

Pregnancies Complicated by Diabetes, Hypertension and Hypothyroidism: Role of Insulin Resistance

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ABSTRACT

During recent times we are dealing with multiple medical complications occurring in a single pregnant woman. It is well known fact that insulin resistance is present during normal pregnancy and it is relatively diabetogenic state. In women with genetic predisposition, diabetes, hypertension and hypothyroidism complicate pregnancy resulting in increased maternal and perinatal morbidity and mortality. There was evidence in the literature regarding insulin resistance and gestational diabetes. This review analysed the literature regarding the association of diabetes, hypertension and hypothyroidism and found that there is a linkage between these three disorders in pregnant state and the insulin resistance develops by multiple molecular mechanisms both centrally and in peripheral tissues. The key mechanism is insulin receptor substrate-1 (IRS-1) which gets inactivated by serine phosphorylation and leads to hyperglycaemia which in turn leads to stimulation of beta cells of pancreas and leads to hyperinsulinaemia. Pancreas has thyroid hormone receptors and this stimulates the secretion of insulin leading hyperinsulinaemia. Hyperglycaemia leading to increase in free fatty acids and together with proinflammatory factors and reactive oxygen species causes endothelial dysfunction and hypertension. More studies are necessary to target insulin receptor to increase insulin sensitivity and prevent these disorders occurring together.

Key words: Insulin Resistance, Pregnancy, Diabetes, Hypothyroidism, Hypertension.

INTRODUCTION

Diabetes mellitus, hypertension and hypothyroidism are the common medical conditions encountered during pregnancy. They most often develop for the first time during pregnancy or may pre-exist. They cause severe maternal morbidity and also affect the developing fetus and result in increased perinatal morbidity and mortality. Increased insulin resistance (IR) has been reported during pregnancy and also in these disorders individually when they occur in the non-pregnant state.

It has been observed that pregnancy brings about many physiological changes in the body including exaggerated atherogenic responses, insulin resistance and dyslipidemia which can lead to the development of pre-eclampsia and gestational diabetes.^[1] Thyroid disorders have been found to have association with insulin resistance by various mechanisms such as altered insulin secretion and lipid levels.^[2,3] So it is plausible that, increased insulin resistance may result in development of these disorders during pregnancy. This review analyses from literature for any evidence regarding insulin resistance as a common pathway for the development of these disorders.

Insulin Resistance and Its Linkages and Effects on the Body

The term is self-explanatory in that there is a resistance at the cellular level for the insulin to bring

about its action. It has been described as a pathological condition where the cells do not respond to its action which could be due to a defect at the receptor level or further downstream. Insulin resistance is defined as inability of a defined concentration of insulin to bring about a predictable biological response at the level of tissue in terms of nutrient metabolism. The effects are impaired glucose disposal at muscles, adipose tissue and hepatic gluconeogenesis.

It is known since decades that pregnancy is a diabetogenic state and carbohydrate intolerance develops due the pregnancy hormones such as human placental lactogen, corticosteroids etc. But these act at the peripheral level to increase the insulin resistance. In predisposed individuals, insulin resistance develops early and may be severe to produce various affects like hypertension, diabetes, hypothyroidism, obesity which have detrimental effects on the outcome of pregnancy. The mechanism of insulin resistance during pregnancy is illustrated in Figure 1.

There is development of proinflammatory or inflammatory state at tissue level which involves many pathways. The proinflammatory markers are mainly cytokines viz; interleukin-1 beta, interleukin-6, tumour necrosis factor-alpha and various other chemokines, adipocytokines etc. These stimulate the signalling of cytokine proteins which

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block the signalling pathways of insulin receptor activity in islet cells of pancreas. There is evidence that C-reactive protein (CRP), a marker of inflammation, is also raised.^[4] The various markers act after genetic expression in skeletal muscle, adipose tissue to inhibit the action of insulin on the insulin receptor mainly by inhibiting phosphokinase.

Insulin resistance during pregnancy is multifactorial. The human placental lactogen increases up to 30 fold and also there is increase in hPGH (human placental growth hormone) appearing after 20 weeks of gestation which causes increase in peripheral insulin resistance. There is increased secretion of insulin during pregnancy to maintain euglycaemia of pregnancy which results in hyperinsulinaemia. In the skeletal muscle and adipose tissue there are defective signalling pathways that were observed. Insulin binds to its receptor and stimulates tyrosine phosphorylation of the subunit of the receptor. This is defective in women who develop gestational diabetes mellitus (GDM). There is an intrinsic defect in insulin receptor tyrosine phosphorylation per receptor protein that could be due to an endogenous inhibitory pathway for receptor signalling resulting in reduced glucose transport in to the skeletal muscle and hence there is hyperglycaemia. This happens due to down regulation of insulin receptor substrate-1 (IRS-1) docking protein which is involved in triggering of phosphatidylinositol 3-kinase (PI3K). There is also down regulation of glucose transporter-4 (GLUT-4) protein in adipose tissue of pregnant women.^[5]

The concept that insulin resistance is the primary mechanism for development of Diabetes was proposed in 1931 by Prof. Wilhelm Falta and confirmed in 1936 by Prof. Harold Percival in London. Recent literature suggests neuronal role in peripheral glucose metabolism by regulation of liver, brown adipose tissue and pancreatic function. The review by Johan Rudd and colleagues unravels the role of CNS in glucose homeostasis and insulin resistance. The areas in the hypothalamus concerned are arcuate nucleus, ventromedial nucleus and lateral hypothalamic area which are connected by neuroregulatory network. The extra hypothalamic nuclei involved are sensory and integrative clusters in hindbrain and parasympathetic and sympathetic preganglionic brainstem neurons. Acute activation of agouti-related peptide (AgRP)

neurons was the key factor that impairs insulin sensitivity and increases the peripheral insulin resistance. Insulin actions on the hypothalamus result in lipolysis and increase in free fatty-acids and lipogenesis in adipocytes by reducing sympathetic tone. Vagus nerve which innervates most of the viscera is affected by the central action of insulin.^[6]

Thyroid hormone receptors that are present in the islets cells of pancreas influence the secretion of insulin. Thyroid hormone promotes the genetic expression of MafA gene which is essential for normal development, proliferation and growth of β cells of pancreas.^[7] Hyperthyroidism promotes gluconeogenesis and hypothyroidism impairs it in liver. Thyrotoxicosis was found to be associated with hyperinsulinaemia and by increasing protein kinase C (PKC), it influences the phosphorylation of insulin receptor thus causing insulin resistance.^[8] There are numerous studies which proved the association of thyroid dysfunction especially subclinical hypothyroidism with metabolic syndrome in which the crux was the dyslipidaemia.^[9,10] Thyroid autoimmunity also plays an important role in development of Insulin Resistance and the various mechanisms leading to IR in thyroid dysfunction was well brought out in an article published by Gabriela Branta.^[11] Oxidative stress has also been suggested as a link between insulin resistance and hypothyroidism.^[12] The various linkages between diabetes, hypertension and hypothyroidism are shown in Figure 2.

Prevalence of hypothyroidism in pregnancy is around 2.5% as per western literature and it varies from 0.4% to 11% worldwide. In India, prevalence ranges from 4.8% to 1% and subclinical hypothyroidism (SCH) is as high as 13.5%.^[13,14] Raised antibodies to either thyroperoxidase (TPO) or thyroglobulin (Tg), also has high prevalence during pregnancy and varies widely from 5 to 15%.^[15]

Although insulin resistance is a physiologic phenomenon in normal pregnancy, in predisposed individuals this could lead to hyperinsulinemia with the development of gestational hypertension, gestational diabetes mellitus, or both.^[16] Gestational diabetes is carbohydrate intolerance of varied severity that begins or is first recognized during pregnancy. The underlying pathophysiology of gestational diabetes is a function of decreased maternal insulin sensitivity or increased insulin resistance. Women with gestational diabetes have decreased insulin sensitivity in comparison with weight-matched control groups.^[17] Pregnancy related hormones such as hPL, progesterone, estrogen, cortisol and prolactin, newer mediators like tumour necrosis factor (TNF) alpha, leptin and interleukin-6 are responsible for increase in insulin resistance of

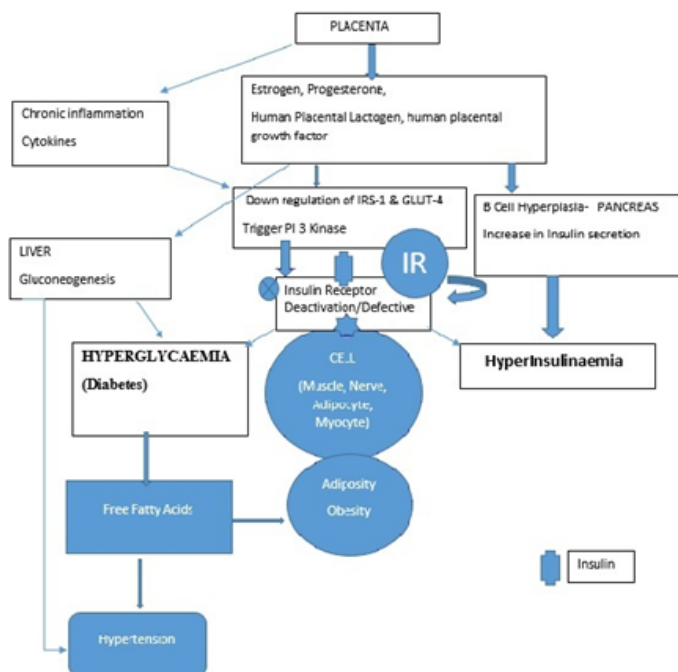


Figure 1: Mechanism of Insulin Resistance during Pregnancy.

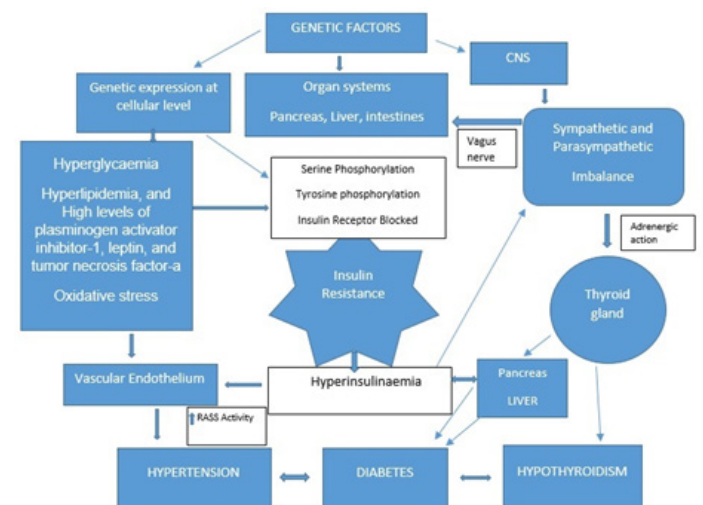


Figure 2: Linkages between Diabetes, Hypertension and Hypothyroidism.

pregnancy. Insulin resistance which is normally compensated by beta cell hyperplasia in pancreas is defective in GDM patients.

The insulin resistance of normal pregnancy is multifactorial with complex mechanisms involved affecting the glucose metabolism. The net effect of the combined hormonal and metabolic changes leads to anti-insulinogenic effect at the peripheral and hepatic tissues leading to development of GDM. Later half of pregnancy due to increased pregnancy related hormones further contributes to insulin resistance.^[5] Compared with healthy pregnant women, GDM patients had higher serum TG concentrations ($P<0.01$), fasting insulin ($P<0.001$) and insulin resistance (HOMA-IR; $P<0.001$). These results suggest that symptoms of insulin resistance are present in women with GDM, which is indicated by higher arterial blood pressure, heart rate, serum triglycerides, insulin and increased insulin resistance.^[18]

A trend of higher insulin and homeostasis model assessment-insulin resistance (HOMA-IR) levels has been observed in women developing hypertension.^[19] Insulin resistance, therefore, has been considered as an independent risk factor for gestational hypertension among nulliparous women.^[20] Increased insulin resistance can activate the sympathetic nervous system and lead to an increase in expression of receptors for endothelin, both of which lead to increased blood pressure.^[1] Hypertension during pregnancy is characterized by the same features that define IR, including hypertension, dyslipidemia, disruption of endothelial and platelet function and related disturbances of prostanoid synthesis, coagulation and fibrinolytic abnormalities, hyperuricemia, atherosclerotic changes and obesity. Metabolic abnormalities like glucose intolerance, hyperinsulinemia, hyperlipidemia and high levels of plasminogen activator inhibitor-1, leptin and tumor necrosis factor-alpha which are associated with insulin resistance and also with hypertension during pregnancy. These observations suggest the possibility that insulin resistance may be involved in the pathogenesis of hypertension during pregnancy and the approaches that improve insulin sensitivity might have benefit in the prevention or treatment of this syndrome.^[21] Women who subsequently developed hypertension during pregnancy had a higher degree of insulin resistance as determined by log-HOMA early in pregnancy, before the onset of clinical manifestations of the disease.^[22] Development of pre-eclampsia as well as GDM is associated with age of the patient, pre-pregnancy BMI and weight gain in early pregnancy.^[23] Pre-eclamptic women were found to have increased TG and free fatty acid levels and decreased high density lipoprotein-cholesterol (HDL-c) levels as compared with normotensive patients as studied by Seely EW, *et al.*^[24] A systematic review by Carpenter MW found that odds ratio for development of GDM was elevated in pregnant women with gestational hypertension and pre-eclampsia and vice versa. He reported that both gestational hypertension and preeclampsia may be more prevalent in gravidas with greater insulin resistance.^[25]

Pregnant women with SCH and hypothyroidism had increased risks of abortions, anemia, preeclampsia, GDM and prematurity, higher caesarean section rate. Neonates of women with SCH had higher incidence poor APGAR score, low birth weight, neonatal ICU admission, intra uterine growth restriction. Increased maternal age and high BMI were associated with higher incidence of subclinical hypothyroidism.^[15,26,27] A systematic review by Nazapour, *et al.* to assess the pregnancy outcomes in thyroid dysfunction reported that subclinical hypothyroidism was associated with adverse pregnancy outcomes such as placental abruption, preterm birth, miscarriage, gestational hypertension, fetal distress, severe preeclampsia and neonatal distress and diabetes.^[28] The manifestations of insulin resistance is summarised in Table 1.

Table 1: Manifestations of insulin resistance.

S. No	Manifestations/ Changes	Description
A	Clinical Manifestations	• Acanthosis Nigricans • Hirsutism • Obesity • Hypertension • Hypothyroidism • Diabetes Mellitus • PCOS-Menstrual Irregularities; Infertility • Recurrent Early Pregnancy loss
B	Biochemical Changes	• Hyperinsulinaemia • Hyperglycaemia • Hypertriglyceridaemia • Hyperuricaemia
C	Oxidative Stress Parameters	• Malondialdehyde (MDA) • Glutathione Peroxidase (GTX) • Catalase (CAT)

CONCLUSION

The literature published regarding gestational diabetes, gestational hypertension, pre-eclampsia and hypothyroidism shows that there is adequate evidence that insulin resistance is the central mechanism at the molecular level though different pathways are involved and they are interlinked. Normal pregnancy itself exhibits insulin resistance and this may be exaggerated in genetically predisposed women leading to the development of these metabolic and endocrine disorders. There are no studies that quantified the level of insulin resistance in order to predict development of these disorders at various cut-off values. Further research is needed to adopt interventions to reduce and optimize the insulin resistance during pregnancy thus preventing the development of these disorders so as to prevent maternal and fetal morbidity and mortality.

ABBREVIATIONS

IRS-1: Insulin Receptor Substrate-1; **IR:** Insulin Resistance; **hPGH:** Human Placenta Growth Hormone; **GDM:** Gestational Diabetes Mellitus; **PI3K:** Phosphatidylinositol 3-Kinase; **GLUT-4:** Glucose Transporter-4; **AgRP:** Agouti-Related Peptide; **PKC:** Protein Kinase C; **SCH:** Subclinical Hypothyroidism; **TPO:** Thyroperoxidase; **Tg:** Thyroglobulin; **TNF:** Tumour Necrosis Factor; **HOMA-IR:** Homeostasis Model Assessment-Insulin Resistance; **HDL:** High Density Lipoprotein.

REFERENCES

1. Kaaja RJ, Greer IA. Manifestations of chronic disease during Pregnancy. JAMA. 2005;294(21):2751-7.
2. Knight BA, Shields BM, Hattersley AT, Vaidya V. Maternal hypothyroxinaemia in pregnancy is associated with obesity and adverse maternal metabolic parameters. Eur J Endocrinol. 2016;174(1):51-7.
3. Agarwal MM, Dhatt GS, Punnose J, Bishawi B, Zayed R. Thyroid function abnormalities and antithyroid antibody prevalence in pregnant women at high risk for gestational diabetes mellitus. Gynecol Endocrinol. 2009;22(5):261-6.
4. Rehman K, Akash MS. Mechanisms of inflammatory responses and development of insulin resistance: How are they interlinked?. J Biomed Sci. 2016;23(1):87.
5. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. Diab Care. 2007;30(Suppl 2):S112-9.
6. Ruud J, Steculorum S, Brüning J. Neuronal control of peripheral insulin sensitivity and glucose metabolism. Nat Commun. 2017;8(1):1-2.

7. Aramata S, Han SI, Kataoka K. Roles and regulation of transcription factor MafA in islet beta-cells. *Endocr J*. 2007;54(5):659-66.
8. Wang C. The Relationship between Type 2 Diabetes Mellitus and Related Thyroid Diseases. *Journal of Diabetes Research*. 2013;390534.
9. Hamdy N, Adly N, Bakr Y, Salem A, Aty SA. Association between subclinical hypothyroidism and metabolic syndrome. *Int J Adv Res*. 2014;2(6):213-26.
10. Waring AC, Rodondi N, Harrison S, Kanaya AM, Simonsick EM, Miljkovic I, *et al*. Thyroid function and prevalent and incident metabolic syndrome in older adults: The health, ageing and body composition study. *Clin Endocrinol*. 2012;76(6):911-8.
11. Brenta G. Why can insulin resistance be a natural consequence of thyroid dysfunction?. *J Thyroid Res*. 2011;2011:152850.
12. Nanda N, Zachariah B, Hamide A. Insulin Resistance among Hypothyroid Patients in India. *Asian J Biochem*. 2012;7(3):151-7.
13. Sannaboraiah A, Upadhyaya R, Garag S, Krishnappa S. Subclinical hypothyroidism in pregnancy and outcomes. *Int J Reprod Contracept Obstet Gynecol*. 2017;6(4):1215-21.
14. Dhanwal DK, Bajaj S, Rajput R, Subramaniam KAV, Chowdhury S, Bhandari R, *et al*. Prevalence of hypothyroidism in pregnancy: An epidemiological study from 11 cities in 9 states of India. *Indian J Endocrinol Metab*. 2016;20(3):387-90.
15. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, *et al*. Guidelines of the american thyroid association for the diagnosis and management of thyroid disease during pregnancy and postpartum: The american thyroid association taskforce on thyroid disease during pregnancy and postpartum. *Thyroid*. 2011;21(10):1081-25.
16. Mastrogiannis DS, Spiliopoulos M, Mulla W, Homko CJ. Insulin resistance: The possible link between gestational diabetes mellitus and hypertensive disorders of pregnancy. *Curr Diab Rep*. 2009;9(4):296-302.
17. Catalano PM, Kirwan JP, Haugel-de Mouzon S, King J. Gestational diabetes and insulin resistance: Role in short and long-term implications for mother and fetus. *J Nutr*. 2003;133(2):1674-83.
18. Szymanska M, Bomba-Opon DA, Wielgos M. Blood pressure and lipid changes in gestational diabetes mellitus. *Neuro Endocrinol Lett*. 2008;29(3):328-33.
19. Negrato CA, Jovanovic L, Tambascia MA, Geloneze B, Dias A, Calderon IMP, *et al*. Association between insulin resistance, glucose intolerance and hypertension in pregnancy. *Metab Syndr Relat Disord*. 2009;7(1):53-9.
20. Wolf M, Sandler L, Jimenez-Kimble R, Shah A, Ecker JL, Thadhani R. Insulin resistance but not inflammation is associated with gestational hypertension. *hypertension*. 2002;40(6):886-91.
21. Solomon CG, Seely EW. Hypertension in pregnancy: A manifestation of the insulin resistance syndrome?. *Hypertension*. 2001;37(2):232-9.
22. Sierra-Laguado J, Garcia RG, Celedón J, Arenas-Mantilla M, Pradilla LP, Camacho PA, *et al*. Determination of insulin resistance using the homeostatic model assessment (HOMA) and its relation with the risk of developing pregnancy-induced hypertension. *Am J Hypertens*. 2007;20(4):437-42.
23. Wendlandt REM, Duncan BB, Belizani JM, Vigor A, Schmidt MI. Gestational diabetes and pre-eclampsia: common antecedents?. *Arq Bras Endocrinol Metab*. 2008;52(6):975-84.
24. Seely EW, Solomon CG. Insulin resistance and its potential role in pregnancy-induced hypertension. *J Clin Endocrinol Metab*. 2003;88(6):2393-8.
25. Carpenter MW. Gestational diabetes, pregnancy hypertension and late vascular disease. *Diab Care*. 2007;30(2):246-50.
26. Sannaboraiah A, Upadhyaya R, Garag S, Krishnappa S. Subclinical hypothyroidism in pregnancy and outcomes. *Int J Reprod Contracept Obstet Gynecol*. 2017;6(4):1215-21.
27. Blumenthal NJ, Eastman CJ. Beneficial effects on pregnancy outcomes of thyroid hormone replacement for subclinical hypothyroidism. *J Thyroid Res*. 2017;4601365.
28. Nazarpour S, Tehrani FR, Simbar M, Azizi F. Thyroid dysfunction and pregnancy outcomes. *Iran J Reprod Med*. 2015;13(7):387-96.

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