol disrupts the processes of early neurogenesis (Garic et al., 2011).

The fact that alcohol also has an effect on NCC of odontogenesis makes the tooth a good representative organ model to study developmental toxicity of ethanol (Bowden et al., 1983; Campos and Duranza, 1988; Kattainen et al., 2001).

**Foetal alcohol exposure and alterations in brain and behaviour**

Ethanol has a neuroteratogenic effect on in vitro generation of neural cells from human embryonic stem cells (Talens-Visconti et al., 2011). These authors found that ethanol exposure affects: (a) cell differentiation into neurons and astrocytes, (b) disrupts the actin cytoskeleton and (c) affects expression of different genes associated with neural differentiation, resulting in the FASD condition (Kumada et al., 2007).

Sustained exposure to alcohol during the period of gastrulation has a negative impact on the developing brain (Fig. 1), reducing the neural cell progenitor pool (Rubert et al., 2006) and causing long-term effects on the forebrain (Ashwell and Zhang, 1996). The cerebral cortex formation as well as the increase in both cortical surface area and neural cell number seems to be critical for the emergence of complex cognitive functions. The neural cell number is in turn dependent on the number of neural progenitor cells, their rate of proliferation and the mitotic cycles they undergo (Rubert et al., 2006). It has been reported that ethanol can induce microcephaly and deficits in cognitive functions and in some behavioural responses (Mattson and Riley, 1998). A critical period for ethanol-induced microcephaly and teratogenesis has been shown to occur during early embryogenesis in the rat brain, a period encompassing the first 10 days of gestation, the equivalent to the first trimester in human (Maier et al., 1997; Guerri, 2002). During this period, the neural progenitor cells, radial glia (RG) are generated, and dysfunctions in its proliferation and survival could lead to an important reduction in the final number of neural cells (Cameron and Rakic, 1994).

The establishment of RG cells from the neuroepithelium precedes the generation and migration of neurons in the cerebral cortex. During early corticogenesis, RG cells generate neurons and then guide the daughter neurons in their migration towards the developing cortical plate (Rakic, 1972;...
Effect of alcohol on cardiac embryo development
Cardiac malformations are frequently seen in FAS, the most common being ventricular septal defects (Sardon et al., 1981), pulmonary artery hypoplasia, interruption of the aortic arch (Terrapon et al., 1977), atrio-ventricular defects, patent ductus arteriosus and Fallot teratology (Loser et al., 1992). Recently, it has been found that exposure of zebrafish embryos to ethanol during development results in structural and functional changes in the heart that mimic malformations that occur in patients with FAS (Dlugos and Rabin, 2010).

In the previous paragraphs, it has been described that alcohol alters the migration of neural crest cells. It is important to emphasize that in both avian and mammalian embryos, a migration pathway is present from the occipital neural crest cells to the cardiac outflow tract, and that a disturbance in this process can result in cardiac septation defects such as aortic pulmonary septum (Carlson, 2005), similar to that observed in cardiac malformations of FAS babies.

Effect of alcohol on liver embryo development
The liver is also affected in FAS, and the characteristic deformities observed are similar to those evidenced in alcoholic liver disease in adult. The more commonly seen features include hepatomegaly and raised levels of serum transaminases. Light microscopy revealed increased parenchymal fat with portal and perisinusoidal spaces containing deposits of intermediated and large size collagen fibres, myofibroblast and occasional Ito cells, as well as subendothelial basement membrane-like material (Lefkowitz et al., 1983). The presence of thick sclerotic central veins in the hepatic lobule has also been evidenced, in conjunction with the occurrence of extrahepatic biliary atresia (Daft et al., 1986). Furthermore, Renaud-Piqueras et al. (1997) demonstrated that prenatal exposure to ethanol affects the morphological, structural and functional features of the Golgi apparatus, thus altering the glycosylation process in foetal hepatocytes, causing finally an accumulation of hepatic proteins. Additionally, Fofana et al. (2010) demonstrate that prenatal alcohol exposure alters protein phosphorylation in rat offspring liver and that the principal pathway affected by these protein alterations includes cell signalling, cellular stress, protein synthesis, as well as glucose, aminoacids, adenosine and energy metabolism.

SUMMARY AND CONCLUSIONS
We have reviewed the principal evidence pointing to the teratogenic effects of prenatal ethanol exposure on placenta, placenta growth, placenta function and foetal development, with emphasis in the development of the central nervous system. These evidences strongly suggest an association between alcohol teratogenic effect, hypoxia and oxidative stress, pinpointing molecular mechanism involved (e.g. apoptosis) and the range of effects. The present review also sums up evidence that could explain some of the abnormalities observed in brain development that could be related to behavioural problems observed in individuals with FAS/FASD.

Some of this evidence suggests that alcohol consumption might produce failures in the normal migration of radial cells, from which the rest of the brain cells would eventually develop.

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