Review *Clin Ter 2024; 175 (1):47-56 doi: 10.7417/CT.2024.5033*

The Impact of Oxidative Stress on Pregnancy. The Neglected Role of Alcohol Misuse

A. D'Angelo[1], M. Peracchini[2], A. Agostini[3], C. Di Matteo[4], M. Fiore[5], M. Ceccanti[6], M. Vitali[7], M. P. Messina[1]

[1]Department of Maternal Infantile and Urological Sciences, Sapienza University of Rome, Rome, Italy; [2]USL Toscana Centro, Ospedale S. Giovanni di Dio, Firenze, Italy; [3]Department of Gynecology and Obstetrics – ASL Viterbo, Viterbo, Italy; [4]ASL 02 Chieti Abruzzo, Italy; [5]Institute of Biochemistry and Cell Biology, IBBC-CNR, Rome, Italy; [6]SITAC, Società Italiana per il Trattamento dell'Alcolismo e le sue Complicanze, Rome, Italy; [7]ASUR Marche, AV4, Ancona, Italy

Abstract

Oxygen is essential for human life. However, it could cause damaging effects on biological systems causing oxidative stress. Oxidative stress defined as "an alteration in the pro-oxidant–antioxidant balance in favor of the former that leads to potential damage" is characterized by the release of Reactive Oxygen Species (ROS). Oxidative stress is now recognized to play a central role in the pathophysiology of many different disorders, including complications of pregnancy such as placental pathology, PreEclampsia (PE), Intrauterine Growth Restriction (IUGR), gestational diabetes, and miscarriage. This narrative review aims to summarize pieces of evidence about the role of oxidative stress in the pathophysiology of the main obstetric complications with particular interest in the neglected role of alcohol abuse. ***Clin Ter 2024; 175 (1):47-56 doi: 10.7417/CT.2024.5033***

Keywords: *oxidative stress, pregnancy, placenta, preeclampsia, IUGR, gestational diabetes, miscarriage*

Introduction

Oxygen is a vital element for living beings and it has both positive benefits and potentially damaging effects on biological systems (1). Oxygen participates in high-energy electron transfers and contributes to the synthesis of Adenosine-5-TriPhosphate (ATP) (2,3). This is vital for complex multicellular beings, but also it is liable to attack any biological molecule as proteins, lipids, or nucleic acids. Although the human body is under constant oxidative attack from Reactive Oxygen Species (ROS) (4), a complex mechanism of antioxidant defenses has evolved to hold this attack in balance. However, sometimes this equilibrium could be perturbed, leading to oxidative stress. Oxidative stress is best defined as an alteration in the pro-oxidant–antioxidant balance in favor of the production of oxidizing species that leads to potential damage (5).

The prooxidant-antioxidant balance could be disrupted by changes in either side of equilibrium (abnormally high generation of ROS or deficiencies in the antioxidant defenses). The cellular outcome depends on the concentration of ROS causing a wide range of effects from homeostatic adaptations to irreversible damage and cell death. Degradation of pathogens, regulation of cardiac and vascular activities, regulation of intracellular calcium concentration, and phosphorylation or dephosphorylation of proteins are among the functions performed by ROS (6).

Oxygen Species ROS are often called "Free radicals" and are defined as species containing one or more unpaired electrons that confer their high reactivity. In biological systems, free radicals are usually generated from elements involving oxygen and nitrogen. The most important free radical is superoxide anion (7).

Oxidative stress is now recognized to play a central role in the pathophysiology of many different disorders, including complications of pregnancy (8–10).

It has been proved that oxidative stress plays a role in alcohol-induced damage (11)(12–14) and its effects can be mitigated by resveratrol in mice (13) and olive oil in the Mediterranean diet (15,16). In human adults, ethanol is oxidized to acetaldehyde using NAD+, mainly by the hepatic enzyme Alcohol DeHydrogenase (ADH) (13). Acetaldehyde is a highly unstable compound and it quickly forms highly toxic free radicals (17–19).

It has been shown that many pediatric syndromes are associated with oxidative stress like Williams syndrome, Down syndrome, Marfan syndrome, Gaucher syndrome, ataxia–telangiectasia, autistic spectrum disorders, Fanconi's anemia, primitive immunodeficiencies and Fetal Alcohol Spectrum Disorders (FASD) or Fetal Alcohol Syndrome (FAS) (6,20). FASD or FAS are "spectrum" (21) of pathological conditions shown both in human and animal models caused by alcohol drinking during pregnancy (22–25). Alcohol is a legal and socially acceptable substance of abuse, but it is also very harmful because of its impact on physical, mental, family and social health (11,14,26–32). Alcohol is also a teratogenic substance capable of causing malformations when pregnant women drink during pregnancy by

Correspondence: Marco Fiore, Dr., PhD, Institute of Biochemistry and Cell Biology, IBBC-CNR, Rome, email: marco.fiore@cnr.it

ISSN 1972-6007

damaging embryonic neural crest cells (33–36). This can result in the birth of a baby with severe birth defects, including a wide range of deformities and disabilities identified as FASD spectrum.

Acute and chronic alcohol use has been shown to increase the production of ROS, lower cellular antioxidant levels, and enhance oxidative stress in many tissues (37,38). In chronic alcoholics, prolonged exposure of kidneys and liver to these compounds can lead to severe damage. Acetaldehyde is transformed into ALDH2 (Aldehyde dehydrogenase 2 family) and finally into acetyl-CoA. Once acetyl-CoA is formed it enters the normal citric acid cycle (17) and disrupts the metabolism of the Krebs cycle. These alterations can shift metabolism towards lipid metabolism, leading to the synthesis of triglycerides in the liver, causing liver steatosis (39).

This narrative review aims to summarize evidence about the role of oxidative stress in the pathophysiology of the main obstetric complications like placental pathology, Pre-Eclampsia (PE), Intrauterine Growth Restriction (IUGR), gestational diabetes, and miscarriage with particular interest in the neglected role of alcohol abuse.

Methods

Studies examined in this narrative review were obtained by searching MEDLINE (last visited May 2022) with keywords "oxidative stress", "alcohol", "pregnancy", "gestation", "placenta", "placentation", "preeclampsia", "IUGR", "gestational diabetes", and "miscarriage". After filtering for species (human) a total of 1559 papers were found. Filtering for titles, the number of works finally included was 57. Other publications included in the review were retrieved through a manual search of the bibliography.

Results

Placental pathology

The placenta is a discoidal organ whose main duty is to mediate the exchange of oxygen and nutrients between mother and baby during pregnancy. This exchange takes place between the placental villi and intervillous space (40). The process of the formation of the placenta is called placentation. It occurs when the blastocyst implants properly in the myometrium, and the invasion of extravillous trophoblasts into the maternal decidua and spiral arteries results in the modeling of spiral arteries and lowering circulation resistance in the intervillous space (41). When placentation is disrupted, it may result in diminishing of placental function, causing intrauterine growth restriction and increased arterial resistance leading to hypertension and preeclampsia (42).

It has been shown that placental development occurs in a relatively low oxygen concentration, supported by secretions from the endometrial glands rather than the maternal circulation (43,44). It has been postulated that this environment protects the developing embryo from oxygen-free radical damage (45). Maternal arterial blood is prevented from entering the intervillous space of the placenta by plugs of extravillous cytotrophoblast cells (EVT) that invade the mouths of the uterine spiral arteries (46). The maternal intraplacental circulation is only fully established towards the end of the first trimester when these plugs dislocate through a mechanism that is currently unknown (47). This phenomenon results in a shift from low oxygen tension to higher oxygen tension in the intervillous space at the end of the first trimester (48).

Although the rise in oxygen in the intervillous space was described as physiological, it results in some placental oxidative stress (48). To compensate for this elevation, a rise in antioxidant activity is observed as the placenta adapts to this new highly oxygenated environment. There is a strong rise in oxidative stress in the trophoblast associated with the onset of maternal blood circulation in the placenta. This coincides with an potentiation in placental activity of the antioxidants glutathione peroxidase and catalase in normal pregnancy (43). In the placenta, the cytotrophoblasts and the villous stromal cells can synthesize new antioxidants when exposed to ROS (49). However, if the capacity to synthesize new antioxidants is not sufficient to counterbalance the excessive amount of ROS, oxidative stress results in DNA and protein damage and lipid peroxidation (45).

Oxidative stress is an important factor in the pathophysiology of many complications during the second and third trimester of pregnancy. As stated above, inadequate placentation could result in an imbalance of oxidant/antioxidant activity leading to a chronic state of oxidative stress (48,50). Oxidative stress can result in several pregnancy complications such as preeclampsia (PE), which is characterized by maternal endothelial cell dysfunction resulting in systemic endovascular inflammation (51). Early PE (below 32 weeks of gestation) is often associated with IUGR (51).

Preeclampsia (PE)

PE is one of the main diseases of pregnancy, characterized by hypertension and proteinuria, that generally affects pregnancies during the second or third trimester of gestation (52–57). PE is defined by maternal hypertension and proteinuria. In severe cases, the mother may develop comorbidities such as Disseminated Vascular Coagulation (DIC), edema, liver failure and eclampsia. Major fetal complications associated with PE are Fetal Growth Restriction (FGR) resulting in low birth weight, prematurity and fetal death (58–63). Although the pathogenic mechanisms of PE are not completely disclosed, local or systemic oxidative stress may explain the pathological features associated with this complication. It is known that the antioxidant capacity is affected in women with PE leading to an imbalance between the existing pro-oxidant and antioxidant systems with consequent oxidative stress (64). It is unclear whether oxidative stress is the cause or result of PE, despite placental insufficiency due to inadequate remodeling of the maternal vascularity that perfuses the intervillous space plays an important role in the development of this syndrome (64). This condition can lead to a complex process of uteroplacental ischemia-reperfusion with the release of cytotoxic factors into the maternal circulation with a consequent elevation in oxidative stress (65,66). Physiologically, the increase in oxidative stress is counterbalanced by the growth in the

synthesis of antioxidants (67), but, when oxidative stress overcomes the antioxidant defense in the placenta, oxidative damage could spread to distal tissues. Indeed, plasma membranes of circulating blood cells can oxidize passing through the ischemic placenta, thus helping to propagate oxidative stress to the distal tissues (68). Oxidative stress of the syncytiotrophoblast is one of the key characteristics of PE (69,70). It seems to be known that stressed syncytiotrophoblast can release a mix of factors such as pro-inflammatory cytokines, exosomes, anti-angiogenic agents and free fetal DNA into the maternal circulation (71). These factors could be responsible for the disruption of maternal endothelial function leading to a systemic inflammatory response, i.e. the clinical syndrome of PE (72).

Fetal Growth Restriction (FGR)

FGR is defined as the inability of the fetus to reach its genetically determined growth potential (52–56,73). Fetal growth depends on the availability of nutrients, which in turn is related to maternal diet (74,75), uteroplacental blood supply (65,76,77), development of placental villi, and the ability of the villous trophoblast and fetoplacental circulation to transport nutrients (58–61,78). Placental complications of pregnancy leading to FGR have their pathophysiological roots in the early stages of placentation and can manifest from the end of the first trimester of pregnancy (79). The action of placental oxidative stress, with associated necrosis and apoptosis of the trophoblastic epithelium of the placental villi, would compromise the placentation process (1,52–56,58–61). In this phase, the trophoblastic invasion is sufficient to allow early placentation phases of pregnancy but too superficial for the complete transformation of the uteroplacental arterial circulation, predisposing to a repetitive phenomenon of ischemia-reperfusion, with consequent chronic oxidative stress in the placenta and at the spread of maternal endothelial cell dysfunction (79). There is general agreement that poor spiral artery remodeling is the cause of placental changes that predispose to maternal vascular FGR (79).

Gestational Diabetes Mellitus (GDM)

The incidence of GDM is globally rising (80) affecting one in every four to five pregnancies (81). It is widely known that hyperglycemia can upregulate markers of chronic inflammation and contribute to augmented reactive oxygen species generation (62,82–88). Therefore, a pregnancy complicated with GDM is more likely to develop oxidative stress compared to uncomplicated pregnancy (89). It has been shown that maternal gestational diabetes during pregnancy can negatively affect fetal growth leading to macrosomia or intrauterine growth restriction (90). Moreover, it was demonstrated that GDM affects fetal neurodevelopment due to hypoxia, inflammation and oxidative stress that may compromise neuronal integrity (80).

Few studies were found about the role of neurotrophins in GDM (36). It was observed that one of the earliest abnormalities in pregnancies complicated with GDM is increased oxidative stress in the placenta (89). Placental release of 8-isoprostane was double in pregnant women with GDM ($P<0.001$) when compared to healthy controls. Superoxide dismutase activity and protein carbonyl content were elevated in placentae obtained from women with GDM ($P<0.04$ and $P<0.004$ respectively), whilst there was no significant difference in the activity of glutathione peroxidase (91).

Imbalances in maternal intake of Long-Chain Polyunsaturated Fatty Acid (LCPUFA) lead to elevated oxidative stress (92). Reports indicate that oxidative stress and LCPUFA such as docosahexaenoic acid influence levels of neurotrophins in mice (93).

During pregnancy, the deficiency of the antioxidant system can lead to embryonic and fetal exposure to the harmful effects of oxidative stress. There is a higher incidence of congenital malformations in the offspring of diabetic women, and some evidence suggests that higher lipid peroxidation levels and lower antioxidant levels may be causative factors (94). Women with GDM are also at an augmented risk for complications such as endothelial dysfunction and cardiovascular diseases (95).

Pharmaceutical approaches to modulate excessive oxidative stress and the associated adverse inflammatory reactions in pregnancy are scarcely practiced due to potential teratogenic effects (81). Recently, the prevention of pregnancy disorders through dietary intake has received more attention as a doable and relatively safe intervention. Dietary intervention (96) may reduce inflammation and the risk of GDM. A reduction and improvement in carbohydrate quality rather than a restriction in the high-fat content in the diet plays a major role. The habitual diet plays an important role in the improvement that can be expected from dietary adaptation as seen in women with GDM (97,98).

Miscarriage

In Italy, miscarriage refers to the unintentional termination of a pregnancy before the 180° day of amenorrhea or when fetal weight is <500 g (99). Recent studies have shown that 8% to 20% of clinical pregnancies end by spontaneous miscarriage before 20 weeks (100). The etiology is still controversial: chromosomal abnormalities, congenital anomalies, and maternal factors such as uterine anomalies, infection, diseases, and idiopathic causes constitute the main known causes (101,102).

Although it is known that oxidative stress is related to infertility both in men and women, it is still unclear if it is significant for the maintenance of a healthy pregnancy (103–109). As mentioned above, normal placentas experience an oxidative burst between 10 and 12 weeks of gestation with increased production of ROS. ROS levels will come back to normal as placental cells gradually acclimate to the newly oxidative surroundings (110). In cases of spontaneous miscarriage, the onset of maternal intraplacental circulation occurs prematurely and sporadically between 8 and 9 weeks of pregnancy in comparison to normal pregnancies (110,111). These placentas showed high levels of HSP70, nitrotyrosine (111,112), and markers of apoptosis in the villi, suggesting oxidative damage to the trophoblast with subsequent termination of the pregnancy (1). Antioxidant enzymes are unable to counterbalance ROS at this point since their expression and activity grow with gestational age (110).

Alcohol

Alcohol harms pregnancy, causing miscarriage (113–115), teratogenesis (116,117), intrauterine growth restriction (118,119), stillbirth (115,120), premature birth (115,120), neonatal and infantile sequelae, as deformities and disabilities, related to Fetal Alcoholic Spectrum Disorders (FASD) (21,121–125). FASD has no genetic etiology and it is caused only by alcohol drinking during pregnancy (6,126–129). It has been suggested that ethanol can induce oxidative stress through many pathways, like redox state changes, production of the reactive product acetaldehyde, damage to mitochondria, direct or membrane effects caused by hydrophobic ethanol, ethanol-induced hypoxia, ethanol effects on the immune system and altered cytokine production and ethanol induction of CYP2E1 (37). CYP2E1 is a P450 that has the highest oxidation activity of alcohol to acetaldehyde. At low alcohol concentrations, CYP2E1 can reach about 10% of the liver's total alcohol oxidation capacity and its activity increases with the concentration of alcohol in the blood (38,130). CYP2E1 expression was detected as early as week 16 in the human fetal liver, and its level may further increase upon exposure to ethanol during pregnancy (131). Overall CYP2E1 expression increases with gestational age, as it was detected in about 37% of the second trimester and about 80% of the third trimester (132). Finally, the presence of CYP2E1 may be a major ROS-generating factor in the fetus following maternal alcohol consumption, and the low clearance rate may make the fetus more susceptible to ethanol-mediated abnormalities. CYP2E1 expression in the placenta may also vary in mothers who drink heavily (4 or more drinks per day – 1 unit = 12 grams of ethanol in Italy) making their fetuses more susceptible to ethanol-enhanced oxidative stress (133).

Moreover, it has been proved that oxidative stress can damage DNA, contributing to morphological and functional developmental disorders in animal models resulting from exposure to ethanol in utero or in embryo culture (134). ROS can cause altered signal transduction and oxidative macromolecular damage, including DNA damage and altered gene expression, which may contribute to teratogenesis (134–138).

The capability of the fetus to metabolize ethanol may vary during pregnancy. Low hepatic levels of Alcohol De-Hydrogenase (ADH) activity in the fetus in the first trimester show that the fetus has a limited capacity to metabolize alcohol early (139). ADH activity gradually increases with gestational age (140).

A link between oxidation and FASD has been shown as a strong effect of alcohol exposure on the hippocampal proteome, culminating with the alternation of around 600 hippocampal proteins playing important roles in the axonal growth regulation, such as annexin A2, nucleobindin-1, and glypican-4, regulators of cellular growth and developmental morphogenesis and, in the cerebellum, cadherin-13, reticulocalbin-2, and ankyrin-2 (141). The increase in ROS in FASD also appears to be due to NOX enzymes belonging to the NADPH-dependent family of enzymes (142). The NOXs enzymes are expressed at the level of microglia, astrocytes, and the vascular system at the cerebral level, with an important role in the appropriate brain development (142). The isoforms most involved in ROS production are NOX2 and NOX4 (143). In FASD patients, it would appear that early exposure to ethanol during pregnancy would increase the activity of NOX isoforms with a significant increase in ROS, cell damage, and ultimately apoptosis (143). This pathway, in conjunction with the above-mentioned activity of CYP2E1, would explain the increase in ROS and the consequent phenotype of FASD patients (144). The teratogenic effects of alcohol are thought to be the ultimate result of the ethanol-induced dysregulation of a variety of intracellular pathways, which ultimately culminate in toxicity and cell death (145). The generation of ROS as the possible result of ethanol exposure produces an imbalance in the intracellular redox state, leading to an overall increase in oxidative stress (146). This would explain the predominant effect that alcohol has on the brain regarding neurobehavioral impairment and deficient brain growth since brain tissue is rich in fatty acids, which chemically are the perfect substrate for ROS (147). As a consequence, fetal brain tissue results in damage during organogenesis, manifesting neurological dysfunctions after birth (146–149).

Notably, antioxidant supplementation during pregnancy could counteract or mitigate the oxidative elevation induced by alcohol abuse as shown also in animal models (13,150–159).

Discussion

Figure 1 summarizes the role of oxidative stress in the pathogenesis of several obstetric complications. This short review aimed to highlight evidence about the role of oxidative stress in the pathophysiology of the main obstetric complications like placental pathology, PE, IUGR, gestational diabetes and miscarriage, with particular interest on the neglected role of alcohol misuse.

Negative effects of alcohol over health have been extensively proved causing dependence (160–164), liver damage (38), cancer (116,165–168) and FASD if drunk during pregnancy (21,35). Also, paternal alcohol use is considered relevant to fetal development (169–173).

Alcohol activity increases oxidative stress by increasing ROS levels and leading to macromolecular damage, endothelial damage, and impaired placentation. Particular attention must be paid to the presence of CYP2E1, probably being a ROS-generating factor in the fetus following maternal alcohol consumption and leading the fetus to be more susceptible to ethanol-mediated abnormalities in heavily drinking mothers (4 or more drinks per day) (89).

It is controversial if the effects of red wine could be mitigated by resveratrol (16): it was observed that animals early exposed to red wine had minor damage, probably due to the antioxidant effects of polyphenols. Data show that resveratrol or other polyphenols can effectively counteract serum free radicals' formation caused by alcohol intake, also contrasting alcohol-induced neurotrophin elevation in the liver. The observation of both negative and positive effects of red wine on health is known as the controversial "French Paradox" (174), showing that in France incidence of coronary heart diseases was low and it may be partly attributed to the protective function of red wine (175,176). Therefore,

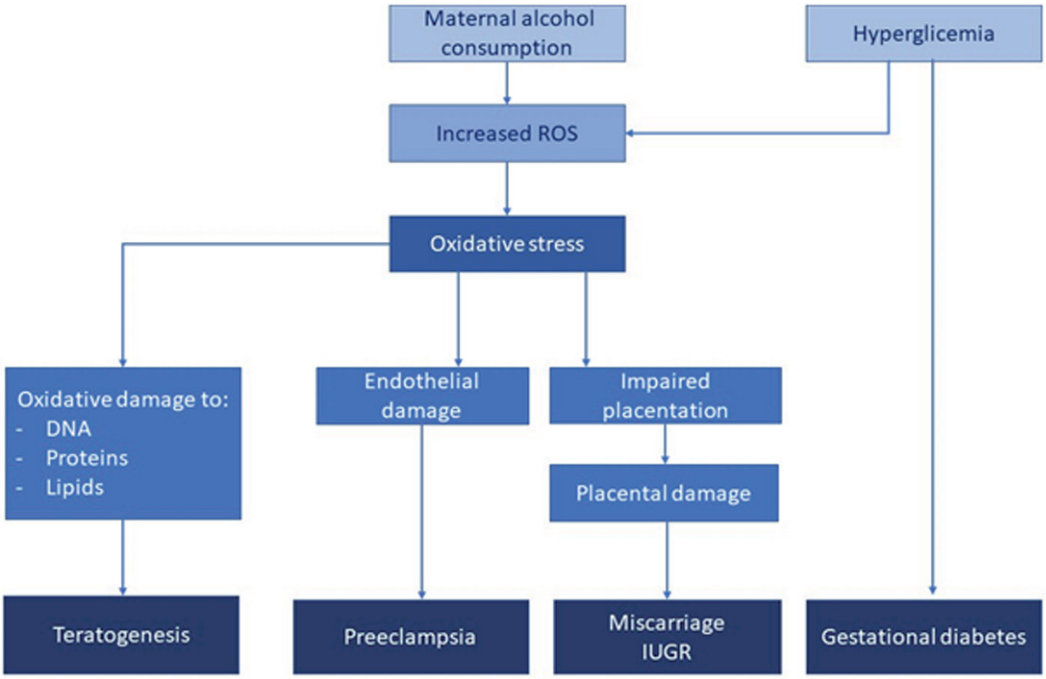

Fig. 1. Role of oxidative stress in the pathogenesis of main obstetric complications. ROS: Reactive Oxygen Species; IUGR: Intra Uterine Growth Restriction

several studies have issued the antitumoral potential of wine phenols, such as resveratrol and quercetin, showing that moderate red wine consumption (12-35 g of ethanol per day) may exert a protective effect (166,177).

It is still not clear if oxidative stress induced by red wine could be somehow mitigated by resveratrol and polyphenols, leading to minor damage to the pregnancy. However, the safest advice that healthcare professionals should give to women during pregnancy or when looking for a child is to completely avoid alcohol consumption (35).

Acknowledgments

Authors thank Sapienza University of Rome, Italy for the financial and logistic support

Conflict of interest

Authors have no conflict of interest to disclose.

References

1. Burton GJ, Jauniaux E. Oxidative stress. Best Pract Res Clin Obstet Gynaecol 2011;25:287–99. doi:10.1016/j.bpobgyn.2010.10.016.
2. Dunn J, Grider MH. Physiology, Adenosine Triphosphate (ATP). StatPearls Publishing; 2020.
3. Allen RC, Tresini M, Keogh BP, et al. Differences in electron transport potential, antioxidant defenses, and oxidant generation in young and senescent fetal lung fibroblasts (WI-38). J Cell Physiol 1999;180:114–22. doi:10.1002/(SICI)1097-4652(199907)180:1<114::AID-JCP13>3.0.CO;2-0.
4. Nita M, Grzybowski A. The Role of the Reactive Oxygen Species and Oxidative Stress in the Pathomechanism of the Age-Related Ocular Diseases and Other Pathologies of the Anterior and Posterior Eye Segments in Adults. Oxid Med Cell Longev 2016;2016. doi:10.1155/2016/3164734.
5. Halliwell B. Chemistry of free radical and related'reactive species'; Transition metal, Hydroxyl radical. Free Radicals Biol Med 1999:53–5
6. Micangeli G, Menghi M, Profeta G, et al. The Impact of Oxidative Stress on Pediatrics Syndromes. Antioxidants 2022;11:1983. doi:10.3390/antiox11101983.
7. Cadenas E, Davies KJA. Mitochondrial free radical generation, oxidative stress, and aging. Free Radic Biol Med 2000;29:222–30. doi:10.1016/S0891-5849(00)00317-8.
8. Toboła-Wróbel K, Pietryga M, Dydowicz P, et al. Association of Oxidative Stress on Pregnancy. Oxid Med Cell Longev 2020;2020. doi:10.1155/2020/6398520.
9. Duhig K, Chappell LC, Shennan AH. Oxidative stress in pregnancy and reproduction. Obstet Med 2016;9:113–6. doi:10.1177/1753495X16648495.
10. Moore TA, Ahmad IM, Schmid KK, et al. Oxidative Stress Levels Throughout Pregnancy, at Birth, and in the Neonate. Biol Res Nurs 2019;21:485–94. doi:10.1177/1099800419858670.
11. Coriale G, Gencarelli S, Battagliese G, et al. Physiological Responses to Induced Stress in Individuals Affected by Alcohol Use Disorder with Dual Diagnosis and Alexithymia. Clin Ter 2020;171:e120–9. doi:10.7417/CT.2020.2201.
12. Parthasarathy R, Kattimani S, Sridhar MG. Oxidative stress during alcohol withdrawal and its relationship with withdrawal severity. Indian J Psychol Med 2015;37:175–80. doi:10.4103/0253-7176.155617.

13. Petrella C, Carito V, Carere C, et al. Oxidative stress inhibition by resveratrol in alcohol-dependent mice. Nutrition 2020;79–80:110783. doi:10.1016/j.nut.2020.110783.
14. Ciafrè S, Ferraguti G, Greco A, et al. Alcohol as an early life stressor: epigenetics, metabolic, neuroendocrine and neurobehavioral implications. Neurosci Biobehav Rev 2020;118:654–68. doi:10.1016/j.neubiorev.2020.08.018.
15. Visioli F, Bellomo G, Galli C. Free radical-scavenging properties of olive oil polyphenols. Biochem Biophys Res Commun 1998;247:60–4. doi:10.1006/bbrc.1998.8735.
16. Fiore M, Messina MP, Petrella C, et al. Antioxidant properties of plant polyphenols in the counteraction of alcohol-abuse induced damage: Impact on the Mediterranean diet. J Funct Foods 2020;71:104012. doi:10.1016/j.jff.2020.104012.
17. Cederbaum AI. Alcohol Metabolism. Clin Liver Dis 2012;16:667–85. doi:10.1016/j.cld.2012.08.002.
18. Pikkarainen PH. Metabolism of ethanol and acetaldehyde in perfused human fetal liver. Life Sci 1971;10:1359–64. doi:10.1016/0024-3205(71)90187-1.
19. Burd L, Blair J, Dropps K. Prenatal alcohol exposure, blood alcohol concentrations and alcohol elimination rates for the mother, fetus and newborn. J Perinatol 2012;32:652–9. doi:10.1038/jp.2012.57.
20. Chudley AE, Conry J, Cook JL, et al. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. CMAJ 2005;172:S1–21. doi:10.1503/cmaj.1040302.
21. Ferraguti G, Merlino L, Battagliese G, et al. Fetus morphology changes by second-trimester ultrasound in pregnant women drinking alcohol. Addict Biol 2020;25:e12724. doi:10.1111/adb.12724.
22. Ceccanti M, De Nicolò S, Mancinelli R, et al. NGF and BDNF long-term variations in the thyroid, testis and adrenal glands of a mouse model of fetal alcohol spectrum disorders. Ann Ist Super Sanita 2013;49:383–90. doi:10.4415/ANN-13-04-11.
23. Fiore M, Mancinelli R, Aloe L, et al. Hepatocyte growth factor, vascular endothelial growth factor, glial cell-derived neurotrophic factor and nerve growth factor are differentially affected by early chronic ethanol or red wine intake. Toxicol Lett 2009;188:208–13. doi:10.1016/j.toxlet.2009.04.013.
24. Fiore M, Laviola G, Aloe L, et al. Early exposure to ethanol but not red wine at the same alcohol concentration induces behavioral and brain neurotrophin alterations in young and adult mice. Neurotoxicology 2009;30:59–71. doi:10.1016/j.neuro.2008.11.009.
25. Williams JF, Smith VC. Fetal Alcohol Spectrum Disorders. Pediatrics 2015;136:e1395–406. doi:10.1542/peds.2015-3113.
26. Ciafrè S, Carito V, Tirassa P, et al. Ethanol consumption and innate neuroimmunity. Biomed Rev 2017;28:49–61. doi:10.14748/bmr.v28.4451.
27. Ciafre S, Fiore M, Ceccanti M, et al. Role of neuropeptide tyrosine (NPY) in ethanol addiction. Biomed Rev 2016;27:27–39. doi:10.14748/bmr.v27.2110.
28. Ciafrè S, Carito V, Ferraguti G, et al. How alcohol drinking affects our genes: An epigenetic point of view. Biochem Cell Biol 2019;97:345–56. doi:10.1139/bcb-2018-0248.
29. Carito V, Ciafrè S, Tarani L, et al. TNF-α and IL-10 modulation induced by polyphenols extracted by olive pomace in a mouse model of paw inflammation. Ann Ist Super Sanita 2015;51:382–6. doi:10.4415/ANN-15-04-21.
30. Ceccanti M, Hamilton D, Coriale G, Carito V, Aloe L, Chaldakov G, et al. Spatial learning in men undergoing alcohol detoxification. Physiol Behav 2015;149:324–30. doi:10.1016/j.physbeh.2015.06.034.
31. Ceccanti M, Coriale G, Hamilton DA, et al. Virtual Morris task responses in individuals in an abstinence phase from alcohol. Can J Physiol Pharmacol 2018;96:128–36. doi:10.1139/cjpp-2017-0013.
32. Ledda R, Battagliese G, Attilia F, et al. Drop-out, relapse and abstinence in a cohort of alcoholic people under detoxification. Physiol Behav 2019;198:67–75. doi:10.1016/j.physbeh.2018.10.009.
33. Carito V, Ceccanti M, Ferraguti G, et al. NGF and BDNF Alterations by Prenatal Alcohol Exposure. Curr Neuropharmacol 2019;17:308–17. doi:10.2174/1570159x15666170825101308.
34. Coriale G, Fiorentino D, Lauro FDI, et al. Fetal Alcohol Spectrum Disorder (FASD): Neurobehavioral profile, indications for diagnosis and treatment. Riv Psichiatr 2013;48:359–69. doi:10.1708/1356.15062.
35. Messina MP, D'Angelo A, Battagliese G, et al. Fetal alcohol spectrum disorders awareness in health professionals: Implications for psychiatry. Riv Psichiatr 2020;55:79–89. doi:10.1708/3333.33022.
36. D'Angelo A, Ceccanti M, Petrella C, et al. Role of neurotrophins in pregnancy, delivery and postpartum. Eur J Obstet Gynecol Reprod Biol 2020;247:32–41. doi:10.1016/j.ejogrb.2020.01.046.
37. Dey A, Cederbaum AI. Alcohol and oxidative liver injury. Hepatology 2006;43:S63-74. doi:10.1002/hep.20957.
38. D'Angelo A, Petrella C, Greco A, et al. Acute alcohol intoxication: a clinical overview. Clin Ter 2022;173:280–91. doi:10.7417/CT.2022.2432.
39. Crabb DW, Bosron WF, Li TK. Ethanol metabolism. Pharmacol Ther 1987;34:59–73.
40. Burton GJ, Fowden AL. The placenta: A multifaceted, transient organ. Philos Trans R Soc B Biol Sci 2015;370. doi:10.1098/rstb.2014.0066.
41. Sato Y, Fujiwara H, Konishi I. Mechanism of maternal vascular remodeling during human pregnancy. Reprod Med Biol 2012;11:27–36. doi:10.1007/s12522-011-0102-9.
42. Krishna U, Bhalerao S. Placental insufficiency and fetal growth restriction. J Obstet Gynecol India 2011;61:505–11. doi:10.1007/s13224-011-0092-x.
43. Jauniaux E, Watson AL, Hempstock J, et al.Onset of maternal arterial blood flow and placental oxidative stress: A possible factor in human early pregnancy failure. Am J Pathol 2000;157:2111–22. doi:10.1016/S0002-9440(10)64849-3.
44. Burton GJ, Watson AL, Hempstock J, et al.Uterine glands provide histiotrophic nutrition for the human fetus during the first trimester of pregnancy. J Clin Endocrinol Metab 2002;87:2954–9. doi:10.1210/jcem.87.6.8563.
45. Burton GJ, Hempstock J, Jauniaux E. Oxygen, early embryonic metabolism and free radical-mediated embryopathies. Reprod Biomed Online 2003;6:84–96. doi:10.1016/S1472-6483(10)62060-3.
46. Burton GJ, Jauniaux E, Watson AL. Maternal arterial connections to the placental intervillous space during the first trimester of human pregnancy: The Boyd Collection revisited. Am J Obstet Gynecol 1999;181:718–24. doi:10.1016/S0002-9378(99)70518-1.
47. Pijnenborg R, Bland JM, Robertson WB, et al.The pattern of interstitial trophoblasticinvasion of the myometrium in early human pregnancy. Placenta 1981;2:303–15. doi:10.1016/S0143-4004(81)80027-6.
48. Schoots MH, Gordijn SJ, Scherjon SA, et al. Oxidative stress in placental pathology. Placenta 2018;69:153–61. doi:10.1016/j.placenta.2018.03.003.

49. Watson AL, Skepper JN, Jauniaux E, et al.Changes in concentration, localization and activity of catalase within the human placenta during early gestation. Placenta 1998;19:27–34. doi:10.1016/S0143-4004(98)90095-9.
50. Rahman I, Biswas SK, Kode A. Oxidant and antioxidant balance in the airways and airway diseases. Eur J Pharmacol 2006;533:222–39. doi:10.1016/j.ejphar.2005.12.087.
51. Cuffe JSM, Holland O, Salomon C, et al. Review: Placental derived biomarkers of pregnancy disorders. Placenta 2017;54:104–10. doi:10.1016/j.placenta.2017.01.119.
52. Stabile G, Gentile RM, Carlucci S, et al. Maternal and fetal outcomes of intraplacental choriocarcinoma complicated by fetomaternal hemorrhage: a systematic review. J Matern Fetal Neonatal Med 2023;36:2285238. doi:10.1080/14767058.2023.2285238.
53. García-Montero C, Fraile-Martinez O, De Leon-Oliva D, et al. Exploring the Role of Mediterranean and Westernized Diets and Their Main Nutrients in the Modulation of Oxidative Stress in the Placenta: A Narrative Review. Antioxidants 2023;12:1918. doi:10.3390/antiox12111918.
54. Cheloufi M, Coulomb A, Abisror N, et al. Massive perivillous fibrin deposition: Diagnosis, obstetrical features, and treatment. Eur J Obstet Gynecol Reprod Biol 2023;292:125–32. doi:10.1016/j.ejogrb.2023.11.024.
55. Calcaterra V, Mannarino S, Garella V, et al. Cardiovascular Risk in Pediatrics: A Dynamic Process during the First 1000 Days of Life. Pediatr Rep 2023;15:636–59. doi:10.3390/pediatric15040058.
56. Liu L, Wen Y, Ni Q, et al. Prenatal ethanol exposure and changes in fetal neuroendocrine metabolic programming. Biol Res 2023;56:61. doi:10.1186/s40659-023-00473-y.
57. Taravati A, Tohidi F. Comprehensive analysis of oxidative stress markers and antioxidants status in preeclampsia. Taiwan J Obstet Gynecol 2018;57:779–90. doi:10.1016/j.tjog.2018.10.002.
58. Puche-Juarez M, Toledano JM, Moreno-Fernandez J, et al. The Role of Endocrine Disrupting Chemicals in Gestation and Pregnancy Outcomes. Nutrients 2023;15. doi:10.3390/nu15214657.
59. Liu H-F, Ge R-L, Wuren T-N. (Research progress on the effect of mitochondrial and endoplasmic reticulum stress caused by hypoxia during pregnancy on preeclampsia and intrauterine growth restriction). Sheng Li Xue Bao 2023;75:714–26.
60. Jańczewska I, Wierzba J, Jańczewska A, et al. Prematurity and Low Birth Weight and Their Impact on Childhood Growth Patterns and the Risk of Long-Term Cardiovascular Sequelae. Children 2023;10. doi:10.3390/children10101599.
61. Joó JG, Sulyok E, Bódis J, Kornya L. Disrupted Balance of the Oxidant–Antioxidant System in the Pathophysiology of Female Reproduction: Oxidative Stress and Adverse Pregnancy Outcomes. Curr Issues Mol Biol 2023;45:8091–111. doi:10.3390/cimb45100511.
62. Ibrahim S, Gaborit B, Lenoir M, et al.Maternal Pre-Existing Diabetes: A Non-Inherited Risk Factor for Congenital Cardiopathies. Int J Mol Sci 2023;24. doi:10.3390/ijms242216258.
63. Aouache R, Biquard L, Vaiman D, et al. Oxidative stress in preeclampsia and placental diseases. Int J Mol Sci 2018;19. doi:10.3390/ijms19051496.
64. Chiarello DI, Abad C, Rojas D, et al. Oxidative stress: Normal pregnancy versus preeclampsia. Biochim Biophys Acta - Mol Basis Dis 2020;1866. doi:10.1016/j.bbadis.2018.12.005.
65. Eiland E, Nzerue C, Faulkner M. Preeclampsia 2012. J Pregnancy 2012;2012. doi:10.1155/2012/586578.
66. Mütze S, Rudnik-Schöneborn S, Zerres K, et al. Genes and the preeclampsia syndrome. J Perinat Med 2008;36:38–58. doi:10.1515/JPM.2008.004.
67. Rani N, Dhingra R, Arya DS, et al. Role of oxidative stress markers and antioxidants in the placenta of preeclamptic patients. J Obstet Gynaecol Res 2010;36:1189–94. doi:10.1111/j.1447-0756.2010.01303.x.
68. Aydin S, Benian A, Madazli R, et al. Plasma malondialdehyde, superoxide dismutase, sE-selectin, fibronectin, endothelin-1 and nitric oxide levels in women with preeclampsia. Eur J Obstet Gynecol Reprod Biol 2004;113:21–5. doi:10.1016/S0301-2115(03)00368-3.
69. Dickinson E, Arnold JRP, Fisher J. Determination of glucose exchange rates and permeability of erythrocyte membrane in preeclampsia and subsequent oxidative stress-related protein damage using dynamic-19F-NMR. J Biomol NMR 2017;67:145–56. doi:10.1007/s10858-017-0092-y.
70. Hubel CA. Oxidative stress in the pathogenesis of preeclampsia. Proc Soc Exp Biol Med 1999;222:222–35. doi:10.1046/j.1525-1373.1999.d01-139.x.
71. Tannetta D, Masliukaite I, Vatish M, et al.Update of syncytiotrophoblast derived extracellular vesicles in normal pregnancy and preeclampsia. J Reprod Immunol 2017;119:98–106. doi:10.1016/j.jri.2016.08.008.
72. Marín R, Chiarello DI, Abad C, et al. Oxidative stress and mitochondrial dysfunction in early-onset and late-onset preeclampsia. Biochim Biophys Acta - Mol Basis Dis 2020;1866:165961. doi:10.1016/j.bbadis.2020.165961.
73. Resnik R. Intrauterine growth restriction. Obstet Gynecol 2002;99:490–6. doi:10.1016/S0029-7844(01)01780-X.
74. Ojeda ML, Nogales F, Romero-Herrera I, et al. Fetal programming is deeply related to maternal selenium status and oxidative balance; experimental offspring health repercussions. Nutrients 2021;13:2085. doi:10.3390/nu13062085.
75. Mancinelli R, Barlocci E, Ciprotti M, et al. Blood thiamine, zinc, selenium, lead and oxidative stress in a population of male and female alcoholics: Clinical evidence and gender differences. Ann Ist Super Sanita 2013;49:65–72. doi:10.4415/ANN-13-01-11.
76. Lunell NO, Sarby B, Lewander R, et al. Comparison of uteroplacental blood flow in normal and in intrauterine growth-retarded pregnancy: Measurements with indium-113m and a computer-linked gammacamera. Gynecol Obstet Invest 1979;10:106–18. doi:10.1159/000299924.
77. Lunell NO, Nylund LE, Lewander R, et al. Uteroplacental blood flow in pre-eclampsia measurements with indium-113m and a computer-linked gamma camera. Hypertens Pregnancy 1982;B1:105–17. doi:10.3109/10641958209037184.
78. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. Am J Obstet Gynecol 2018;218:S745–61. doi:10.1016/j.ajog.2017.11.577.
79. Jauniaux E, Poston L, Burton GJ. Placental-related diseases of pregnancy: Involvement of oxidative stress and implications in human evolution. Hum Reprod Update 2006;12:747–55. doi:10.1093/humupd/dml016.
80. Van Lieshout RJ, Voruganti LP. Diabetes mellitus during pregnancy and increased risk of schizophrenia in offspring: a review of the evidence and putative mechanisms. J Psychiatry Neurosci 2008;33:395–404.
81. Prins JR, Schoots MH, Wessels JI, et al. The influence of the dietary exposome on oxidative stress in pregnancy complications. Mol Aspects Med 2022:101098. doi:10.1016/j.mam.2022.101098.

82. Ren Y, Zeng Y, Wu Y, et al. The Role of Gut Microbiota in Gestational Diabetes Mellitus Affecting Intergenerational Glucose Metabolism: Possible Mechanisms and Interventions. Nutrients 2023;15. doi:10.3390/nu15214551.
83. Ukke GG, Boyle JA, Reja A, et al. Lifestyle Interventions to Prevent Type 2 Diabetes in Women with a History of Gestational Diabetes: A Systematic Review and Meta-Analysis through the Lens of Health Equity. Nutrients 2023;15. doi:10.3390/nu15214666.
84. Gu ZJ, Song QJ, Gu WQ, et al. New approaches in the diagnosis and prognosis of gestational diabetes mellitus. Eur Rev Med Pharmacol Sci 2023;27:10583–94. doi:10.26355/eurrev_202311_34338.
85. Sgayer I, Odeh M, Wolf MF, et al. The impact on pregnancy outcomes of late-onset gestational diabetes mellitus diagnosed during the third trimester: A systematic review and meta-analysis. Int J Gynecol Obstet 2023. doi:10.1002/ijgo.15254.
86. Li P, Li Y, Zhang Y, et al. Incidence, temporal trends and risk factors of puerperal infection in Mainland China: a meta-analysis of epidemiological studies from recent decade (2010-2020). BMC Pregnancy Childbirth 2023;23:815. doi:10.1186/s12884-023-06135-x.
87. Tsironikos GI, Potamianos P, Zakynthinos GE, et al. Effectiveness of Lifestyle Interventions during Pregnancy on Preventing Gestational Diabetes Mellitus in High-Risk Women: A Systematic Review and Meta-Analyses of Published RCTs. J Clin Med 2023;12:7038. doi:10.3390/jcm12227038.
88. Luc K, Schramm-Luc A, Guzik TJ, et al.Oxidative stress and inflammatory markers in prediabetes and diabetes. J Physiol Pharmacol 2019;70. doi:10.26402/jpp.2019.6.01.
89. Jadhav A, Khaire A, Joshi S. Exploring the role of oxidative stress, fatty acids and neurotrophins in gestational diabetes mellitus. Growth Factors 2020;38:226–34. doi:10.1080/08977194.2021.1895143.
90. Gunnell D, Rasmussen F, Fouskakis D, et al.Patterns of fetal and childhood growth and the development of psychosis in young males: a cohort study. Am J Epidemiol 2003;158:291–300.
91. Coughlan MT, Vervaart PP, Permezel M, et al. Altered placental oxidative stress status in gestational diabetes mellitus. Placenta 2004;25:78–84. doi:10.1016/S0143-4004-(03)00183-8.
92. Dhobale M. Neurotrophic Factors and Maternal Nutrition During Pregnancy. Vitam Horm 2017;104:343–66. doi:10.1016/bs.vh.2016.10.011.
93. Sona C, Kumar A, Dogra S, et al.Docosahexaenoic acid modulates brain-derived neurotrophic factor via GPR40 in the brain and alleviates diabesity-associated learning and memory deficits in mice. Neurobiol Dis 2018;118:94–107. doi:10.1016/j.nbd.2018.07.002.
94. Lappas M, Hiden U, Desoye G, Froehlich J, Mouzon SH De, Jawerbaum A. The role of oxidative stress in the pathophysiology of gestational diabetes mellitus. Antioxidants Redox Signal 2011;15:3061–100. doi:10.1089/ars.2010.3765.
95. Di Fulvio P, Pandolfi A, Formoso G, et al. Features of endothelial dysfunction in umbilical cord vessels of women with gestational diabetes. Nutr Metab Cardiovasc Dis 2014;24:1337–45. doi:10.1016/j.numecd.2014.06.005.
96. Simon MS, Heilbrun LK, Boomer A, et al. A randomized trial of a low-fat dietary intervention in women at high risk for breast cancer. Nutr Cancer 1997;27:136–42. doi:10.1080/01635589709514515.
97. García-Patterson A, Balsells M, Yamamoto JM, et al. Usual dietary treatment of gestational diabetes mellitus assessed after control diet in randomized controlled trials: subanalysis of a systematic review and meta-analysis. Acta Diabetol 2019;56:237–40. doi:10.1007/s00592-018-1238-4.
98. Yamamoto JM, Kellett JE, Balsells M, et al. Gestational diabetes mellitus and diet: A systematic review and meta-analysis of randomized controlled trials examining the impact of modified dietary interventions on maternal glucose control and neonatal birth weight. Diabetes Care, vol. 41, American Diabetes Association Inc.; 2018, p. 1346–61. doi:10.2337/dc18-0102.
99. Dulay A. Aborto Spontaneo. Man MSD 2020. https://www.msdmanuals.com/it-it/casa/problemi-di-salute-delle-donne/complicanze-della-gravidanza/aborto-spontaneo
100. Agarwal A, Aponte-Mellado A, Premkumar BJ, et al. The effects of oxidative stress on female reproduction: A review. Reprod Biol Endocrinol 2012;10:49. doi:10.1186/1477-7827-10-49.
101. Colley E, Hamilton S, Smith P, et al. Potential genetic causes of miscarriage in euploid pregnancies: A systematic review. Hum Reprod Update 2019;25:452–72. doi:10.1093/humupd/dmz015.
102. Magnus MC, Wilcox AJ, Morken NH, et al. Role of maternal age and pregnancy history in risk of miscarriage: Prospective register based study. BMJ 2019;364. doi:10.1136/bmj.l869.
103. Liu M, Wu K, Wu Y. The emerging role of ferroptosis in female reproductive disorders. Biomed Pharmacother 2023;166:115415. doi:10.1016/j.biopha.2023.115415.
104. Mu F, Huo H, Wang M, et al. Omega-3 fatty acid supplements and recurrent miscarriage: A perspective on potential mechanisms and clinical evidence. Food Sci Nutr 2023;11:4460–71. doi:10.1002/fsn3.3464.
105. Muhammad T, Wan Y, Lv Y, et al. Maternal obesity: A potential disruptor of female fertility and current interventions to reduce associated risks. Obes Rev 2023;24:e13603. doi:10.1111/obr.13603.
106. Monaco-Brown M, Lawrence DA. Obesity and Maternal-Placental-Fetal Immunology and Health. Front Pediatr 2022;10:859885. doi:10.3389/fped.2022.859885.
107. Md Amin NA, Sheikh Abdul Kadir SH, Arshad AH, et al. Are Vitamin E Supplementation Beneficial for Female Gynaecology Health and Diseases? Molecules 2022;27. doi:10.3390/molecules27061896.
108. Zejnullahu VA, Zejnullahu VA, Kosumi E. The role of oxidative stress in patients with recurrent pregnancy loss: a review. Reprod Health 2021;18:207. doi:10.1186/s12978-021-01257-x.
109. Ishii T, Yasuda K, Miyazawa M, et al. Infertility and recurrent miscarriage with complex II deficiency-dependent mitochondrial oxidative stress in animal models. Mech Ageing Dev 2016;155:22–35. doi:10.1016/j.mad.2016.02.013.
110. Watson AL, Skepper JN, Jauniaux E, Burton GJ. Susceptibility of Human Placental Syncytiotrophoblastic Mitochondria to Oxygen-Mediated Damage in Relation to Gestational Age1. J Clin Endocrinol Metab 1998;83:1697–705. doi:10.1210/jcem.83.5.4830.
111. Jauniaux E, Gulbis B, Burton GJ. Physiological implications of the materno-fetal oxygen gradient in human early pregnancy. Reprod Biomed Online 2003;7:250–3. doi:10.1016/S1472-6483(10)61760-9.
112. Hempstock J, Jauniaux E, Greenwold N, et al. The Contribution of Placental Oxidative Stress to Early Pregnancy

Failure. Hum Pathol 2003;34:1265–75. doi:10.1016/j.humpath.2003.08.006.
113. Avalos LA, Roberts SCM, Kaskutas LA, et al.Volume and type of alcohol during early pregnancy and the risk of miscarriage. Subst Use Misuse 2014;49:1437–45. doi:10.3109/10826084.2014.912228.
114. Nybo Andersen AM, Kragh Andersen P, Feodor Nilsson S, et al. Authors' reply: Risk factors for miscarriage from a prevention perspective: A nationwide follow-up study. BJOG An Int J Obstet Gynaecol 2014;121:1440. doi:10.1111/1471-0528.12857.
115. Bailey BA, Sokol RJ. Prenatal alcohol exposure and miscarriage, stillbirth, preterm delivery, and sudden infant death syndrome. Alcohol Res Heal 2011;34:86–91.
116. Fiore M, Minni A, Cavalcanti L, et al. The Impact of Alcohol Consumption and Oral Microbiota on Upper Aerodigestive Tract Carcinomas: A Pilot Study. Antioxidants 2023;12. doi:10.3390/antiox12061233.
117. Mandal C, Halder D, Jung KH, et al. In utero alcohol exposure and the alteration of histone marks in the developing fetus: An epigenetic phenomenon of maternal drinking. Int J Biol Sci 2017;13:1100–8. doi:10.7150/ijbs.21047.
118. Lundsberg LS, Illuzzi JL, Belanger K, et al.Low-to-moderate prenatal alcohol consumption and the risk of selected birth outcomes: A prospective cohort study. Ann Epidemiol 2015;25:46-54.e3. doi:10.1016/j.annepidem.2014.10.011.
119. Gauthier TW, Brown LAS. In utero alcohol effects on foetal, neonatal and childhood lung disease. Paediatr Respir Rev 2017;21:34–7. doi:10.1016/j.prrv.2016.08.006.
120. Cornman-Homonoff J, Kuehn D, Aros S, et al. Heavy prenatal alcohol exposure and risk of stillbirth and preterm delivery. J Matern Fetal Neonatal Med 2012;25:860–3.
121. Fiore M, Petrella C, Coriale G, et al. Markers of Neuroinflammation in the Serum of Prepubertal Children with Fetal Alcohol Spectrum Disorders. CNS Neurol Disord - Drug Targets 2022;21:854–68. doi:10.2174/1871527320666211201154839.
122. Mamluk L, Edwards HB, Savović J, et al. Low alcohol consumption and pregnancy and childhood outcomes: Time to change guidelines indicating apparently "safe" levels of alcohol during pregnancy? A systematic review and meta-analyses. BMJ Open 2017;7:e015410. doi:10.1136/bmjopen-2016-015410.
123. Ruisch IH, Dietrich A, Glennon JC, et al.Maternal substance use during pregnancy and offspring conduct problems: A meta-analysis. Neurosci Biobehav Rev 2018;84:325–36. doi:10.1016/j.neubiorev.2017.08.014.
124. Popova S, Lange S, Probst C, et al. Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. Lancet Glob Heal 2017;5:e290–9. doi:10.1016/S2214-109X(17)30021-9.
125. Ferraguti G, Ciolli P, Carito V, et al. Ethylglucuronide in the urine as a marker of alcohol consumption during pregnancy: Comparison with four alcohol screening questionnaires. Toxicol Lett 2017;275:49–56. doi:10.1016/j.toxlet.2017.04.016.
126. Ceci FM, Fiore M, Agostinelli E, et al. Urinary Ethyl Glucuronide for the Assessment of Alcohol Consumption During Pregnancy: Comparison between Biochemical Data and Screening Questionnaires. Curr Med Chem 2021;29:3125–41. doi:10.2174/0929867328666211125100329.
127. Gupta KK, Gupta VK, Shirasaka T. An Update on Fetal Alcohol Syndrome—Pathogenesis, Risks, and Treatment. Alcohol Clin Exp Res 2016;40:1594–602. doi:10.1111/acer.13135.
128. Nutt D, Hayes A, Fonville L, et al. Alcohol and the brain. Nutrients 2021;13. doi:10.3390/nu13113938.
129. Popova S, Dozet D, Shield K, et al. Alcohol's impact on the fetus. Nutrients 2021;13. doi:10.3390/nu13103452.
130. Fanfarillo F, Ferraguti G, Lucarelli M, et al. The Impact of Alcohol-Induced Epigenetic Modifications in the Treatment of Alcohol Use Disorders. Curr Med Chem 2023;31. doi:10.2174/0109298673256937231004093143.
131. Carpenter SP, Lasker JM, Raucy JL. Expression, induction, and catalytic activity of the ethanol-inducible cytochrome P450 (CYP2E1) in human fetal liver and hepatocytes. Mol Pharmacol 1996;49:260–8.
132. Johnsrud EK, Koukouritaki SB, Divakaran K, et al. Human Hepatic CYP2E1 Expression during Development. J Pharmacol Exp Ther 2003;307:402–7. doi:10.1124/jpet.103.053124.
133. Rasheed A, Hines RN, McCarver-May DG. Variation in induction of human placental CYP2E1: Possible role in susceptibility to fetal alcohol syndrome? Toxicol Appl Pharmacol 1997;144:396–400. doi:10.1006/taap.1997.8152.
134. Bhatia S, Drake DM, Miller L, et al. Oxidative stress and DNA damage in the mechanism of fetal alcohol spectrum disorders. Birth Defects Res 2019;111:714–48. doi:10.1002/bdr2.1509.
135. Dong J, Sulik KK, Chen SY. Nrf2-mediated transcriptional induction of antioxidant response in mouse embryos exposed to ethanol in vivo: Implications for the prevention of fetal alcohol spectrum disorders. Antioxidants Redox Signal 2008;10:2023–33. doi:10.1089/ars.2007.2019.
136. Miller L, Shapiro AM, Wells PG. Embryonic catalase protects against ethanol-initiated DNA oxidation and teratogenesis in acatalasemic and transgenic human catalase-expressing mice. Toxicol Sci 2013;134:400–11. doi:10.1093/toxsci/kft122.
137. Miller-Pinsler L, Pinto DJ, Wells PG. Oxidative DNA damage in the in utero initiation of postnatal neurodevelopmental deficits by normal fetal and ethanol-enhanced oxidative stress in oxoguanine glycosylase 1 knockout mice. Free Radic Biol Med 2015;78:23–9. doi:10.1016/j.freeradbiomed.2014.09.026.
138. Miller-Pinsler L, Sharma A, Wells PG. Enhanced NADPH oxidases and reactive oxygen species in the mechanism of methanol-initiated protein oxidation and embryopathies in vivo and in embryo culture. Arch Toxicol 2016;90:717–30. doi:10.1007/s00204-015-1482-0.
139. Hines RN, Gail McCarver D. The ontogeny of human drug-metabolizing enzymes: Phase I oxidative enzymes. J Pharmacol Exp Ther 2002;300:355–60. doi:10.1124/jpet.300.2.355.
140. Smith M, Hopkinson Da, Harris H. Developmental changes and polymorphism in human alcohol dehydrogenase. Ann Hum Genet 1971;34:251–71. doi:10.1111/j.1469-1809.1971.tb00238.x.
141. Davis-Anderson KL, Wesseling H, Siebert LM, et al. Fetal regional brain protein signature in FASD rat model. Reprod Toxicol 2018;76:84–92. doi:10.1016/j.reprotox.2018.01.004.
142. Memo L, Gnoato E, Caminiti S, et al. Fetal alcohol spectrum disorders and fetal alcohol syndrome: The state of the art and new diagnostic tools. Early Hum Dev 2013;89:S40-43. doi:10.1016/S0378-3782(13)70013-6.
143. Chater-Diehl EJ, Laufer BI, Castellani CA, et al. Alteration of gene expression, DNA methylation, and histone methylation in free radical scavenging networks in adult mouse hippocampus following fetal alcohol exposure. PLoS One 2016;11. doi:10.1371/journal.pone.0154836.

144. Hewitt AJ, Walker KR, Kobus SM, et al. Differential effects of chronic ethanol exposure on cytochrome P450 2E1 and the hypothalamic-pituitary-adrenal axis in the maternal-fetal unit of the guinea pig. Neurotoxicol Teratol 2010;32:164–70. doi:10.1016/j.ntt.2009.12.002.
145. Mattson SN, Crocker N, Nguyen TT. Fetal alcohol spectrum disorders: neuropsychological and behavioral features. Neuropsychol Rev 2011;21:81–101. doi:10.1007/s11065-011-9167-9.
146. De La Monte SM, Kril JJ. Human alcohol-related neuropathology. Acta Neuropathol 2014;127:71–90. doi:10.1007/s00401-013-1233-3.
147. Goodlett CR, Horn KH, Zhou FC. Alcohol teratogenesis: Mechanisms of damage and strategies for intervention. Exp Biol Med 2005;230:394–406. doi:10.1177/15353702-0323006-07.
148. Derme M, Piccioni MG, Brunelli R, et al. Oxidative Stress in a Mother Consuming Alcohol during Pregnancy and in Her Newborn: A Case Report. Antioxidants 2023;12:1216. doi:10.3390/antiox12061216.
149. Saccone G, Sen C, Di Mascio D, et al. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection. Ultrasound Obstet Gynecol 2021;57:232–41. doi:10.1002/uog.23107.
150. Micek A, Alshatwi AA, Paladino N, et al. Association between alcoholic (poly)phenol-rich beverage consumption and cognitive status in older adults living in a Mediterranean area. Int J Food Sci Nutr 2023;74:362–72. doi:10.1080/09637486.2023.2199182.
151. Carito V, Ceccanti M, Cestari V, et al. Olive polyphenol effects in a mouse model of chronic ethanol addiction. Nutrition 2017;33:65–9. doi:10.1016/j.nut.2016.08.014.
152. Machado IF, Miranda RG, Dorta DJ, et al. Targeting Oxidative Stress with Polyphenols to Fight Liver Diseases. Antioxidants 2023;12. doi:10.3390/antiox12061212.
153. Serio F, Imbriani G, Acito M, et al. Moderate red wine intake and cardiovascular health protection: a literature review. Food Funct 2023;14:6346–62. doi:10.1039/d3fo01004j.
154. Hadefi A, Arvanitakis M, Trépo E, et al.Dietary strategies in non-alcoholic fatty liver disease patients: From evidence to daily clinical practice, a systematic review. United Eur Gastroenterol J 2023;11:663–89. doi:10.1002/ueg2.12443.
155. Jahmidi-Azizi N, Oliva R, Winter R. Alcohol-Induced Conformation Changes and Thermodynamic Signatures in the Binding of Polyphenols to Proline-Rich Salivary Proteins. Chem - A Eur J 2023:e202302384. doi:10.1002/chem.202302384.
156. Villalva M, Martínez-García JJ, Jaime L, et al.Polyphenols as NLRP3 inflammasome modulators in cardiometabolic diseases: a review of in vivo studies. Food Funct 2023;14:9534–53. doi:10.1039/d3fo03015f.
157. Zangade SB, Dhulshette BS, Patil PB. Flavonoid-metal ion Complexes as Potent Anticancer metallodrugs: A comprehensive Review. Mini-Reviews Med Chem 2023;24. doi:10.2174/0113895575273658231012040250.
158. Tang Z, Zhan L, He R, et al. Hepatoprotective Effect of Tea Composite Solid Beverage on Alcohol-Caused Rat Liver Injury. Foods 2023;12:4126. doi:10.3390/foods12224126.
159. Petrella C, Di Certo MG, Gabanella F, et al. Mediterranean Diet, Brain and Muscle: Olive Polyphenols and Resveratrol Protection in Neurodegenerative and Neuromuscular Disorders. Curr Med Chem 2021;28:7595–613. doi:10.2174/0929867328666210504113445.
160. Ceci FM, Francati S, Ferraguti G, et al. Behavioral dysregulations by chronic alcohol abuse. Motivational enhancement therapy and cognitive behavioral therapy outcomes. Riv Psichiatr 2022;57:1–9. doi:10.1708/3749.37321.
161. Vitali M, Sorbo F, Mistretta M, et al. Dual diagnosis: An intriguing and actual nosographic issue too long neglected. Riv Psichiatr 2018;53:154–9. doi:10.1708/2925.29418.
162. Ciafrè S, Carito V, Ferraguti G, et al. Nerve growth factor in brain diseases. Biomed Rev 2018;29:1–16. doi:10.14748/bmr.v29.5845.
163. Ceci FM, Ferraguti G, Petrella C, et al. Nerve Growth Factor, Stress and Diseases. Curr Med Chem 2020;28:2943–59. doi:10.2174/0929867327999200818111654.
164. Vitali M, Sorbo F, Mistretta M, et al. Drafting a dual diagnosis program: A tailored intervention for patients with complex clinical needs. Riv Psichiatr 2018;53:149–53. doi:10.1708/2925.29417.
165. Ceci FM, Ceccanti M, Petrella C, et al. Alcohol Drinking, Apolipoprotein Polymorphisms and the Risk of Cardiovascular Diseases. Curr Neurovasc Res 2021;18:150–61. doi:10.2174/1567202618666210406123503.
166. Kontou N, Psaltopoulou T, Soupos N, et al. Alcohol consumption and colorectal cancer in a mediterranean population: A case-control study. Dis Colon Rectum 2012;55:703–10. doi:10.1097/DCR.0b013e31824e612a.
167. Walter A, Etienne-Selloum N, et al. Intake of grape-derived polyphenols reduces C26 tumor growth by inhibiting angiogenesis and inducing apoptosis. FASEB J 2010;24:3360–9. doi:10.1096/fj.09-149419.
168. Ferraguti G, Terracina S, Petrella C, et al. Alcohol and Head and Neck Cancer: Updates on the Role of Oxidative Stress, Genetic, Epigenetics, Oral Microbiota, Antioxidants, and Alkylating Agents. Antioxidants 2022;11. doi:10.3390/antiox11010145.
169. Ceccanti M, Coccurello R, Carito V, et al. Paternal alcohol exposure in mice alters brain NGF and BDNF and increases ethanol-elicited preference in male offspring. Addict Biol 2016;21:776–87. doi:10.1111/adb.12255.
170. Tanaka H, Suzuki N, Arima M. Experimental studies on the influence of male alcoholism on fetal development. Brain Dev 1982;4:1–6.
171. Abel EL. Paternal contribution to fetal alcohol syndrome. Addict Biol 2004;9:127–33. doi:10.1080/13556210410001716980.
172. Klassen RW, Persaud TVN. Experimental studies on the influence of male alcoholism on pregnancy and progeny. Exp Pathol 1976;12:38–45. doi:10.1016/s0014-4908-(76)80031-2.
173. Terracina S, Ferraguti G, Tarani L, et al. Transgenerational Abnormalities Induced by Paternal Preconceptual Alcohol Drinking. Findings from Humans and Animal Models. Curr Neuropharmacol 2021;19:1158–1173. doi:10.2174/1570159x19666211101111430.
174. Parodi PW. The French paradox unmasked: The role of folate. Med Hypotheses 1997;49:313–8. doi:10.1016/S0306-9877-(97)90197-3.
175. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet 1992;339:1523–6. doi:10.1016/0140-6736(92)91277-F.
176. Ferrières J. The French paradox: Lessons for other countries. Heart 2004;90:107–11. doi:10.1136/heart.90.1.107.
177. Crockett SD, Long MD, Dellon ES, et al. Sandler RS. Inverse relationship between moderate alcohol intake and rectal cancer: Analysis of the North Carolina colon cancer study. Dis Colon Rectum 2011;54:887–94. doi:10.1007/