Drugs therapy against dysthyroidism induced oxidative stress in pregnant women with Gestational Diabetes Mellitus - a review

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ABSTRACT

Thyroid hormones play an important role in glucose metabolism and homeostasis. This review focuses on the relationship between oxidative stress and disruption of thyroid hormones in association with gestational diabetes. During a normal pregnancy, oxidative stress enhances antioxidant mechanisms, thyroid hormones play particularly important role that operate on the antioxidant balance, during pregnancy a severe iodine deficiency would affect the synthesis and secretion of T4 or T3 which stimulates excretion of TSH which shown associated with oxidative stress by, increase the production of reactive oxygen species and changes in anti-oxidative factors. Increased oxidative stress is a widely accepted participant in the development and progression of diabetic tissue damage during pregnancy or what we call gestational diabetes. This study highlights the importance of evaluating and controlling the variation of thyroid hormones and the oxidative stress markers in pregnant women to properly control the complications of pregnancy including gestational diabetes, suggesting to use antioxidant supplements with the systematic treatment of gestational diabetes or dysthyroid to protect against complications of pregnancy on the woman or the fetus.

Key words: Gestational Diabetes, Dysthyroidism, Oxidative stress, Drugs therapy, Pregnancy

1. INTRODUCTION

GDM is defined by the World Health Organization (WHO) as an anomaly of carbohydrate homeostasis leading to hyperglycemia of variable severity [1,2], beginner or diagnosed for the first time during pregnancy of the third trimester and responsible for feto-maternal

complications [3] glucose intolerance was not present or recognized prior to pregnancy.GDM affect 7% of pregnancies each year [4]. After birth many pregnant women with previously undiagnosed type 2 diabetes are often mistakenly diagnosed as having gestational diabetes [5]. Until now, there is not any directly cause of GDM but several risk factors are introduced as causative factors of developing gestational diabetes mellitus such as advanced age (≥35 yrs.), overweight or obesity, family history of diabetes [6], excessive gestational weight gain, excessive central body fat deposition, short stature (<1.50 m), excessive fetal growth, hypertension or preeclampsia in the current pregnancy, and polycystic ovary syndrome [7]. Thyroid hormones play several roles at the metabolic, physiological and nutritional level of target cells [8]. Thyroid hormones perform a wide array of metabolic functions including regulation of lipid, carbohydrate, protein and electrolyte and mineral metabolisms [9]. The effect of thyroid hormones on respiration in the mitochondria gives it a major role in the cellular modulation of oxidative stress [10]. Many studies have suggested that the cause of progression GDM is Reactive oxygen species and oxidative stress [11]. Reactive oxygen species (ROS) are free radicals resulting from the metabolism of oxygen [12]. The increased free radical production and antioxidant depletion in gestational diabetes to be a causative factor in increasing the risk of congenital anomalies and some investigators have reported increased lipid peroxidation and significant depletion in antioxidant capacity during the development of gestational diabetes [13]. The current review focuses on the explain the relationship between oxidative stress and disruption of thyroid hormones in association with gestational diabetes.

2. PATHOPHYSIOLOGY AND COMPLICATIONS OF GESTATIONAL DIABETES MELLITUS

Maternal age is an established risk factor for gestational diabetes mellitus (GDM) [14], in clinical practice it has been shown that age 40 years is a powerful risk factor for the progression of gestational diabetes [15]. Maternal obesity in early pregnancy is an important risk factor for GDM. The relationship between maternal body mass index (BMI) and hyperglycemia is poorly characterized because mass index (BMI) has not been calculated accurately in early pregnancy [16], glucose intolerance and obesity may play a role in the development GDM, a strong family history of diabetes mellitus (FHD) has emerged as a risk factor for GDM [17], exactly as the results of Moosazadeh's (2016) study found that the odd odds ratio (OR) of gestational diabetes appears to be primarily associated with family history of diabetes, which is to be a powerful diagnostic and predictive factor of this disease which contribute also to mainly improve the health care measures of the pregnant woman [18]. Polycystic ovary syndrome, a history of delivering big baby, history of recurrent abortions, and hypertension, or pregnancy-related hypertension are other risk factors for GDM and taking some types of anti-psychotic or steroid medications [19], unhealthy diet and race [20].Women with gestational diabetes mellitus have a higher risk of pre-eclampsia characterized by elevation of blood pressure and presence of protein in the urine [21], shoulder dystocia, caesarean section increase the risk of developing type 2 diabetes in the future for the mother. Preterm delivery neonatal, hypoglycemia and admission to the neonatal intensive care unit was shown to be associated with maternal hyperglycemia [22]. Risks for the baby above average weight, which can make birth more difficult. Hypoglycemia (abnormal glucose drop) at birth because their own insulin production is high, severe episodes of hypoglycemia may provoke seizures in the baby. An increased risk of type 2 diabetes in adulthood [23], excessive birth weight**,** extra glucose in bloodstream crosses the placenta, which triggers the baby's pancreas to make extra insulin [24]. This can be the cause for baby to grow too large (macrosomia) and preterm delivery. The aforementioned increase in placental transport of glucose, amino acids, and fatty acids stimulate the fetus's endogenous production of insulin and insulin-like growth factor 1 (IGF-1) [25].

3. OXIDATIVE STRESS AND PREGNANCY

Pregnancy is physiological conditions in which women are prone to oxidative stress due to increased production of free radicals in the mitochondria of the placenta which promotes oxidative stress [26]. Oxidative stress plays a pivotal role in the development of placental related diseases, the mechanisms involved in the alterations of oxygen (O_2) homeostasis and evaluated the consequences for human pregnancy [27]. The enzymatic or non-enzymatic antioxidants interact with the free radicals which neutralizes them and decreases the state of oxidative stress in pregnant women [28], oxidative stress plays important roles in embryo development, implantation, placental development and function, fetal development, and labor antioxidant enzymes include glutathione peroxidase and superoxide dismutase [29]. The placenta, a hormone-rich tissue, is an important source of pro-oxidizing agents and of antioxidant enzymes that maintaining lipid peroxidation under control which increases during normal pregnancy [30]. The serum MDA levels in the second trimester are significantly higher than the first trimester [31] because during pregnancy is based on the products of lipid peroxidation produced in the placenta could pass into maternal blood and act as agents triggering damage in other tissues, which are secreted mainly on the maternal side of the placenta and remain in the maternal circulation for some time [32]. Increased lipid peroxidation markers are observed during normal pregnancy, disturbances in the maternal compartment may cause oxidative stress, which in turn leads to changes in the placenta DNA by gene methylation and therefore a functional change in the placenta [33]. The fetal development and

the physiological change in the pregnant woman enhances the oxygen demand following an increased metabolic activity which induces a high production of ROS and installation of a state of oxidative stress. [34].

4. OXIDATIVE STRESS AND GESTATIONAL DIABETES

Pathologic pregnancies including gestational diabetes mellitus (GDM) are associated with a heightened level of oxidative stress, owing to both over production of free radicals and/or a defect in the antioxidant defenses [35]. The relative immaturity of the antioxidant system facilitates the exposure of embryos and fetuses to the damaging effects of oxidative stress [36], the increase secretion of tumor necrosis factor- (TNF-) from the placenta and adipose tissue from women with GDM under conditions of high glucose and propose that an altered oxidative homeostasis in women with GDM may be involved [37]. During gestational diabetes, there is an increase in lipid oxidation by lipid pesroxydation with weak enzymatic antioxidant defense. As in type 2 diabetes mellitus, glycemic levels in patients with GDM correlate with concentrations of lipid peroxides [38]. The imbalance between antioxidants and the production of radicals which have an effect in the reproductive system and in the development of the embryo responsible for the state of oxidative stress during pregnancy, also iron supplementation during pregnancy contributes to the increase of oxidative stress in pregnant women who take it, in particular an increase in maternal and placental plasma MDA [39]. The progression and complications of diabetes is under the responsibility of oxidative stress in the majority of cases, which induces changes in the activities of antioxidant enzymes in various tissues [40].

5. OXIDATIVE STRESS AND THYROID HORMONES DURING GESTATIONAL DIABETES

Oxidative stress and thyroid hormones

Thyroid hormones are chemical substances made by the thyroid gland. They help regulate growth and the rate of chemical reactions (metabolism) [41], and are involved in the circadian rhythms, among other essential functions. The thyroid gland secretes two essential hormones T3 and T4 under stimulation of TSH a hormone produced by the pituitary gland which has all under hypothalamic control in the brain [42,43]. In the normal physiological state an oxidant / antioxidant balance has been induced by the thyroid hormones, since both hyperthyroidism and hypothyroidism have been shown to be associated with oxidative stress [44]. Also hyperthyroidism is a hyper metabolic state accompanied by increased oxygen utilization, increased production of reactive oxygen species and consequently measurable changes in anti-oxidative factors [45]. The metabolic action of thyroid hormones (TH) are directly linked to the production of free radicals and to oxidative stress [46] by several mechanisms, for example that, TH causes the acceleration of basal metabolism which includes an increase in the rate of catabolic and anabolic reactions [47]. various cells and tissues which results in a great energy expenditure, in the mobilization of the fuel, in the oxidation of the fuel for the extraction of energy and the consumption of oxygen which would also lead to a large production of ROS in the mitochondria ref in large part [48]. Thyroid hormones also promote the extra-mitochondrial production of ROS by modifying the activity of the enzymes involved in the production and elimination of ROS [49]. In another way, T3 has a radical activity induced by the decrease in antioxidant defenses which leads to oxidative stress [50]. Excess TSH and thyroid hormones can produce DNA damage through an oxidative effect of the phenolic group, which is similar to that of steroidal estrogens [51]. Other studies have confirmed that hypothyroidism causes lipid peroxidation and protein oxidation with an increase in protein carbonyls [52].

Thyroid hormones during Gestational Diabetes

The mother during pregnancy exposes to complex metabolic and hormonal changes. Among metabolic changes, loss of carbohydrate control balance which can lead to overt diabetes or abnormal glucose tolerance [53]. Also the woman during the pregnancy can also exhausted the function of the thyroid gland and the metabolism of the secreted hormones [54]. There is a relationship between dysthyroidism and diabetesmellitus [55].La sécrétion élevé des hormones thyroidienne dans les premier semaine de grossesse metre les femme plus à risque d'atteinte de diabète gestationnel [56].There is a correlation between thyroid disease and GDM , blood glucose levels during pregnancy is influenced by various physiological hormones such as estrogen, thyroid-binding globulin (TBG), human chorionic gonadotropin (hCG), and placental insulin enzyme, all of which are affected by maternal thyroid function [57]. It has been reported that risk of GDM was higher in pregnant women with subclinical hypothyroidism compared to euthyroid pregnant women [58].Researchers have found high levels of triiodothyronine (T3) in pregnant women with gestational diabetes more than four times that of women in control [59]. The researchers also discovered that an elevated T3 / T4 ratio which associated with fetal risk of gestational diabetes, this ratio indicates a high activity of secretase enzyme converting T4 to T3 [60]. In another way, mechanisms explaining hypothyroidism during pregnancy by the concentration of iodine and the protein thyroglobulin (Tg), the effect of Wolff-Chaikoff causes the elevation of the Tg levels in which iodine prevents the thyroid from synthesizing the thyroid hormone, which causes the increase in

the thyroid stimulating hormone TSH [61]. weak correlations have been shown between the concentration of iodine and the hormone TSH in women during pregnancy this probably explain by a severe iodine deficiency would affect the synthesis and secretion of T4 or T3 which stimulates excretion of TSH [62].

6. PROPOSED DRUGS

According to the developmental mechanisms of gestational diabetes in pregnant women described above we suggest some solution or drug that can protect or reduce the severity of disease.

Hypoglycemic agents

As part of hyperglycemia treatment During pregnancy, you can be offered two types of tablets to keep your blood sugar balanced: metformin and glibenclamide [63]. Metformin lowers liver glucose levels and increases sensitivity to pancreatic insulin. Glibenclamide lowers blood sugar by stimulating your pancreas to produce more insulin [64].The use of oral hypoglycemic agents during pregnancy has undesirable effects such as the potential risks of neonatal hypoglycemia and teratogenicity associated with placental transfer to the fetus [65].Other oral agents such as Alpha-glucosidase inhibitors, Dipeptidyl peptidase IV (DDP IV) inhibitors and Glucagon-like peptide-1 (GLP-1) receptor agonists have limited safety to the fetus if utilized in pregnancy [66]. Based on this, the potential risks outweigh the benefits and they are not considered viable treatment options for the management of GDM [67].Despite emerging evidence supporting the use of glyburide or metformin in the management of GDM, many guidelines continue to recommend insulin as the first-line therapy [68].Insulin is used as an injection. Depending on the type of insulin in is injected before meals, at bedtime or upon waking [69]. The use of insulin is often associated with hypoglycaemia and increased weight. Moreover, this treatment is inconvenient and expensive because it requires refrigerated storage and skilled handling [70]. Women with gestational diabetes are advised to do at least 30 minutes of moderate to intense exercise, such as brisk walking, swimming, dancing, low-impact aerobics, or active play with children [71]. During the first trimester of pregnancy, women should also avoid the exercises that require them to lie on their backs, which could put pressure on certain blood vessels and accidentally limit blood flow to the baby [72].

Antidysthyroidism medications

In the case of dysthyroidism associated with pregnancy and to control this dysthyroidism and protect against the development of gestational diabetes pregnant women should use drugs regulating the synthesis and secretion of thyroid hormones.treatment for Hyperthyroidism is based on Antithyroid drugs (also called thionamides) are most often used to treat an overactive thyroid (hyperthyroidism). These drugs block the formation of thyroid hormone by the thyroid gland [73]. Two antithyroid drugs are currently available propylthiouracil and methimazole which have several benefits and a few risk [74]. Women in the first trimester of pregnancy use propylthiouracil because it has less side effect on fetal development. Since there have been rare cases of liver damage in people taking propylthiouracil [75], about Hypothyroidism patients which are treated with a daily dose of levothyroxine, a man-made version of the thyroid hormone thyroxine (T4) [76]. It acts just like the hormone of thyroid gland normally makes. The right dose can make feel a lot bette [77].

Antioxidant drugs

Because the oxidative stress which is associated with pregnancy and thyroid hormones alteration, which can lead to gestational diabetes, we suggest that anti-oxidant medication be given as a preventive aspect against pregnancy complications, among which is gestational diabetes. Dietary constituents of antioxidant vitamins and trace elements may play an important role in protecting against oxidant damage [78]. Antioxidant therapies given alone, such as ascorbic acid, glutathione, acetylcysteine, or vitamins A, E, and C, or in combination with trace elements such as zinc, selenium and copper improve the state of pregnancy womens [79]. Specifically, antioxidants work to attenuate changes in cellular energetics, protect microvascular circulation, reduce tissue lipid peroxidation, improve enzymatic antioxidant activities, and decrease the free radical production [80]. Phytochemicals in the diet also can exert on different targets that can relieve multiple pathological processes, including oxidative damage, chronic inflammation, inhibitors and growth terminators and prevention of various diseases associated with oxidative stress including gestational diabetes [81].

7. CONCLUSION

Pregnant women have many physiological and biochemical changes, including those related to thyroid hormones which affect carbohydrate metabolism, which causes an imbalance in the oxidant / antioxidant balance and severe oxidative stress which leads to

several pregnancy complications including Gestational Diabetes suggesting to use antioxidant supplements with the systematic treatment of gestational diabetes or dysthyroidism to protect against complications of pregnancy on the woman or her fetus.

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The authors declare that there are no conflicts of interests.

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All data associated with this study are present in the paper.

REFERENCE

1. MirghaniDirar A, Doupis J. Gestational diabetes from A to Z. World J Diabetes. 2017; 8(12):489-511.
2. Silva-Zolezzi I, Samuel TM, Spieldenner J. Maternal nutrition: opportunities in the prevention of gestational diabetes. Nutr Rev. 2017;75(suppl 1):32-50.
3. Tudosa R, Vartej P, Horhoianu I, et al. Maternal and fetal complications of the hypothyroidism-related pregnancy. Maedica (Buchar). 2010 Apr;5(2):116-23.
4. Bonaventura CT, Alex E, Hannah ED. Gestational diabetes mellitus: challenges in diagnosis and management. Journal of Diabetes & Metabolic Disorders 2015; 14: 42.
5. Reece AE, Gustavo L, Wiznitzer A. Gestational diabetes: the need for a common ground 14. Lancet 2009; 373: 1789–97.
6. Larrabure TG, Martinez S, Luque FM et al.Prevalence and risk factors of gestational diabetes mellitus: findings from a universal screening feasibility program in Lima, Peru.BMC Pregnancy Childbirth. 2018; 18(1): 303.
7. Renata SP, Fernanda CR, Bibiana AR., et al.Risk factors for gestational diabetes mellitus in a sample of pregnant women diagnosed with the disease. DiabetolMetabSyndr, 2015; 7: (Supp11), A80.
8. Derouiche S, Djouadi A, Belimi N et al. Blood Glucose, some Electrolytes Levels and Stress Oxidative Status of Female Hyperthyroid Patients under Treatment. J. Adv. Res. BioChem. Pharma. 2018; 3(1&2): 1-6.
9. Siddiqui K, Bawazeer N, Joy SS. Variation in macro and trace elements in progression of type 2 diabetes. ScientificWorldJournal. 2014; 2014: 461591.
10. Campos C, Casado Á. Oxidative stress, thyroid dysfunction & Down syndrome. Indian J Med Res. 2015; 142(2): 113-9.
11. Sudharshana KAM, Ambarisha B, Shivani LC et al. Evaluation of oxidative stress and proinflammatory cytokines in gestational diabetes mellitus and their correlation with pregnancy outcome.Indian J EndocrinolMetab. 2018; 22(1): 79-84.
12. Derouiche S, Abbas K, Djermoune M. Changes in metabolism of Zinc andcarbohydrate and testis oxidative stress of diabetic rats fed zinc-over dose diet. Int J Biol Med Res. 2017; 8(3): 6041-6045.
13. Vida MP, Zamzam P. Antioxidant status and risk of gestational diabetes mellitus: a case-control study.Clin NutrRes. 2017; 6(2): 81–88.
14. Kalok A, Peraba P, Shah SA, et al. Screening for gestational diabetes in low-risk women: effect of maternal age. 2018; doi10.1515/hmbci-2017-0071.
15. Terence T, Lai-Fong H, Ben CP, Wing CL. Maternal age and prevalence of gestational diabetes mellitus. 2006; 29(4): 948-949.
16. Tomedi LE, Simhan HN, Chang CC, et al. Gestational weight gain, early pregnancy maternal adiposity distribution, and maternal hyperglycemia. Matern Child Health J. 2014; 18(5):1265-70.
17. Nuriye BD. Frequency of gestational diabetes mellitus and the associated risk factors.2015; 31(1): 194-197.
18. Moosazadeh M, Asemi Z, Lankarani KB, et al. Family history of diabetes and the risk of gestational diabetes mellitus in Iran: A systematic review and meta-analysis. 2017; 11(Suppl 1): S99-S104.
19. Dandjinou M, Sheehy O, Bérard A. Antidepressant use during pregnancy and the risk of gestational diabetes mellitus: a nested case-control study. BMJ Open. 2019; 9(9): e025908.
20. Brenda M. Type 1, type 2, and gestational diabetes risk factor the Journal of Clinical and Applied Research and Education. 2019; 40(suppl01): S12-S25.
21. Sanjay G. GirijaW.Preeclampsia–Eclampsia.2014; 64(1):4–13.
22. Howard B, Gagnon R, Mathew S. Diabetes in Pregnancy. 2016.doi.org/10.1016/ j.jogc. 2016.04.002.
23. Stewart A, Malhotra A. Gestational diabetes and the neonate: challenges and solutions. 2015(5),p 31-39.

24. RadminH.Gestational Diabetes Mellitus (GDM): Here are the facts. 2018: 1-17.
25. Jasmine FP, Joanna LS, Philip NB et al. The Pathophysiology of gestational diabetes mellitus. Int. J. Mol. Sci. 2018; 19 (3342).
26. Saikumar P, Jaya B, Renuka MRD. Oxidative Stress in Pregnancy. IOSR journals. 2013; 3 (6): 12-13.
27. Eric J, Poston L, Graham JB. Placental-related diseases of pregnancy: involvement of oxidative stress and implications in human evolution. Human Reproduction Update. 2006; 12(6): 747-755 .
28. Anna B, Krzysztof R .Oxidative stress in pregnant women. Archives of Perinatal Medicine. 2013; 19(3):150-155.
29. Kate D, Lucy CC, Andrew HS. Oxidative stress in pregnancy and reproduction. Obstet Med. 2016; 9(3): 113–116.
30. Sainz RM, Reiter RJ, Mayo JC, et al. Changes in lipid peroxidation during pregnancy and after delivery in rats: effect of pinealectomy. J ReprodFertil. 2000; 119(1): 143-9.
31. Arribas L, Almansa I, Miranda M, Muriach M, Romero FJ, Villar VM. Serum Malondialdehyde Concentration and Glutathione Peroxidase Activity in a Longitudinal Study of Gestational Diabetes. PLoS One. 2016;11(5):e0155353.
32. Napso T, Hannah EJY, Jorge L et al. The role of placental hormones in mediating maternal adaptations to support pregnancy and lactation. 2018; doi: 10.3389/fphys.2018.01091.
33. Samir D, Dalal D, Noura A. Effect of routine iron supplementation on copper level and oxidative stress status in pregnant women. Asian Pac J Reprod 2020; 9(2): 64-69.
34. Lucca DL, Fabiane R, Letícia B et al. Oxidative profile and δ-aminolevulinatedehydratase activity in healthy pregnant women with iron supplementation. Int. J. Environ. Res. Public Health . 2016; 13(463).
35. Lappas M, Hiden U, Desoye G, Froehlich J, Hauguel-de Mouzon S, JawerbaumA.The role of oxidative stress in the pathophysiology of gestational diabetes mellitus. Antioxid Redox Signal. 2011; 15(12): 3061-100.
36. Martha L, Ursula H, Gernot D, et al. The role of oxidative stress in the pathophysiology of gestational diabetes mellitus. Antioxidants & Redox Signaling. 2011;15(12).
37. Coughlan M, Vervaart P, Permezel M, et al.Altered placental oxidative stress status in gestational diabetes mellitus. Placenta. 2004; 25(1): 78-84.
38. Xinhua C, Theresa OS. Oxidative stress: Changes in pregnancy and with gestational diabetes mellitus. 2005; 5(4): 282–288.
39. Devrim E, Tarhan I, Erguder IB, Durak I. Oxidant /antioxidant status of placenta, blood, and cord blood samp les from pregnant women supplemented with iron. J SosGynecolInvestig. 2006; 13(7): 502- 505.
40. Derouiche S, Atoussi N, Guediri S. The Study of Socioeconomic and Clinic Risk Factors of Breast Cancer in Algerian Women Population. Frontiers in Biomedical Technologies. 2018; 5(3-4): 51-57.
41. Rashmi M, Yan YL, Gregory AB.Thyroid hormone regulation of metabolism.2014; 94(2): 355–382.
42. Bridget B. Thyroid Gland: Overview How this endocrine-realted thyroid gland functions, and what symptoms might be a clue for hyperthyroidism and hypothyroidism, 2019; p 3
43. Shahid MA, Sharma S. Physiology, Thyroid Hormone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm. nih.gov/books/NBK500006.
44. Mancini A, Chantal DS, Sebastiano R et al. Thyroid hormones, oxidative stress, and inflammation. 2016; 12 pages.
45. Derouiche S, Rezzag-mohcen OS, Serouti A. Triazinone herbicide metribuzin induced acute liver injury: A study of animal model. J Acute Dis 2018; 7(4): 152-157.
46. Villanueva I, Alva-Sánchez C, Pacheco-Rosado J. The role of thyroid hormones as inductors of oxidative stress and neurodegeneration. Oxid Med Cell Longev. 2013; 2013: 218145.
47. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev. 2014; 94(2): 355-82.
48. Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiol Rev. 2014; 94(3): 909-50.
49. Venditti P, Di Meo S. The Role of Reactive Oxygen Species in the Life Cycle of the Mitochondrion. Int J Mol Sci. 2020; 21(6): 2173.
50. Nocella C, Cammisotto V, Pigozzi F et al. Impairment between Oxidant and Antioxidant Systems: Short- and Long-term Implications for Athletes' Health. Nutrients. 2019; 11(6): 1353.
51. Mughal BB, Fini JB, Demeneix BA. Thyroid-disrupting chemicals and brain development: an update. Endocr Connect. 2018; 7(4): R160-R186.
52. Cheserek MJ, Wu GR, Ntazinda A et al. Association between Thyroid Hormones, Lipids and Oxidative Stress Markers in Subclinical Hypothyroidism. J Med Biochem. 2015; 34(3): 323-331.
53. Derouiche S, Doudi D, Atia, N. Study of Oxidative Stress during Pregnancy. Global Journal of Pharmacy & Pharmaceutical Sciences. 2018; 4(5).ID.555646.
54. Alemu A, Terefe B, Abebe M, Biadgo B. Thyroid hormone dysfunction during pregnancy: A review. Int J Reprod Biomed (Yazd). 2016;14(11):677-686.
55. Hage, M. Mira, S. Z. & Sami,T.A.(2011).Thyroid Disorders and Diabetes Mellitus.Doi: 10.4061/2011/439463.
56. Sahay RK, Nagesh VS. Hypothyroidism in pregnancy. Indian J EndocrinolMetab. 2012; 16(3): 364-70.

57. Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. Physiological changes in pregnancy. Cardiovasc J Afr. 2016; 27(2): 89-94.
58. Maraka S, Ospina NM, O'Keeffe DT, Espinosa De Ycaza AE, Gionfriddo MR, Erwin PJ, Coddington CC 3rd, Stan MN, Murad MH, Montori VM. Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-Analysis. Thyroid. 2016; 26(4): 580-90.
59. Panuganti PL, Hinkle SN, Rawal S, Grunnet LG, Lin Y, Liu A, Thuesen ACB, Ley SH, Olesen SF, Zhang C. Lactation Duration and Long-Term Thyroid Function: A Study among Women with Gestational Diabetes. Nutrients. 2018; 10(7): 938.
60. Rawal S, Tsai MY, Hinkle SN, et al. A Longitudinal Study of Thyroid Markers across Pregnancy and the Risk of Gestational Diabetes. J ClinEndocrinolMetab. 2018; 103(7): 2447-2456.
61. Leung AM, Braverman LE. Consequences of excess iodine. Nat Rev Endocrinol. 2014; 10(3): 136-42.
62. Chung HR. Iodine and thyroid function. Ann PediatrEndocrinolMetab. 2014; 19(1): 8-12.
63. Kalra B, Gupta Y, Singla R, Kalra S. Use of oral anti-diabetic agents in pregnancy: a pragmatic approach. N Am J Med Sci. 2015; 7(1): 6-12.
64. Thulé PM. Mechanisms of current therapies for diabetes mellitus type 2. AdvPhysiol Educ. 2012; 36(4): 275-83.
65. Kavitha N, De S, Kanagasabai S. Oral Hypoglycemic Agents in pregnancy: An Update. J ObstetGynaecol India. 2013; 63(2): 82-7.
66. Chaudhury A, Duvoor C, Reddy Dendi VS, et al. Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. Front Endocrinol (Lausanne). 2017;8:6.
67. Reece SW, Parihar HS, LoBello C. Metformin in gestational diabetes mellitus. Diabetes Spectr. 2014; 27(4): 289-95.
68. Singh AK, Singh R. Metformin in gestational diabetes: An emerging contender. Indian J EndocrinolMetab. 2015;19(2): 236-44.
69. Hirsch IB. Type 1 Diabetes Mellitus and the Use of Flexible Insulin Regimens. Am Fam Physician. 1999; 60(8): 2343-2352.
70. Faraci M, Di Prima FA, Valenti O et al. Treatment of gestational diabetes: oral hypoglycemic agents or insulin? J Prenat Med. 2011; 5(3): 63-4.
71. Padayachee C, Coombes JS. Exercise guidelines for gestational diabetes mellitus. World J Diabetes. 2015; 6(8) :1033-44.
72. Cooper DB, Yang L. Pregnancy And Exercise. In: StatPearls. Treasure Island (FL): Stat Pearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/ NBK430 821/
73. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016; 388(10047): 906-918.
74. Abraham P, Acharya S. Current and emerging treatment options for Graves hyperthyroidism. TherClin Risk Manag. 2010; 6: 29-40.
75. Inoue M, Arata N, Koren G, Ito S. Hyperthyroidism during pregnancy. Can Fam Physician. 2009; 55(7): 701-3.
76. Hennessey JV, Espaillat R. Current evidence for the treatment of hypothyroidism with levothyroxine/levotriiodothyronine combination therapy versus levothyroxine monotherapy. Int J ClinPract. 2018; 72(2): e13062.
77. Chakera AJ, Pearce SH, Vaidya B. Treatment for primary hypothyroidism: current approaches and future possibilities. Drug Des DevelTher. 2012; 6: 1-11.
78. Aydemir T, Oztürk R, Bozkaya LA, Tarhan L. Effects of antioxidant vitamins A, C, E and trace elements Cu, Se on CuZn SOD, GSH-Px, CAT and LPO levels in chicken erythrocytes. Cell BiochemFunct. 2000; 18(2): 109-15.
79. Mistry HD, Williams PJ. The importance of antioxidant micronutrients in pregnancy. Oxid Med Cell Longev. 2011; 2011: 841749.
80. Horton JW. Free radicals and lipid peroxidation mediated injury in burn trauma: the role of antioxidant therapy. Toxicology. 2003; 189(1-2): 75-88.
81. Derouiche S, Degachi O, Gharbi K. Phytochemistry analysis and modulatory activity of Portulacaeoleracea and Aquilariamalaccensis extracts against High-fructose and high-fat diet induced immune cells alteration and heart lipid peroxidation in Rats. Int Res J Bio Sci 2019; 8(4): 6-11.