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Clinical Study of High Dose Calcium to Prevent Pregnancy Specific Hypertensive Disorders, Their Severity, Still A Research Agenda!

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Abstract

Background: Worldwide hypertensive disorders of pregnancy (HDsP) continue to be leading causes of maternal, perinatal severe morbidity mortality, long term disabilities. Prevention of HDsP, their severity through high dose calcium supplementation is being suggested. However, whether calcium really helps is still not established. So, research continues.

Objectives: Present study was carried out to know the efficacy of high dose daily calcium from midpregnancy on reduction in occurrence of HDsP, their severity and perinatal outcome.

Material Methodology: Study was done with 1200 women, (600 cases, 600 controls) of 18-39 years with, 20 $\pm$ 2 weeks pregnancy, no obvious medical disorders in mothers, no ultra sonographically diagnosed anomaly in fetus at entry to study. Study cases (S) received 2 gms oral calcium daily, similar controls (C) were not given calcium. Research assistant was not part of the care providers, but kept track of everything. Women got antenatal care, clinicians not knowing which women got extra calcium. Desired information, pregnancy outcome, complications during pregnancy, birth weight, neonatal outcome, admission of baby to neonatal intensive care unit and compliance to calcium tablets in study subjects was collected by research assistant using pretested tool.

Results: HDsP occurred in 7.5% S cases, 7.33% C group. Amongst group S 9.43% Primigravida, 4.3% Multigravida developed HDsP (gestational hypertension 6%, preeclampsia 1.16%, eclampsia 0.33%). In group C 8.04% primigravida, 3.08% multigravida developed HDsP, (6%GH, 1% preeclampsia, 0.33% eclampsia), Total 8.8% perinatal deaths occurred in S cases who had HDsP, 2.27% in C, with HDsP and no maternal death.

Conclusion: No benefit was found with high dose calcium. On the contrary, perinatal outcome was poorer. More research is needed about high dose calcium for HDsP, their severity, perinatal outcome.

Keywords: Hypertensive Disorders of Pregnancy; Occurrence; Severity; Perinantal outcome

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Introduction

Worldwide hypertensive disorders of pregnancy (HDsP) continue to be the leading causes of maternal and perinatal severe morbidity and mortality, and long-term disabilities. Over all 7-10% incidence of HDsP, amongst antenatal admissions has been reported in India [1]. Some researchers reported that HDsP were responsible for around 7% of maternal deaths [2]. Khan et al [3] reported 16% of annual global maternal mortality due to HDsP. WHO [4] reported that the incidence of preeclampsia was seven times higher in developing countries and the risk of a woman dying of preeclampsia/eclampsia was 300 times higher than that of a woman in a high-income country [5] so attempts at prevention of HDsP and their severity continue. Over the years researchers have suggested that calcium may be playing a major role in the etiology of HDsP. Some studies have revealed changes in blood/ urinary calcium in women with HDsP [6]. However, others reported that it was intracellular calcium which made the difference [7]. Hofmeyr et al [8] reported impairment of calcium metabolism with low circulating vitamin D linked to the risk of HDsP. Prevention of HDsP and their severity through high dose calcium supplementation is being suggested. However, whether calcium really helps is still not established. So, research continues.

Objective

Present study was carried out to know the efficacy of high dose daily calcium from midpregnancy on reduction in occurrence of HDsP, their severity and perinatal outcome.

Material and Methodology

The study was carried out in Obstetrics Gynecology of Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha, Maharashtra, India, after approval of the ethics' committee of the institute and informed consent of the women. Study cases were women of 18-39 years of age (Plan was for 15 to 45 yrs but no one was below 18 and no one above 39 yrs) with 20 $\pm$2 weeks pregnancy with no obvious medical disorders in the mother and no anomalies in the fetus on ultrasonography at the time of entry to the study. Study subjects as per criteria were recruited from the regular antenatal clinic of obstetrics gynecology as per inclusion and exclusion criteria. Keeping in mind the drop outs at various stages, and noncompliance 1500 women were registered for 1200 study subjects needed (600 cases and 600 controls), 750 each for study and controls. (Flow chart 1) Considering these values, sample size was calculated by the sample size formula considering the minimal allowable error of 20%. The desired information was collected with the help of pretested tool. The study subjects were randomly divided into two arms. One was given high dose calcium oral 2 gms daily in divided doses from 20$\pm$2 weeks of pregnancy onwards till delivery and a week postpartum, study S group. Equal number of women of the similar duration of pregnancy with similar inclusion and exclusion criteria were enrolled as controls, C group. High dose calcium was not given to controls. The controls as well as study cases continued to get their regular care and took whatever supplements they were advised by their clinicians, and were not deprived of anything they were getting or would have got. Whatever was happening was happening to controls as well as study cases. Only difference was high dose calcium given to study cases. Over all similar patients from antenatal clinic were included who had similar food too. Serum calcium was not measured because of problems of funds and also mission was to use research findings as translational research as hypothesis was high dose calcium should reduce occurrence of HDsP and or reduce severity and perinantal improve perinantal outcome. Though it was not a blinded study as Group S women knew that they were getting calcium, but the system of care of pregnant women did not allow bias in results. Research assistant was not part of the service providing team. Regular service providers did not know which women were

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getting high dose calcium as it was not part of the regular records made. The research assistant recorded details of happenings of pregnancy, birth and post birth on everyday basis. Information of pregnancy outcome, complications during pregnancy, birth weight and neonatal outcome, including admission of the baby to neonatal intensive care unit (NICU) was collected by research assistant. Over all of 1500 cases included, 750 in study and 750 controls, Information collection was stopped when both arms, Study as well as Controls had 600 delivered women each, the sample size needed. In between there were drop outs, but were not considered as nearly 25% extra cases were recruited as per inclusion and exclusion criteria. Compliance to calcium tablets in study subjects was checked. Analysis was done by chi square test and p value was calculated.

Results

Overall, 7.5% (45 out of 600 cases) women developed HDsP in the study cases and amongst controls also, 7.33% (44 out of 600 cases) developed HDsP. Amongst 600 study subjects, there were 371 primigravida and 35 (9.43%) developed HDsP and there were 229 multigravida and 10 (4.3%) developed HDsP. Amongst 600 controls, there were 373 primigravida and 30 (8.04%) developed HDsP and there were 227 multigravida and 7 (3.08%) developed HDsP. Amongst the cases who received high dose calcium, Group S gestational hypertension occurred in 36 (6%), preeclampsia in 7 (1.16%) and eclampsia in 2 (0.33%). Amongst those who did not receive high dose calcium (Group C), 36 women (6%) developed GH, 6 (1%) developed preeclampsia and 2 (0.33%) eclampsia. (Table I and Table II). Amongst 600 study cases, 396 (66%) had vaginal births (VB) and 204 (34%) caesarean births (CB). Amongst 600 controls, 437 (72.84%) had VB and 163 (27.16%) CB. Of 600 study cases, 96 (16%) had preterm births and amongst 600 controls, 80 (13.33%) had preterm births (P value 0.039). In study cases there were 12 intrauterine deaths (IUDs), (foetus dead before labor), three were cases of severe GH with oligohydroamnios and foetal growth restriction (FGR), 3 were of oligohydroamnios and FGR and one was a case of placental abruption, and one was of placenta praevia. One baby had congenital anomaly missed during USG done around 20 weeks and in 3 cases causes were not obvious. In addition, there was one still birth (SB), (baby born dead, though was live prelabour) and six early neonatal deaths (NNDs) occurred in study cases. Amongst controls, there were 8 IUDs, two in women with severe preeclampsia and placental abruption, 2 in women with severe oligohydroamnios and FGR, one had anomalous baby, missed during sonography done at inclusion and in 3 cases causes were not known. There was no SB in controls but 3 NNDS occurred. In the study subjects, of 45 women who developed HDsP, 13 (28.8% of 45) babies were low birth weight (LBW) live, one (2.22% of 45) IUD, one (2.22of 45%) SB and 2 (4.4% of 45) NNDS occurred. (Table III). In controls amongst 44 women who had HDsP, 6 (13.6% of 44) women had live LBW babies (P value 0.493), one (4.5% of 44) had IUD. There was neither any Intrapartum death nor NND. Overall, amongst the study cases in women who developed HDsP, there were 28.8% LBW, and 35.5%, small for gestational age (SGA)babies, compared to13.6% LBW babies and 13.6% SGA babies amongst controls with HDsP (P value 0.321). Also, preterm births were more in the study subjects who developed HDsP (42.2%), than controls who developed HDsP (22.7%) (P value 0.432). Five women developed severe sickness amongst study cases (0.83%), all were primigravida of 20-29 years. Of them two were out of 45 women who developed HDsP amongst study cases.

Amongst controls also 4 (0.66%) women developed severe sicknesses, in controls 2 were primigravida and 2 multigravidas. 3 between 20-29 years and one was between 30-39 years, but none was out of 44 women who develop HDsP (P value 0.364). There was no maternal death, neither in study nor controls. Perinatal deaths were significantly more amongst HDsP

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cases of study group (8.8%) than amongst HDsP cases of control group (2.27%) (P value0.046).

Discussion

Poon et al [9] reported that Pre-eclampsia kills around 76 000 women and 500000 babies every year. It is believed that the mortality rates are high in low-income countries because of lack of desired maternal care. The only currently available pre-eclampsia cure is believed to be delivery of the placenta, which sheds excessive proinflammatory substances to the maternal cardiovascular system, though post-partum eclampsia, even late postpartum eclampsia (upto one month) is known to occur [10]. It also should be remembered that genesis of HDsP in body is believed to start much earlier in pregnancy [11]. May be some women, before they become pregnant, are prone to get the disorders. Brown et al [12] opined that pre-eclampsia was an unpredictable multifaceted syndrome which could rapidly develop into life-threatening conditions, such as eclampsia and other dysfunctions due to multiorgan involvement. Prevention is essential, is obvious. After various clinical trials, some researchers reported reduced incidence of preeclampsia with high dose calcium supplementation, others reported association of lower blood pressure with higher dietary calcium [13]. Jiang et al [14] did a study and reported that there was a gap between high-income countries and low-and middle-income countries, with alarmingly low calcium intake in pregnant women in Low Middle Income Countries (LIMC). There was a spectacular discrepancy in the incidence of preeclampsia, eclampsia, and associated mortality between low- and high-income settings. The reasons reported have been many, but experimental studies consistently suggested that calcium supplements for populations with low dietary calcium reduced the risk of pre-eclampsia, particularly the associated morbidity and mortality [6]. However, Hofmeyr et al [8] reported that there was limited evidence of high-dose calcium supplementation in reduction of hypertension, pre-eclampsia, and admission to NICU and it needed too be confirmed by larger and high-quality trials. We to believe that it is essential to do more studies. A review of 1880 citations was done by Jiang et al [14], in which 105 works met the inclusion criteria, data of 73958 women from 37 countries was used by the researchers. The mean calcium intake was 948.3mg/day for high income countries (HICs) and 647.6mg/day for LMICs. Calcium intake below 800 mg/day was reported from 5 (29%) HICs and 14 (82%) LMICs countries. It was believed that mapping calcium intake during pregnancy worldwide and identifying populations with low calcium intake should provide the evidence base for more targeted actions to improve calcium intake. Randomized trials revealed the potential of 1.5 to 2 gms of oral Calcium carbonate every day in divided doses in reducing the risk of HDsP by 50% [8,15] greatest for women at higher risk of preeclampsia, and for those with low baseline calcium intake. However, Cormick and colleagues [16] have suggested that supplementation of only400-500mg calcium daily should normalize calcium in low-intake populations. Bujold et al [17] did a trial to know the effects of calcium supplementation of 500 mg from early pregnancy and reported no significant effects with pre pregnancy and early pregnancy calcium supplementation. Hofmeyr et al [8] also reported that calcium supplementation commenced before pregnancy until 20 weeks of pregnancy, compared with placebo, did not show a significant reduction in recurrence of pre-eclampsia. In the present study, in study and controls every day food intake was similar as well as overall similar patients from antenatal clinic were included. Serum calcium was not done because of funds problems and mission was to use research findings as translational research as hypothesis was high dose calcium should reduce occurrence of HDsP, their severity and improve perinatal outcome. With high dose calcium was given from mid pregnancy onwards. Overall incidence of HDsP in the study cases was 7.5% and controls (no extra calcium) also it was 7.33%. There was no difference in the

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occurrence of HDsP with high dose daily calcium from mid pregnancy. Actually, incidence was little higher, 9.43% amongst primigravida 4.3% amongst multigravida, in those women who received high dose calcium compared to controls, HDsP in primigravida 8.04% and 3.08%in multigravida. GH occurred in 6%women, preeclampsia in 1.16% and eclampsia 0.33% amongst cases who were given high dose calcium. Amongst controls also 6% developed GH, 1% preeclampsia and 0.33% eclampsia. Overall, amongst HDs Pcases in study group, there were more LBW, (28.8%), and SGA (35.5%) babies compared to controls, 13.6% LBW and 13.63% SGA amongst HDsP cases. Imdad et al [18] reported that Calcium supplementation during pregnancy was associated with an extra gain of 85 g in the intervention group compared with controls, in contrast to the results, of the present study for which any references could not be found. Though no effect has been reported in 2 cochrane systematic reviews which revealed that calcium supplementation had no effect on LBW babies [19]. Researchers at Johns Hopkins Medicine reported that taking calcium in the form of supplements may raise the risk of plaque buildup in arteries and heart damage [20] Anderson et al [21] reported that when a substantial amount of the calcium was derived from bolus intake of calcium supplements, it accelerated arterial calcification and raised the risk of cardiovascular events. Similar things might happen in placenta in some women and these aspects need more research. Also, preterm births occurred more often amongst cases with HDsP in the present study group 42.2%, and 22.7% amongst controls. Farber et al [22] in their study found that Calcium chloride increased systemic vascular resistance, and uterine smooth muscle contractility. Aninora et al [23] found in their study that there was a significant correlation between the levels of calcium to the strength of uterine contractions. So, this aspect also needs more studies. Five women (4.4%) developed severe illnesses amongst study cases, age between 20-29 years, all primigravida, 2 out of 45 women who developed HDsP. Over all 4 women had severe sicknesses in control cases, 2 primigravida and 2 multi gravida, but none was from cases who developed HDsP amongst controls. All these things point to vascular pathology. There was no maternal death, neither in study cases nor controls. Perinatal deaths were more amongst cases of HDsP in study group (8.8%) than controls (2.27%). In the controls who developed HDsP, 3.6% babies had LBW and there were 4.5% IUDs. There was no SB or NND amongst HDsP cases of control group. There was neither benefit of high dose of calcium in prevention of HDsP, nor in severity of HDsP. On the contrary there were more preterm births and perinatal deaths. It seems a lot of more research is needed about the role of high dose calcium in prevention of HDsP and their severity and reduction in perinatal deaths. Limitations of the present study were that calcium was not measured at any stage because of lack of resources and also plan was translational. Also, because it was blinded on both sides it was not possible to know the exact details of calcium intake by women in their daily life in food or during antenatal care. Plans were for translation into practice in day-to-day care because of low-cost doable preventive intervention in a country with low resources and overall high burden of HDsP and mortality of mothers and babies due to HDsP. However, second point was also the strength because the person doing analysis was blinded of effects. The study was done to know the advantages of high dose of calcium in prevention of severity of HDsP and improving perinatal outcome to whatever numbers. The study was planned because some studies showed positive effects and others did not. We believe that more studies with bigger numbers and serum calcium and urinary calcium management are needed.

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Flow Chart

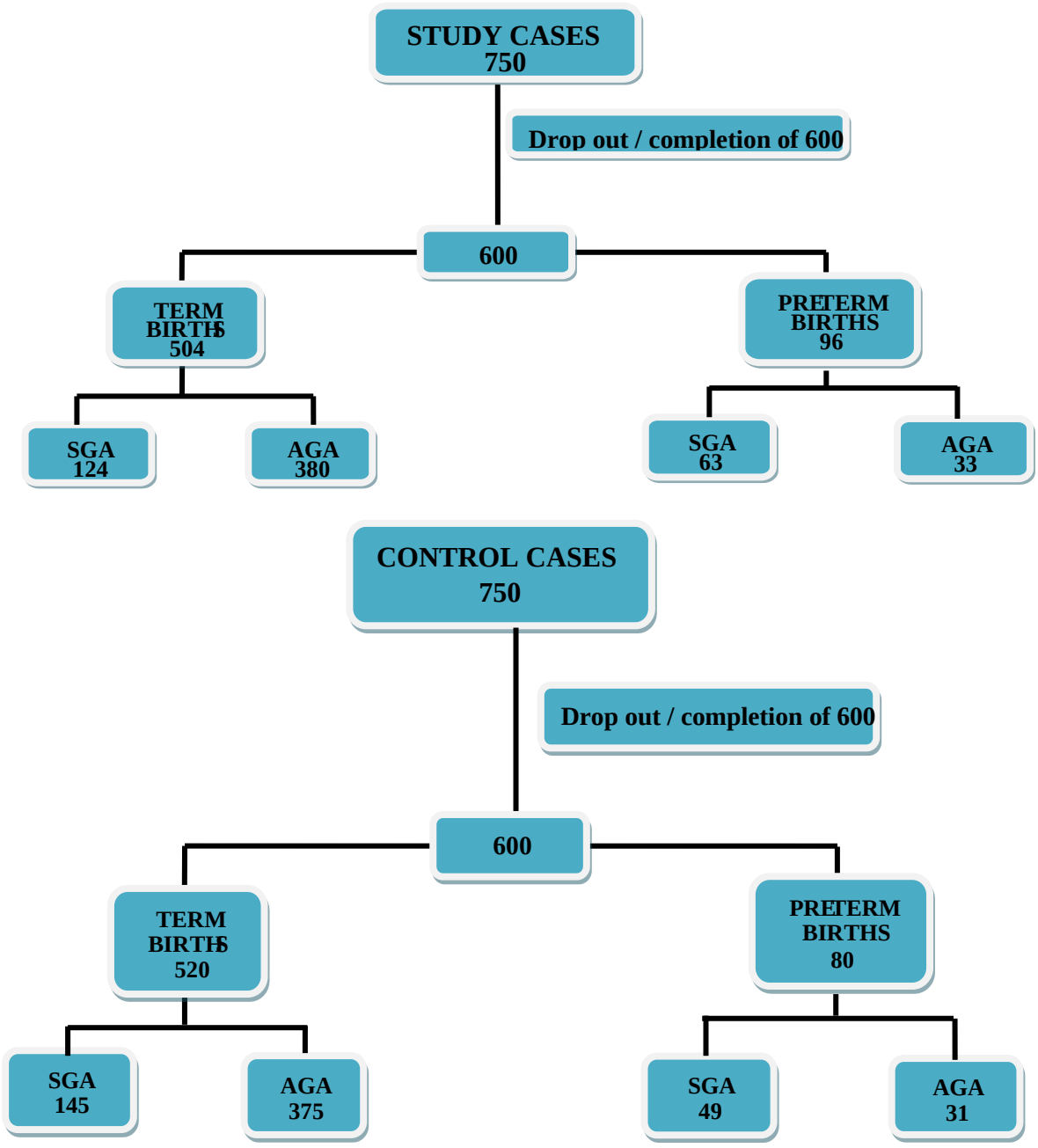

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Table I: Age and parity.				
Age	**Primigravida**	**P1 -P2**	**P3 -P5**	**Total**
18-19 YRS	**10**	**0**	**0**	**10**
STUDYCases	**HDsP- 0**	**0**		0
	16	**0**	**0**	**16**
CONTROLS Cases	**HDsP- 3**	**0**	**0**	**3**
20-24 YRS	**275**	**73**	**0**	**348**
STUDY	**HDsP- 23**	**3**	**0**	**26**
	268	**86**	**0**	**354**
CONTROLS	**HDsP-21**	**3**	**0**	**24**
25-29 YRS	**77**	**110**	**0**	**187**
STUDY	**HDsP- 10**	**3**	**0**	**13**
CONTROLS	**76**	**108**	**1**	**185**
	HDsP- 4	**3**	**0**	**7**
30-34 YRS	**7**	**39**	**2**	**48**
STUDY	**HDsP- 2**	**5**	**1**	**8**
CONTROLS	**11**	**27**	**1**	**39**
	HDsP- 2	**1**	**0**	**3**
35-39 YRS	**2**	**5**	**2**	**7**
STUDY	**HDsP- 0**	**0**	**0**	**0**
	2	**4**	**0**	**6**
CONTROLS	**HDsP- 0**	**0**	**0**	**0**
TOTAL				
STUDY	**371** **HDsP- 65**	**227** **18**	**02** **01**	**600** **84**
CONTROLS	**373**	**225**	**02**	**600**

Table II: hypertensive disorders and their severity.				
	CONTROLS NO	**%**	**STUDY NO**	**%**
	600	100.0	600	100.0
NO HDsP	556	92.66	555	92.5
MILD GH	32.0	5.33	32.0	5.33
SEVERE GH	4.00	0.66	4.00	0.66
MILD PRE-ECLAMPSIA	6.00	1.00	3.00	0.05
SEVERE PREECLAMPSIA	0.00	0.00	4.00	0.66
ECLAMPSIA	2.00	0.33	2.00	0.33
HDsP -Hypertensive disorders of Pregnancy GH- Gestational Hypertension.				

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TABLE III: Perinatal Outcome in Study and Controls.

		Amongst Over all cases		AmongstcaseswithHDsP	
	Total	NO	%	NO	%
IUD	CONTROLS	8	1.33	1	0.16
	STUDY	**12**	**2.00**	**1**	**0.16**
LBW	CONTROLS	193	32.16	6	1.00
	STUDY	**156**	**26.00**	**13**	**2.16**
SGA	CONTROLS	190	31.66	6	1.00
	STUDY	**183**	**30.50**	**16**	**2.66**
STILL BIRTH	CONTROLS	0	0	0	0
	STUDY	**1**	**0.16**	**1**	**0.16**
NND	CONTROLS	3	0.50	0	0
	STUDY	**6**	**1**	**2**	**0.33**
PRTERM BIRTHS	CONTROLS	23	3.83	10	1.66
	STUDY	**20**	**3.33**	**19**	**3.16**

IUD – Intra Uterine Death
LBW – Low Birth Weight

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