Maternal Serum Insulin in Hypertensive Disorders of Pregnancy and Neonatal Outcome

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Abstract: *Background:* Complications of hypertensive disorders, during pregnancy (HDP), labour, postpartum have been recognized for centuries. Focus has shifted from maternal to materno-neonatal outcome, because effects of HDP on maternal metabolism have significant impact on perinatal outcome. Possibility of linkage of hyperinsulinemia leading to hypoglycaemia, growth retardation is real.

Objective: Study was conducted to know relation of maternal serum insulin to the severity of hypertensive disorders and its effects on neonatal outcome.

Material methods: Case control study was carried out over two years. Fasting blood sugar, insulin, post glucose blood sugar were estimated.

Results: Overall 13.32% women who delivered during study period had HDP. Of these 964 women, 609(63.17%) had mild HDP, 12 (1.97%) of them had elevated insulin, 9 (75%) of 12 had LBW, [(2 neonatal deaths, 4(33.33%) still births, 3(25%) admitted to neonatal intensive care NIC)]. Eighty three (8.6%) had severe HDP, 12(14.45%) of them had elevated serum insulin, 8 (66.33%) of 12 had LBW babies (2 NND, 2 still births, one admitted to NIC), significant ($p<0.001$) difference from 71 with severe HDP with normal insulin. One hundred eight (11.2%) had mild preeclampsia, 21(19.44%) with elevated insulin, [17 (81%) of 21 had LBW babies, 4 (19.04%) NND, 3(14.28%) admitted to NIC, one (4.76%) septicemia. 9 (42.85%) still born, perinatal loss significantly higher ($p<0.001$), than 87 with mild preeclampsia and normal insulin. One hundred fifteen (11.9%) women had severe PE, 52(45.21%) had elevated serum insulin, 16(30.76%) LBW babies, 13(25%) still births, 13 (25%) babies admitted to NIC, one of 13 (1.92%)died (LBW), difference (significant ($p<0.05$) from 63 severe PE with normal insulin. Fourty nine (5.08%) women had eclampsia, 24 (48.97%) of them had elevated insulin, of them 7 (29.16%) had LBW, 13(54.16%) still births, 13 (54.16%) admitted to NIC, one (4.16%) NND, significantly more than in 25 with normal insulin ($p<0.02$). In HDP maternal insulin levels correlated significantly with perinatal outcome irrespective of severity of HDP.

Conclusion: While there was linkage of maternal serum insulin to the severity of HDP, the change in the insulin level affected the perinatal outcome more than the severity of HDP.

Keywords: Hyperinsulinemia, Neonatal outcome, Hypertension, Hypoglycaemia, Perinatal outcome.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) and their complications during pregnancy, labour, postpartum have been recognized for centuries, but "whys" remain poorly understood [1, 2]. There is now a growing body of evidence linking HDP with insulin resistance [3-7]. A high increase in blood glucose and insulin during pregnancy with HDP could lead to abnormalities of fetal weight, preterm delivery, neonatal hypoglycemia, septicemia and neonatal death [8-12]. All the women with HDP do not have FGR and low birth weight (LBW) babies but quite a few do have [13-15]. It is possible that, insulin plays a role. Looking at the significantly higher incidence of fetal growth restriction (FGR) among women with high insulin levels [16, 17], possibility of hyperinsulinemia leading to hypoglycaemia and thus growth retarded baby seems significant.

OBJECTIVE

Study was conducted to know the relationship of maternal serum Insulin levels on severity of hypertensive disorders of pregnancy effect on the neonatal outcome.

MATERIAL AND METHODS

The present case control study was carried out over a period of two years. Women with singleton pregnancy with gestational age more than 20 weeks and hypertensive disorders excluding chronic hypertension, pre-pregnancy diabetes, renal disease, coagulation disorders, epilepsy or any other major medical disorder, were included in the study, after taking informed written consent. Fasting blood sugar, insulin and post glucose blood sugar were estimated and repeated weekly. These women were followed up for maternal-neonatal outcome till delivery and 7 days postpartum, if the baby was admitted in Neonatal Intensive Care Unit (NICU) till the discharge of the baby. Still births (SB), LBW, neonatal deaths (NND), admission to the NICU and the indication for the admission were analyzed.

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RESULTS

During the study period of two years, there were 7233 women delivered, 964 (13.32%) had HDP, [686 (71.2%) rural, 278 (28.8 %) urban], rural significantly more than 60% overall rural (p<0.005), 58 (6%) were in their teens, significantly more than 4% overall teenage cases (P value <0.005), however majority of the women with HDP (768 (79.6%)) were of 20-24 years and 138 ≥ 25 yrs (13.1 %). Primigravida [777 (80.6 %)] were highly significantly more than overall 42% primigravida during the study period (P value <0.005). Of the 964 women, 634 (65.7 %) were term (≥ 37 weeks) and 330 (34.30%) preterm (<37 weeks) at admission with HDP.

Of the total 964 study subjects, 609(63.17%) had **mild HDP**, 12 (1.97%) of them had elevated serum insulin, 9 (75%) of these 12 had LBW babies, [2 NND, (one due to septicemia, one preterm), 4(33.33%) SB and 3(25%) babies were admitted to NICU] compared to 117 (19.5%) LBW babies, 10 (1.67%) stillbirths, 6 (1%) NND and 21 (3.51%) admissions to NIC (p<0.001) amongst 597 cases of mild PIH with normal insulin levels. Among babies admitted to NIC, 28.57% died out of the cases with normal insulin levels compared to 66.66% NND amongst babies in NIC of the mothers with elevated insulin levels.

Of all the study subjects, 83 (8.6%) had **severe HDP,** 12(14.45%) of them had elevated serum insulin. Eight (66.33%) of these 12 had LBW babies (2 NND and 2 SB, one baby was admitted to NIC, well on discharge), significant (p<0.001) difference from the 71 women with severe PIH but normal insulin, 10 (14.08%) LBW babies, 5(7.04%) NICU admissions and 2 NND (2.81%). Among NICU admissions 2 NND occurred in babies of mothers with normal insulin but in the elevated serum insulin cases 2 NND occurred in the babies who didn't get admitted to NIC at birth, suggesting that maternal insulin levels affected the babies' health in the absence of other neonatal problems.

Of the total 964 cases, 108 (11.2%) women had **mild preeclampsia** (PE), 21(19.44%) of them had elevated insulin. Of these 21 babies, 17 (81%) were LBW, 4 (19.04%) NND, 3(14.28%) admitted to NIC and one (4.76%) septicemia. 9(42.85%) SB (5 preterm), significantly higher (p<0.001) than 8 (9.2%) LBW babies, 8(9.2%) SB, 10 (1.5%) admissions to NICU, of which 2 (2.3%) NND amongst the 87 women with mild preeclampsia and normal insulin.

One hundred fifteen (11.9%) women were of **severe PE**, 52(45.21%) of them had elevated serum insulin, 16(30.76%) of them had LBW, 13(25%) SB, 13 (25%) babies were admitted to NICU and one (1.92%) NND (LBW) occurred, significantly more (p<0.05) than 63 women with severe PE with normal insulin levels, 11 (17.46%) SB, 14 (22.22%) LBW babies, (all preterm) and 8 babies (12.69%) were admitted to NICU, of which 7 (11.11%) died.

Of the 964 cases with hypertensive disorders, 49(5.08%) had **eclampsia,** 24 (48.97%) of them had elevated insulin. Of them 7 (29.16%) had LBW, 13(54.16%) SB, 13 (54.16%) were admitted to NICU and one (4.16%) died. Of the 25 women of eclampsia with normal insulin, 6 (24%) had SB, 4(16%) LBW babies, 3(12%) NND occurred, 3(12%) were admitted to the NICU, later died, significant difference (P value <0.02).

DISCUSSION

Relationship between hyperinsulinemia and high blood pressure affecting maternal and feto-neonatal outcome has been reported [18-21]. In pregnancy, the alterations in the metabolism of carbohydrate and insulin may be playing a role in the etiogenesis and effects of hypertensive disorders of pregnancy. Many features of the insulin resistance syndrome have been associated with HDP, hyperinsulinemia, glucose intolerance, obesity, and lipid abnormalities [22-24]. The documentation of these features before the onset of hypertension in pregnancy suggests that insulin resistance or associated abnormalities may have a role in this disorder [25-27]. 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. Elevated second-trimester insulin levels characterize the subsequent development of preeclampsia which supports the hypothesis that hyperinsulinemia and insulin resistance may contribute to the pathogenesis of preeclampsia [28]. Maternal mean blood-glucose and serum insulin in pregnancy correlated significantly with neonatal weight, It has been studied that maternal insulin sensitivity had stronger correlation with fetoplacental growth in comparison with maternal demographic or morphometric factors [29-31]. Whether the elevated insulin by way of causing hypoglycaemia leads to growth restriction or is it the higher insulin levels with severe disease that gives rise to higher percentage of LBW babies is not well understood.

In the present study of 609 women with mild PIH, 12(1.64%) had hyperinsulinemia. Of 83 women with severe PIH, 12(17.39%) had elevated insulin levels. Twenty one (19.4%) of 108 women with mild PE had elevated insulin. Of 115 women with severe PE, 52(45.2%) had elevated insulin and of 49 women with ecclampsia, 24(48.97%) had hyperinsulinemia. As the severity of HDP increased the derangements in the insulin increased, suggesting a positive relationship between the severity of the disease and serum hyperinsulinemia. Further to this elevation of insulin women with similar severity of HDP, the perinatal outcome was poorer in cases with hyperinsulinemia. Other researchers have also reported poor perinatal outcome in the women with HDP with elevated insulin levels compared to normal insulin levels in women with HDP [32, 33].

Pregnancy is a physiological state which has significant alterations in glucose and insulin metabolism [34-36]. HDP affect maternal glucose metabolism, which further has impact on perinalal outcome [37]. Many factors play a role in the pathogenesis of FGR, including the maternal blood glucose level and serum insulin [38]. The principle modulator of this hyperinsulinemia in pregnancy is hyperoestroge-naemia.

All women with hypertensive disorders do not have hyperinsulinemia and growth restriction. In the present study details of babies were recorded in mild and severe cases in relation to hyperinsulinemia. There was clear difference in cases with hyperinsulinemia, with similar severity of HDP. It was revealed that women with elevated insulin levels have a higher percentage of LBW babies and poorer perinatal outcome compared to women with normal insulin levels in women with similar severity of disease. Other researchers have also reported more perinatal deaths among women with hyperinsulinemia and suggested that more research is needed about carbohydrate metabolism in HDP for further understanding of the patho-physiology involved [39, 40].

In the present study of hypertensive disorders of the 609 women with mild PIH, 12 had elevated insulin levels of whom one had preterm delivery, 3 were appropriate for gestational age (AGA), 3 had SB, 9 were LBW, compared to 119 (19.5 %) FGR babies, 20 (3.3 %) perinatal deaths. Of the 12 women with severe PIH and elevated insulin levels, 3 (25%) had FGR compared to 10 (14.49%) of 69 women with severe PIH with normal insulin levels. There were 12 (17.39%) perinatal deaths in women with severe PIH with elevated insulin compared to 7 of 14 (50%) neonatal deaths in the women with severe PIH with normal insulin levels. Of the 21 women with mild preeclampsia and elevated insulin levels, 6 (28.5 %) had FGR compared to 8 (9.2%) of the 87 of mild preeclampsia with normal insulin levels and perinatal deaths were 14(16.09 %) compared **10 (11.49%) perinatal deaths among the women with HDP with normal insulin levels.** Twenty two (35.4 %) of 62 women with severe preeclampsia and elevated insulin had FGR compared to 14 (26.4%) cases of FGR amongst of the 53 with severe preeclampsia with normal insulin. Thirteen (41.9%) of the 31 women with eclampsia with elevated insulin had FGR compared to 4 (22.2%) of the 18 eclamptic women with normal insulin (P value <0.001). Researchers have also reported that alterations in glucose and insulin in pregnancy have critical impact on the birth outcome and later the growth of the offspring [41-43]. Perinatal outcome was affected by serum insulin in women with hypertensive disorders. There are not many studies from resource poor countries and more research is needed.

CONCLUSION

Perinatal outcome was affected by serum insulin in women with hypertensive disorders. While there was linkage of maternal serum insulin to the severity of HDP, the change in the insulin level affected the

Table 1: Severity of Hypertensive Disorders and Fasting Serum Insulin in Pregnant Women

Insulin	MPIH	SPIH	MPE	SPE	ECL
Normal	597	71	87	63	25
Elevated	12(1.64%)	12(17.39%)	21(19.4%)	52(45.21%)	24(48.97%)
Total	**609**	**83**	**108**	**115**	**49**

PIH- Pregnancy Induced Hypertension, MPIH=Mild PIH, SPIH=Severe PIH, MPE= Mild preeclampsia, SPE= Severe preeclampsia, ECL= Eclampsia

Table 2: Parity/ Gestational Age and Serum Insulin in hypertensive Women

P	I	MPIH(609)			SPIH(83)			MPE(108)			SPE(115)			ECL(49)		
		A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
P0	I<27	17	116	404	0	9	33	2	16	36	2	23	15	0	5	6
	I>27	0	2	6	0	2	7	0	4	6	2	21	22	3	12	6
Total		**17**	**118**	**410**	**0**	**11**	**40**	**2**	**20**	**42**	**4**	**44**	**37**	**3**	**17**	**12**
P1+	I<27	3	19	40	1	10	17	1	13	18	4	6	3	0	4	3
	I>27	0	1	1	0	4	1	2	4	5	3	10	4	1	8	1
Total		**3**	**20**	**41**	**1**	**14**	**18**	**3**	**17**	**23**	**7**	**16**	**7**	**1**	**12**	**4**
Grand Total		**20**	**138**	**451**	**1**	**25**	**58**	**5**	**37**	**65**	**11**	**60**	**44**	**4**	**29**	**16**

P= Parity, I= Serum Insulin Level, MPIH- Mild PIH, SPIH- Severe PIH,MPE- Mild Preeclampsia, SPE-Severe Preeclampsia, ECL-Eclampsia, ≤27 ml, I r>27 mlU/ml, P-parity T-Total, GT-Grand Total
A-Gestation <28 weeks, B-29-37weeks, C ≥ 37 weeks, I -Insulin

Table 3: Severity of Hypertensive Disorders, Fasting Serum Insulin Levels, Neonatal Outcome

HDP	Serum Insulin	Preterm Delivery	Septicemia	NICU	NND	LBW	SB	TOTAL
MPIH (609)	**NI**	00	00	21	06	117	10	**597**
	EI	01	01	03	02	09	03	**12**
	Total	01	01	24	07	126	13	**609**
SPIH (83)	**NI**	00	00	05	02	10	05	**69**
	EI	00	00	06	02	08	02	**12**
	Total	00	00	11	04	18	07	**81**
MPE (108)	**NI**	00	00	10	02	08	08	**87**
	EI	00	01	03	04	17	09	**21**
	Total	00	01	13	06	25	17	**108**
SPE (115)	**NI**	00	00	08	07	14	11	**53**
	EI	00	00	13	01	26	13	**52**
	Total	00	00	21	08	40	24	**115**
ECL (49)	**NI**	00	00	03	03	04	06	**18**
	EI	00	00	13	01	16	04	**24**
	Total	00	00	16	04	20	10	**49**
TOTAL (964)		**01**	**02**	**65**	**40**	**229**	**72**	**964**

HDP- Hypertensive disorders of pregnancy, SB= still birth, LBW= low birth weight, NND= Neo natal death, NICU= neonate admitted to NICU, AGA= Appropriate for gestational age, NI=Normal Insulin level, EI=Elevated Insulin, TW=Total

perinatal outcome more than the severity of HDP. There are not many studies from resource poor countries and more research is needed.

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