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ABNORMAL TROPHOBLASTIC INVASION IN PREGNANCY INDUCED HYPERTENSION, PREECLAMPSIA, AND ECLAMPSIA

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ABSTRACT

The aim of this study was to elucidate the role of beta-human chorionic gonadotropin in predicting pregnancy-induced hypertension, preeclampsia, and eclampsia. It was a cross-sectional study over six months on 100 pregnant women between 13 and 18 weeks of gestation presenting at Abbasi Shaheed Hospital, Karachi. Serum beta-hCG levels were estimated at two time points of the second trimester to determine the relationship with hypertensive disorders. In results, it was shown that there was a close association of increased levels of β-hCG with ≥2 MoM with the progression of hypertensive complications. The values for β-hCG were remarkably greater in women who developed PIH, preeclampsia, or eclampsia. This therefore advocates the use of β-hCG as an early marker for these complications, thus improving clinical management and also reducing adverse outcomes for both the mother and the fetus.

Keywords: *β-hCG, pregnancy-induced hypertension, preeclampsia, eclampsia, trophoblastic invasion, predictive biomarker.*

INTRODUCTION

Hypertensive disorders of pregnancy are really a challenge for the medical science system because these consequences reflect various difficult clinical issues, both in developed and developing countries and correspond to a significant proportion of the burden of illness and mortality. This health condition was shown to be critical as found out by the meta-analysis conducted by the World Health Organization in June 2014. Based on this, it was reported that hypertensive diseases account for 14% of total maternal deaths. (Say et al., 2014; Schneider et al., 2021)

Hypertensive disorders of pregnancy include chronic hypertension, gestational hypertension, preeclampsia, chronic hypertension with superimposed preeclampsia, and eclampsia. Several hypotheses are offered to explain the intricate etiopathogenesis of PIH. Yet, the true etiology and inception of the disorder are unknown. The present topic under active research involves the pursuit of an appropriate predictive marker that would alert the possibility of PIH development. Due to such a marker, these mothers could be included as high-risk. This means there will be more intensive monitoring and management. (Gemechu et al., 2020; von Dadelszen & Magee, 2016)

Some biochemical and hormonal assays have been proposed for earlier intervention in probable cases of PIH. However, no test is appropriately diagnostic. It should also be remembered that PIH is associated with mid-trimester beta-hCG surges that are precipitated by a hypersecretory reaction from the immunologically modified trophoblast. This is one of the significant features of PIH. (Abdi et al., 2018; Mosimann et al., 2020)

Human chorionic gonadotropin, commonly shortened to hCG, is a hormone that only occurs in pregnancy and is produced by cells called trophoblasts. It plays a role in the control of several events associated with pregnancy, including progesterone biosynthesis, implantation, uterine growth and function of immune cells. It also contributes to placental development in addition to involvement in angiogenesis and partly due to vasculogenesis through its interaction with the vascular endothelial growth factors (VEGFs). Future studies have established a presumed link between highly elevated hCG levels with clinical symptoms and signs in the case of pre-eclampsia. (Borisova et al., 2017; Theofanakis et al., 2017; Zhang et al., 2021)

Preeclampsia can even threaten both the mother's and the foetus's health due to morbidities and mortality. Despite the large scientific amount of efforts invested in this topic, yet till now, no specific mechanism which leads to preeclampsia was identified. The abnormalities in pathogenesis are possibly played by placentation that soon undergoes hyperinflammatory response due to the disturbance in pro- and anti-angiogenic factors. The various studies have targeted levels of hCG and the risk of preeclampsia. (Ramos et al., 2017; Zhang et al., 2021).

In this second trimester, we attempted to measure whether maternal beta-hCG levels can serve as a potential predictor of PIH and the time by which it will be apparent. Exploring this relationship and uncovering insights that may change the preventative and intervention tactics in the treatment of PIH, thereby improving the health outcomes for both mothers and their unborn children, is the two primary focuses of this study.

Literature Review

There is a literature on hypertensive disorders in pregnancy, and all such works by different writers consistently underscore that proper trophoblastic invasion is important for normal placental function. Invasion therefore plays an important role in the conversion of maternal spiral arteries from the high-resistance, low-capacity vessels into the low-resistant, high-capacity ones whose ability is enhanced in supplying the growing fetus with needed nutrients and oxygen. It is also during the early stages of pregnancy that cytotrophoblast cells invade the maternal decidua to such a depth that they remodel spiral arteries, thereby enabling the placenta to work properly. When this otherwise normal process is defective, as is commonly the case with pregnancies complicated by preeclampsia or PIH, then the invasion is shallow and incomplete. This failure will leave the high-resistance arteries intact; subsequently, the perfusion of the placenta will be poor, and therefore ischemic and under oxidative stress. These conditions are believed to initiate a cascade of subsequent events leading to systemic manifestations of hypertensive disorders; that is, hypertension, proteinuria, and edema (Chau et al., 2017).

A significant amount of research had been conducted into the relationship between underinvasion of trophoblasts and preeclampsia and PIH. These hypertensive disorders share the characteristic feature of shallow trophoblastic invasion, which leads to less adequate remodeling of spiral arteries. This aberrant invasion upsets the balance between pro-angiogenic and anti-angiogenic factors, thus leading to functional vascular impairment. Some studies have also established a robust correlation between raised levels of beta-human chorionic gonadotropin (β-hCG) and bad trophoblastic invasion. β-hCG is produced by trophoblast cells and supports early pregnancy by maintaining the corpus luteum, thus appropriate levels for the progesterone. An abnormally increased level of β-hCG during the second trimester signifies suboptimal development of the placenta especially linked to hypertensive disorders such as PIH and preeclampsia (Mosimann et al., 2020). The abnormal placentation reflected by the high levels of β-hCG leads to hypoperfusion, ischemia, and the release of various factors that disrupt maternal endothelial function, one of the hallmarks of preeclampsia.

A meta-analysis conducted by Ramos et al. in 2017 provides robust evidence for the association of elevated β-hCG levels with the risk of developing hypertensive disorders during pregnancy. Significant clinical trials data was looked at to draw the conclusions of the study. Pregnant women with highly elevated levels of β-hCG significantly during the second trimester were several folds more susceptible to develop cases of preeclampsia compared to those at normal levels of β-hCG.

Analysis thereby showed that levels of β-hCG could predict risk among women, with high chances of hypertensive complications. Such predictive ability is also essential because, through evaluation, the pregnancy conditions can be noted early on to be at high risk. This opens avenues for closer monitoring and intervention strategies at an early stage to produce a better outcome for both mother and fetus.

Besides acting as a marker for poor placental development, elevated β-hCG has also been directly implicated in endothelial dysfunction, the centerpiece of hypertensive disorders during pregnancy. Endothelial dysfunction features impaired vasodilation and increased vascular resistance and hypertension. High levels of β-hCG have been invoked to stimulate the production of soluble fms-like tyrosine kinase-1 (sFlt-1), an anti-angiogenic factor significantly involved in the pathophysiologic aspect of preeclampsia. By binding and inhibiting the soluble protein vascular endothelial growth factor (VEGF), sFlt-1 impairs normal vessel maintenance as well as development by inhibiting vascular function. This systemic endothelial dysfunction expresses clinically in various ways, primarily resulting in hypertension, proteinuria, and generalized edema within the patient, the common clinical manifestations of preeclampsia (Abdi et al., 2018).

Recently, it has also been suggested that excess β-hCG causes oxidative stress through the unbalance levels of pro-angiogenic and anti-angiogenic factors within the placenta. Oxidative stress being a consequence of overproduction of ROS further deteriorates the endothelial lining of blood vessels, hence worsening the pre-existing vascular dysfunction found in hypertensive pregnancy. These damages may, in turn lead to other harmful factors to be released into the maternal circulation and perpetuating yet another cycle of vascular injury and dysfunction. Cumulatively, these processes form the characteristic clinical signs and symptoms of preeclampsia and other hypertensive disorders posing significant risks to both maternal and fetal health.

Generally, β-hCG has been noted in the literature to have a multi-functional role in the pathogenesis of complications of hypertension disorder during pregnancy. The elevation of β-hCG is observed in relation to defective placentation associated with endothelial dysfunction, a determinant of severity in preeclampsia and PIH. β-hCG acts as a critical biomarker of predictive significance through its implication in the interruption of the pro-angiogenic signaling pathway, promotion of oxidative stress, and its relation to shallow trophoblastic invasion. Further research will be done to determine how β-hCG actually affects placental and vascular health, yet its utility as an early predictive marker in the diagnosis of hypertensive disorders is established (Ramos et al., 2017; Mosimann et al., 2020).

Methodology

This is a cross-sectional study conducted over six months at Abbasi Shaheed Hospital, Karachi, from September 2019 to February 2020. One hundred pregnant women between 18 and 40 years of age with a gestation ranging from 13 to 18 weeks were taken into consideration. Pregnant women suffering from chronic hypertension, renal disease, or autoimmune diseases were excluded from the study.

Data Collection:

Serum β-hCG levels were tested at two points in the second trimester: from 13 to 18 weeks and from 24 to 28 weeks. This gestational age parameter is represented in multiples of the median (MoM), accounting for potential variation due to gestational age.

Outcome Measures:

Incidence of hypertensive disorders, breaking down into PIH, preeclampsia, and eclampsia. It utilized ANOVA and descriptive statistics to analyze the data. The research was a test of association between β-hCG and the outcome concerning hypertensive conditions.

Results

Out of 100, 68% of pregnant women, as it turned out, had normal pregnancies, where 17% experienced PIH, 11% preeclampsia, and 4% eclampsia. Parity and age group correlate insignificantly with the development of hypertensive disorders ($p=0.650$ and $p=0.551$, respectively).

Table: Distribution of Patients by Age Group

Age Group (years)	Normal Pregnancy	PIH	Preeclampsia	Eclampsia	Total
18-25	22	7	5	1	35
26-30	25	6	4	2	37
31-35	14	2	2	1	19
36-40	7	2	0	0	9
Total	**68**	**17**	**11**	**4**	**100**

(Above Table indicating the most patients with the disorders hypertensive that are fell within age groups of 18-30)

Table: Patient Distribution Based on β-hCG Levels at First Visit (13-18 Weeks)

β-hCG MoM Level	Normal Pregnancy	PIH	Preeclampsia	Eclampsia	Total
<2 MoM	71	5	2	0	78
≥2 MoM	9	12	9	4	34

(Table above shows that there is a highly correlated β-hCG elevation and hypertensive disorders, where 34 out of 100 patients were found to have elevated β-hCG levels above 2 MoM).

Table: Comparison of β-hCG Levels by Diagnosis (24-28 Weeks)

Diagnosis	Mean β-hCG Level (mIU/mL)
Normal Pregnancy	45,866.54
PIH	105,109.88
Preeclampsia	155,575.36
Eclampsia	142,225.25

The mean values of β-hCG in hypertensive disorders were appreciably higher compared with that in normal pregnancies. The mean levels of β-hCG in patients with PIH, preeclampsia, and eclampsia were more than twice that seen in patients with normal pregnancies ($p < 0.001$).

Discussion

The results of the present study suggest that high levels of β-hCG in the second trimester (≥2 MoM) are significantly associated with an increased risk for PIH, preeclampsia, and eclampsia. As presented in Table III, most patients with a raised level of β-hCG develop hypertensive disorders; thus, β-hCG screening is highly relevant for predicting complications during early pregnancy.

Literature has well documented the relationship between β-hCG levels and hypertensive disorders, showing several research studies that point to the interpretation that abnormal levels of β-hCG reflect abnormal placentation. In hypertensive pregnancies, poor trophoblastic invasion leads to placental ischemia, which triggers the release of anti-angiogenic factors, including sFlt-1, that causes systemic endothelial dysfunction (Ramos et al., 2017; Mosimann et al., 2020). This study is in congruence with prior researches whose findings had already identified β-hCG to be one of the markers of placental insufficiency and hypertensive complications (Zhang et al., 2021).

Furthermore, the presence of β-hCG has shed light on the use of this enzyme as a prospective tool for an early indication of risky pregnancy. The earlier identification of raised levels of β-hCG allows closer monitoring, timely intervention, which may prevent or at least avoid hypertensive disorders or their more severe manifestations, avoiding the preterm delivery, low birth weight, and the maternal mortality rate (Gemechu et al., 2020).

Conclusion

It confirms the high association of elevated β-hCG levels in the second trimester with hypertensive disorders such as PIH, preeclampsia, and eclampsia. Thus, β-hCG levels ≥2 MoM can function as a fairly reliable predictive biomarker for clinicians to identify at-risk women at an earlier stage of pregnancy.

Improvements may thus be achieved through the routine prenatal care introduction of β-hCG screening, mainly in resource-limited settings. Further research involving larger populations is important to validate the above findings and optimize clinical guidelines in the basis of β-hCG-based screening.

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