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ROLE OF REACTIVE OXYGEN SPECIES AND APOPTOTIC GENES IN BAD OBSTETRIC HISTORY

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Abstract

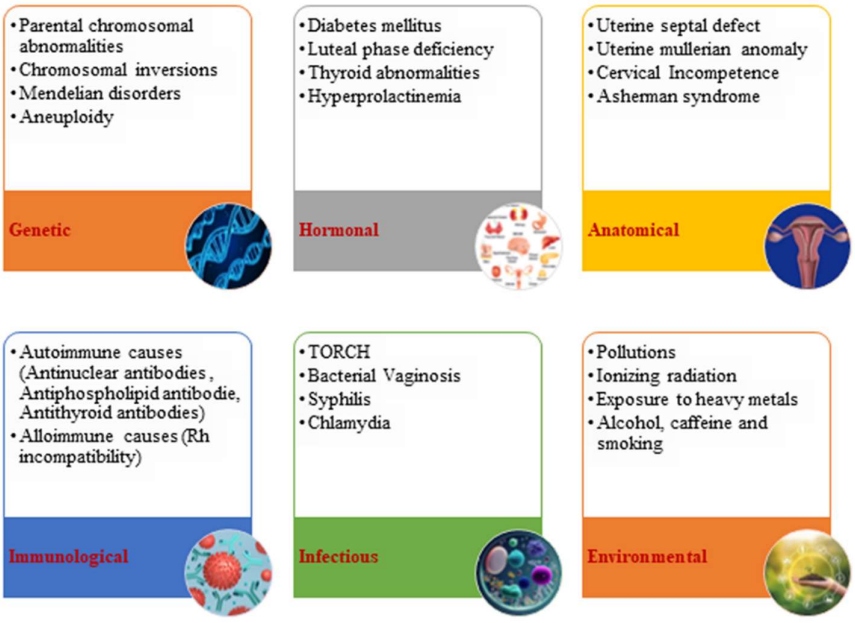
Bad Obstetric History (BOH), which refers to a range of outcomes during pregnancy like miscarriages, stillbirths, and preterm births is still not fully understood when it comes to the molecular mechanisms involved, despite advancements in obstetric care. This overview addresses the functions of apoptotic genes and Reactive Oxygen Species (ROS) in the pathogenesis of BOH. ROS plays a major role in cellular processes. However, when there is a production of ROS due to stress, it can lead to damage and dysfunction at the cellular level. In cases of BOH, increased levels of ROS have been linked to issues with development problems at the maternal interface and damage to fetal tissue. Apoptosis is a regulated form of cell death that plays a role in maintaining tissue balance. When apoptosis pathways are disrupted or imbalanced, it leads to increased or decreased cell death. Both scenarios can negatively impact pregnancy outcomes. The expression and activity of genes like members of the Bcl 2 family, p53, and caspases have been associated with pregnancy complications such as recurrent miscarriages and stillbirths. This summary examines research findings on how ROS and apoptotic genes interact with each other within the context of BOH. This review brings attention to the targets that could be targeted for treatments to reduce oxidative stress and re-establish the balance in pregnancies that are affected. Moreover, this summary emphasizes the importance of conducting studies to understand the network of cellular processes involved in BOH. Ultimately, these efforts will lead to improved therapeutic approaches to care.

Key words: Apoptosis, Bad obstetric history, Oxidative stress, Reactive oxygen species, Recurrent pregnancy loss.

Introduction

Pregnancy loss can be difficult for the couple as well as the attending obstetrician, particularly if it happens repeatedly [1, 2]. The worldwide incidence of BOH is said to be around 1-2%. Merely 40-50% of instances involving women with bad obstetric histories have an established underlying contributing cause [1-3]. Still, about one-third of these instances are classified as unexplained etiologies because they lack a documented underlying cause [4]. Examination of the uterine environment is a standard part of the assessment to identify the reasons behind miscarriages. If pregnancy does occur, the endometrium needs to develop properly so that it can continue to support and nourish the developing pregnancy. Processes that interfere with normal embryonic and endometrial interactions can result in pregnancy failure [5]. The exact causes of bad obstetric history are not yet fully understood, but it is known that several factors, such as genetic, endocrinological, anatomical, immunological, environmental, infectious, and lifestyle, can contribute to its development. Common causes of BOH and its underlying factors are depicted in Figure *1* [6-9].

Figure 1: Common causes of BOH



Reactive oxygen species and antioxidants in BOH

Reactive oxygen species are highly reactive and unstable molecules that have a role in many cellular and physiological processes [10, 11]. Superoxide anion radicals ($O2^{-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH^{\bullet}$) are the common types of ROS [12]. Reactive oxygen species attack the lipids, proteins, and nucleic acids in the cells and cause peroxidative damage. Overexpression of ROS is toxic to human cells and can cause BOH, which includes Intrauterine Growth Restriction (IUGR), Recurrent Pregnancy Loss (RPL), and spontaneous

abortion during pregnancy [13]. ROS also play a crucial role in the process of placentation, contributing to cell signaling, trophoblast invasion, and vascular development. However, excessive ROS production results in placental dysfunction and pregnancy complications. Figure 2 shows the role of ROS in placentation and how it leads to BOH.

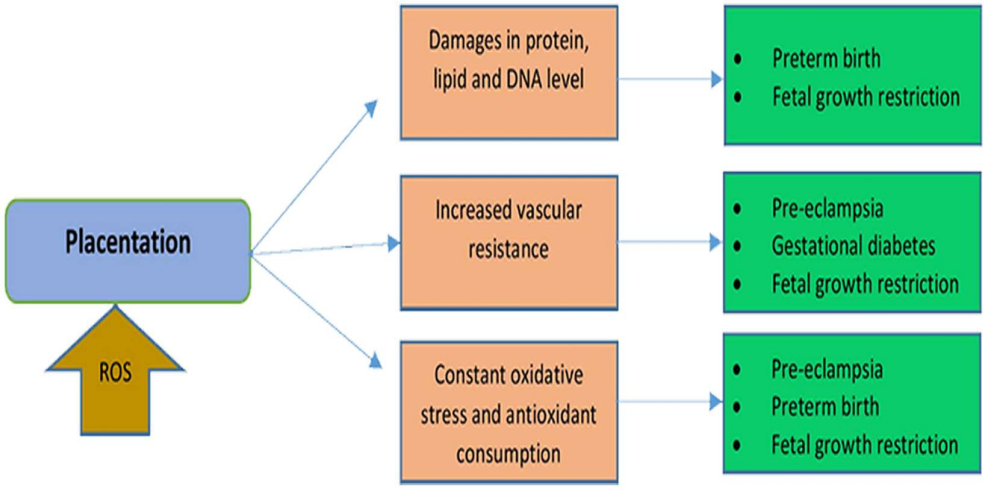


Figure 2. Role of ROS in placenta: An increased level of ROS leads to oxidative stress, which can cause abnormal placentation if the antioxidant - ROS balance is disturbed. This is because oxidative stress can overpower antioxidants and induce cellular senescence by making the placenta more vascular-resistant. Pre-eclampsia, fetal growth restriction, gestational diabetes mellitus, and preterm birth are the complications related to it.

Our body has a well-functioning antioxidant system that helps protect us from the damage caused by ROS [14]. ROS generation in cells and the body's capacity to eliminate them are out of balance, which leads to oxidative stress [15]. In several investigations on humans and animals, ROS and antioxidants have been discovered in the reproductive system. However, the exact source of ROS production in the female reproductive tract is still unclear. Reactive oxygen species and antioxidants have been found in the follicular fluid, endometrium, tubal fluid, oocytes, and embryos [16-19]. An imbalance in pro-oxidant and anti-oxidant systems in the follicular fluid may lead to abnormal development of oocytes and impaired fertility, as well as damage to the oocyte's DNA [12]. Reactive oxygen species act on the cellular molecules of the embryo and may block or retard early embryonic development [19]. Enough evidence is available to suggest that embryos produce ROS, which may originate from embryo metabolism and the surrounding environment [20, 21].

Antioxidants prevent free radical damage by preventing the formation of scavenging radicals or by promoting their decay [22]. Antioxidants inhibit oxidant attacks on carbohydrates, lipids, proteins, and DNA in different ways. The most common enzymatic antioxidant, superoxide dismutase, converts superoxide to H_2O_2 in both the cytosol and mitochondria. Oxidative stress

is produced by the altered action of this enzyme or its associated enzymes [23]. Non-enzymatic antioxidants include ascorbate (vitamin C), α-tocopherols such as tocopherol (vitamin E), and carotenoids such as β-carotene, all of which scavenge and neutralize free radicals [14, 24]. There are no clear advantages to using antioxidants to prevent BOH in all pregnant women since some research suggests that oxidative stress may only be important in certain populations of pregnant women [25]. Recent theories have reinforced the concept that antioxidants, such as ALA, can protect the fetus against oxidative stress, particularly toward the end of pregnancy. ALA (α-lipoic acid) has come out as a promising treatment for bad obstetric outcomes; however, the impact of antioxidant supplementation or a diet abundant in antioxidants on reducing oxidative stress remains unknown [14, 24, 26]. Further research in this field is required to understand how to diminish oxidative stress during pregnancy and to develop effective treatments for bad obstetric outcomes. Table 1 shows the beneficial effects of ROS and antioxidants in the female reproductive systems of various animals and humans [13].

Table 1: Effect of ROS and antioxidants in female reproductive system

Oxidant/antioxidant	Functions	Reference
↑ expression of GSTm2	Preparation of uterus for blastocyst implantation	[27]
↑ expression of SOD1 in early pregnancy	Directions of luteal functions	[28]
↑ SOD1, GPX and GST activities in early pregnancy	Rescue Corpus luteum form apoptosis	[29]
↑ CAT, SOD and GPX in placental and fetal tissues	Defence against ROS toxicity in feto-placental system	[30]
↑ GPX and GSR activities	Regulator of H_20_2 and cell death in placental progression	[31]
Silence the expression of GPX4	Affect the functions of embryonic brain and heart.	[32]
↑ CAT and GPX and oviduct GSH in oestrus cycle	Govern hydrogen peroxide during fertilization	[33]
↑ CAT and GPX, and GSH in placental tissues	Regulates hydrogen peroxide and activation of placental differentiation	[34]
↑ uterine peroxide at blastocyst attachment	Defense to negative effects of hydrogen peroxide actions	[35]
↓ hydrogen peroxide and superoxide radical	Control uterine contractions	[36]

Role of apoptosis

Apoptosis is essential for various physiological processes, including tissue development, maintenance, and the elimination of damaged or unnecessary cells [37]. Reactive oxygen species impair placental development, which results in destroying the protein, lipid, and DNA of placental cells, leading to apoptosis [14]. Apoptosis can be activated either by intrinsic or

extrinsic pathways [38]. Some studies suggest that crossover can occur between these two pathways [39, 40]. Disproportionate apoptosis, either inadequate or excessive, is a reason for many diseases, including neurodegenerative diseases, ischemic damage, autoimmune disorders, and many types of cancer [41].

Caspase family

Caspases act as key mediators in apoptosis by cleaving specific cellular proteins and facilitating the orderly dismantling of the cell. The apoptotic process involves both initiator caspases and executioner caspases [42]. Caspase-8 and caspase-9 come under initiator caspases. Caspase-8 is activated in response to extrinsic signals, such as the binding of death ligands to death receptors on the cell surface. This is known as the extrinsic pathway [43]. Caspase-9 is activated in response to intrinsic signals, such as DNA damage or cellular stress, leading to the release of cytochrome c from the mitochondria. This is known as the intrinsic pathway [44]. Once initiated, caspase-8 or caspase-9 triggers executioner caspases, such as caspase-3, caspase-6, and caspase-7 [45]. The activation of executioner caspases leads to the cleavage of structural and nuclear proteins, resulting in cell shrinkage, nuclear fragmentation, and the formation of apoptotic bodies. These apoptotic bodies are engulfed and digested by neighboring phagocytic cells, or macrophages.

The regulation of caspase activation is tightly controlled by various factors, including inhibitors of apoptosis proteins (IAPs) and Bcl-2 family proteins [46]. Dysregulation of caspase activity can contribute to various diseases, including BOH. To know the role of caspases in BOH, more research is needed to clarify the specific pathways and mechanisms involved in it. The role of caspases in apoptotic pathways is shown in Figure 3.

Bcl-2 family

B-cell lymphoma-2 (Bcl-2) plays a crucial role in regulating apoptosis [47]. Based on their structure and function, they are classified into three categories: pro-apoptotic proteins, anti-apoptotic proteins, and BH3-only proteins. Anti-apoptotic proteins inhibit apoptosis by preventing the release of cytochrome c from mitochondria and thereby promoting cell survival [48]. Examples are Bcl-2, Bcl-XL (Bcl-extra-long), and Mcl-1 (myeloid cell leukemia 1) [49]. Pro-apoptotic proteins facilitate apoptosis through the release of cytochrome c from the mitochondria. It also plays a role in mitochondrial outer membrane permeabilization (MOMP), leading to the release of apoptogenic factors [50]. Examples are Bax, Bak, and Bok [51]. Excess of pro-apoptotic proteins and deficiency of anti-apoptotic proteins lead to increased apoptosis in trophoblast cells, contributing to bad obstetric history. BH3-only proteins can promote apoptosis by either inhibiting anti-apoptotic proteins or by activating pro-apoptotic proteins. Examples are Bim, Bid, Bad, Noxa, and Puma [52].

Anti-apoptotic vs. pro-apoptotic Bcl-2 members of the family play a critical role in determining whether a cell undergoes apoptosis. Pro-apoptotic cells are activated when cells receive a signal for apoptosis, which increases the permeability of the mitochondrial membrane and leads to

the release of apoptogenic factors, which finally triggers the apoptotic cascade. The complex interactions and balances among various members of the Bcl-2 family are essential for controlling the survival and death of the cells.

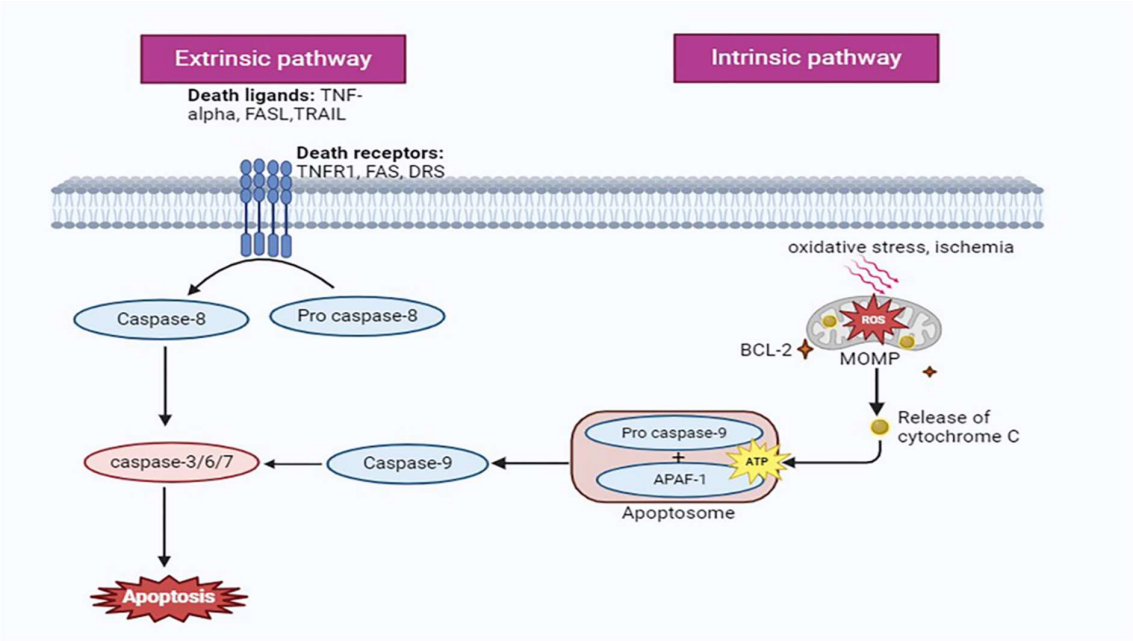


Figure 3. Apoptosis pathway: Apoptosis works through extrinsic and intrinsic pathways. The intracellular pathway is initiated by signals within the cell, such as DNA damage, oxidative stress, etc. These signals cause the activation of pro-apoptotic members of the BCL-2 family (e.g., Bax, Bak). These proteins cause mitochondrial outer membrane permeabilization (MOMP) and the release of cytochrome C into the cytoplasm. Cytochrome C binds to APAF-1 (apoptotic protease activating factor-1) and ATP, forming the apoptosome complex. It activates pro-caspase 9 to caspase 9 (initiator caspase). Later, caspase 9 induces apoptosis directly by activating executioner caspases, such as caspases 3/6/7. The extrinsic pathway is initiated by external signals such as death ligands (TNF-alpha, FASL, and TRAIL) through their receptors (TNFR1, FAS, and DRS). These death ligands activate pro-caspase 8 to caspase 8 (initiator caspase). Later, it induces apoptosis directly by activating executioner caspases such as caspases 3/6/7 [53, 54].

P53 gene

The p53 gene, also known as TP53 (tumor protein 53), is a critical gene that plays a central role in preventing the formation and progression of cancer. It is classified as a tumor suppressor gene because its normal function is to regulate the cell cycle and prevent the development of tumors. Even though the major role of the p53 protein in tumor suppression is well established, recent studies have shown a novel function of p53, i.e., p53 regulates blastocyst implantation and maternal reproduction. This function of p53 is mediated by a multi-functional cytokine called leukemia inhibitory factor (LIF) [55].

Key roles of p53 in apoptosis

P53 is involved in the regulation of DNA repair mechanisms. In response to DNA damage, p53 can induce cell cycle arrest to allow for DNA repair. When DNA damage is severe and irreparable, p53 can initiate apoptosis as a means to eliminate cells with damaged DNA and prevent the formation of potentially harmful mutations. Direct activation of pro-apoptotic gene transcription by p53 is possible for genes belonging to the Bcl-2 family, such as Bax. Bax promotes apoptosis by inducing the permeability of the outer membrane of mitochondria, which leads to the release of cytochrome c [48, 56]. Villalpando-Rodriguez and Gibson mentioned that p53 can bind to and inhibit the anti-apoptotic protein Bcl-2, further promoting apoptosis. P53 can initiate the expression of death receptors, such as the CD95 / Fas receptor and its ligand FasL. The binding of FasL to Fas triggers the extrinsic apoptotic pathway [57].

It is important to note that the precise role of p53 in apoptosis can be context-dependent. While p53 is generally considered a pro-apoptotic factor, under certain circumstances or in specific cellular contexts, p53 may have anti-apoptotic functions. The intricate regulation of apoptosis by p53 reflects its central role in maintaining cellular homeostasis and preventing the development of cancer. Atia TA stated that apoptotic p53 protein overexpression, along with decreased anti-apoptotic Bcl-2 expression in placental tissue during early pregnancy, could lead to pregnancy failure [37].

P53 may function as a post-zygotic selection step to inhibit the proliferation of embryonic and trophoblastic cells. Furthermore, investigations have shown that an abundance of p53 protein is produced by the human placenta in abnormal pregnancies; thus, p53 is suspected to be an important factor in the pathogenesis of placental disorders through the induction of trophoblastic apoptosis [58]. A genetic polymorphism of p53 codon 72 is widely studied for its role in reproductive medicine. However, results on the correlations among polymorphism, recurrent pregnancy loss, and recurrent implantation failure are still inconclusive.

Conclusion

Oxidative stress and apoptosis are two important molecular pathways that are involved in various reproductive processes, such as implantation, placentation, and fetal development. Any impairment in these pathways can lead to adverse pregnancy outcomes, including bad obstetric history. Based on plenty of studies and records, the major causes of BOH appear to be ROS and oxidative stress. Prospective inquiries ought to prioritize the enhancement of intracellular ROS decomposition and the augmentation of antioxidant accessibility. The minimization of reproductive complications will be attempted by employing natural bioactive compounds to target signaling molecules. Many of the steps involved in implantation-apoptosis, angiogenesis, and maintaining genomic stability are also functions regulated by p53, and thus, assumingly, they could also play a broader role in species survival by facilitating implantation efficiency. Therefore, investigating the relationship between oxidative stress, apoptosis-related genes, and p53 gene polymorphism in patients with bad obstetric histories is essential to better understanding the molecular mechanisms involved in this condition. Identifying potential

biomarkers such as p53 gene polymorphism and developing novel diagnostic and therapeutic strategies based on oxidative stress and apoptotic pathways may help reduce the incidence of BOH and improve pregnancy outcomes.

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