FACTORS ASSOCIATED WITH ADVERSE PREGNANCY OUTCOME AMONG MOTHERS WITH TOXEMIA: A STUDY BASED IN DISTRICT HOSPITAL, PURULIA, WEST BENGAL, INDIA, 2007

By

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CERTIFICATION

This is to certify that this dissertation, entitled 'Factors associated with adverse pregnancy outcome among mothers with toxemia: a study based in district hospital, Purulia, West Bengal, India, 2007, submitted by **Dr. Sobhan De,** in partial fulfillment of the requirements for the degree of Master of Applied Epidemiology, is the original work done by him and has not been submitted earlier, in part or whole, for any other (Publication or degree) purpose.

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DIRECTOR

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Date: the 10th January, 2008 Dr. Sobhan De

Factors associated with adverse pregnancy outcome among mothers with toxemia: a study based in district hospital, Purulia, West Bengal, India, 2007

De, Sobhan[i], Ramakrishnan, R[ii]

Background

Among different pregnancy related medical complication up to 8% attributed to toxemia worldwide[1]. It remains one of the major causes of maternal and neonatal mortality and morbidity worldwide[2]. This includes pregnancy induced hypertension and pre-eclampsia. Toxemia in pregnancy generally develops after 24 weeks of gestation. Hypotheses about toxemia have proposed causal roles for placental abnormalities, immunologic dysfunction, coagulation abnormalities, endothelial damage, endocrine abnormalities, genetic factors, and dietary factors[3,4] including the consumption of too little protein, magnesium, calcium, or zinc, and the consumption of too much sodium or fatty acids[5] [6]. Complications for the women include coagulopathy, renal failure, stroke and eclampsia. Eclampsia[7] is the worst outcome condition, in a woman with pre-eclampsia. Eclampsia is associated with life-threatening complications, such as pulmonary edema, renal and hepatic failure, disseminated intravascular coagulopathy, and HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome. The reported rate of eclampsia in the Western world is 1 in 2000 to 1 in 3000 deliveries.[8] The maternal mortality rate associated with eclampsia ranges from 100 to 6000 per 100,000, and the perinatal mortality ratio ranges from 150 to 400 per 1000.[9] The reported maternal mortality rates from eclampsia range from 0.5% in some centers in the United States to as high as 14% in Mexico. Maternal mortality, to the tune of 9.1% (Africa, Asia), 16.1% (developed countries), and 25.7% (Latin America) reported by these disorders[10]. For the baby complications include preterm delivery and intra uterine

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growth restriction[6], which are associated with increased risk of developmental delay and chronic diseases in childhood. In the long term, women and foetuses affected by these disorders may be prone to cardiovascular disease in adult life[11,12,13,14]. In fact, 15% of all preterm births are indicated for pre-eclampsia. Preterm birth is associated with increased mortality rates and long-range neurological disability. Pre-eclampsia also increases the risk of intrauterine growth restriction (IUGR). Other than acute problems, alarmingly IUGR may confer a long-term burden in the form of future cardiovascular risk. Up to 18% of foetal deaths are associated with hypertensive disorders[15].

There are several risk factors; playing role in development of toxemia in pregnancy includes nulliparity, extremes of age, genetic factor and paternal factors. But no modifiable risk factor identified in that pathway. The outcome of pregnancy can be modified. There are already identified factors which can modify the outcome significantly includes prenatal care directed for early detection, referral and qualified obstetric care[16]. In developed countries, where taking certain steps like prenatal care has reduced maternal mortality attributable to pre-eclampsia, the condition primarily affects fetal well-being through intrauterine growth retardation, preterm birth, low birth weight, and perinatal death[17]. The increased infant morbidity and mortality rates are attributable to preterm delivery. Health Evidence Network workshop[18] similarly suggests screening for pre-eclampsia at antenatal visits. From another public health perspective, it is alarming that the rate of pre-eclampsia has increased by 40% between 1990 and 1999[19] worldwide.

However the rates are significantly higher in the non-industrialized countries. In a study in Mumbai over a 36-month period, a total of 29,562 deliveries were recorded, of which 1,238 patients developed Pre-eclampsia (4.18%) and 34 developed eclampsia (0.11%).[20] The maternal mortality rate associated with eclampsia ranges from 100 to 6,000 per 100,000, and the perinatal mortality rate ranges from 150 to 400 per 1000. Both eclampsia and its preceding condition, pregnancy-induced hypertension, occur in varying degrees in different parts of India.[21]

As part of goal to reduce the MMR, Reproductive and Child Health programme II is being implemented. Certain steps had already been taken to improve coverage and quality of prenatal care services. Maternity benefit scheme was also in place to support the

socioeconomically backward community. The present maternal mortality ratio in West Bengal, a state in India is 240. And 17% of those deaths were attributed to eclampsia. Case fatality ranged from 6%-19%[22] in the state. District Purulia of West Bengal had similar figures. Maternal mortality ratio in the year 2006 was 248. Thirty three percent of maternal deaths were attributed to eclampsia. The case fatality ratio of eclampsia was 8.3%[23] in district indicated that the quality of health care services accorded in is similar to state. The proportion of death due eclampsia may be due to more number of cases in the district. Pre-eclamptic condition gives rise to adverse outcome like eclampsia. Hence the increased number of pre-eclamptic mother in Purulia was a cause of concern to the district health managers. We decided to study the cause of development of eclampsia and other adverse outcome among mothers suffering from toxemia with the following objectives.

Our study objective was to identify the modifiable risk factors significantly associated with adverse outcome in mothers suffering from toxemia in pregnancy in the district of Purulia, 2007 and to suggest measures thereof.

Methods

Study population

We defined study population as the pregnant mothers suffering from obstetrician diagnosed toxemia in pregnancy (included gestational hypertension[24] and or pre-eclampsia[25]) those were admitted and delivered in district hospital Purulia, West Bengal, India, during the period 10th August to 2nd December 2007. We excluded those who were suffering from any chronic diseases not directly attributable to pregnancy or diagnosed before pregnancy started or post caesarian and twin pregnancy.

Study design

We conducted a retrospective cohort study. We recruited them on admission and followed them till delivery. We interviewed the study participants at hospital in postpartum period to collect information retrospectively using structured questionnaire. We collected the above information from close family members in case subjects were incommunicado.

Operational definitions and outcome

We defined any of the adverse foetal or maternal adverse outcomes as outcome. Maternal adverse outcome included *abruptio placentae*, eclampsia, post partum haemorrhage, operative vaginal delivery and caesarian section[26]. We included prematurity, IUGR, low birth weight, birth time asphyxia and stillbirth as adverse foetal outcome.

Sample size calculation

We made following assumptions for sample size calculation: (i) ratio of exposed per non exposed as one, (ii) risk ratio worth detecting 2.5, (iii) attack rate among non-exposed 30%, (iv) alpha (α) risk 5%, power 90% and (v) non-response of 5%. We calculated a sample size of 300 using EPITABLE software.

Data collection

We collected information on demographic, socioeconomic, education, personal habits and addiction; details of antenatal care, knowledge related to pregnancy and childbirth, availability of financial assistance under maternity benefit scheme (Janani Suraksha Yojana[27]) interviewing study participants using a structured close-ended questionnaire. We trained paramedical staffs and engaged them in interview. Interviewer also reviewed the antenatal card, prescription, laboratory reports, hospital records to collect information about antenatal care, blood pressure, clinical signs and symptoms, outcome and advice, using data abstraction form. We estimated the economic status of the family by a method used by RCH studies[28] and graded them with score. We used composite scoring method to determine the adequacy of prenatal care using Kotelchuk index model.[29]

Laboratory data

We collected reports of serum haemoglobin and proteinuria of the subjects from hospital laboratory register. For haemoglobin estimation laboratory used acid haematin method and proteinuria estimated using dipstick method.

Data entry and statistical analysis

We examined the characteristics of study subjects. We conducted univariate analysis to examine the association between different variables with outcome and calculated risk ratio (RR) of each variable with 95% confidence interval (CI). We calculated dose response of adequacy of prenatal care utilization with graded exposure. We used multivariate logistic regression to control for potential confounding variables. We derived Adjusted Odds Ratio (AOR) and its 95% CI from the coefficients of the logistic models and their standard errors. We performed all statistical analyses using Epi Info 3.3.2.

Quality assurance

Peer group reviewed our study protocol. We discussed about uniform case definition for recruitment of participants in doctors' meeting. We used pretested questionnaire in participant's mother language that was standardized by translation and back translation. We employed random cross checking, cross-validated every 5^{th} interview and did concurrent observation for consistency. We ensured use of standardized instruments to measure blood pressure and weight and standardized test kit and uniform method for laboratory specimen analysis.

Human subjects protection

Our study participants were from vulnerable population group as they were pregnant and female sex. We engaged female interviewers as much as possible. Interviewer spent 15 minutes with the participants. We explained our objective and benefits thereof in their mother language and obtained written voluntary consent in presence of a witness. We kept study participants identity confidential and did not put any identifier in the data collection instruments. We submitted our study protocol to institutional ethical committee of National Institute of Epidemiology, Chennai and obtained due clearance from them. We did not provide any money or kinds for engagement of participants in this study. Participants gained some knowledge about risk of toxemia in pregnancy and this may help them in future.

Result

Basic characteristics

We recruited 295 subjects as per selection criteria. We excluded five mothers as they were referred out due to complication. The basic characters of the study population: Mean age was 21.5 (Standard deviation: 3.6 years, Range: 15-30years). Most of them were nullipararous. Almost half of the mothers belonged to scheduled caste and tribe community. Family economic status of 78% mothers was < grade 5 (Median: 2, Range: 1-10). One third of the study participants and their spouses were illiterate. Most of the mothers were from joint family with average family size of 5 (Median 5; Range 2-18). Thirty eight percent of mothers did attend ANC one month prior to delivery. A doctor did not examine One third of the mothers. Almost 50% mothers were not tested for proteinuria and no referral advice was given to 45%. Thirty four percent of mother reported sub centre distance > 2 kilometer. Only 12% of the mothers were visited by health worker > 3 times. Ten percent of them had received JSY money. Thirty six percent of the participant had adequacy of antenatal care index score > 2 (Median: 2, Mode: 1). More than half of the mothers were unaware about risk in this pregnancy. One fourth of the mother had not received institutional delivery advice and 44% not received salt restriction advice. We observed oedema among 68% mother. Thirty five percent and 34% mother complained of blurring of vision and severe headache respectively (Table 1).

Analytical epidemiology

We examined individual associated risk factors of adverse outcome. In the univariate analysis we identified that several components of prenatal care were significantly associated with adverse outcome. They were, not tested for haemoglobin (RR 1.5); not examined by doctors at private clinic (RR 1.6); mothers who were not visited by health worker at home (RR 1.6); mothers not examined by a doctor (RR 1.5); not estimated for proteinuria (RR 1.5); not referred (RR 1.9); adequacy of prenatal care index utilization score > 2 (RR 0.6). Other factors like socioeconomic status < grade 5, not eating non vegetarian, non receipt of maternity benefit scheme money, belonging to scheduled caste and tribe, rural residence, illiteracy, knowledge of salt restriction advice, knowledge of risk, knowledge of institutional delivery were also significantly associated with adverse pregnancy outcome (Table 2). Each

level of adequacy of prenatal care utilization index was associated with incremental risk of adverse pregnancy outcome (Range: 1.7-1.9, Chi Square for linear trend: 44.3, $p < 0.0001$] (Table 3).

We examined the multi-collinearity for the variables that were significant in the univariate analysis. We selected statistically significant variables, which were not highly correlated with each other for the logistic model. The model indicated that some of the variables that were significantly associated with adverse pregnancy outcome in univariate analysis were no longer significant when adjusted for the other variables. In the multivariate model the illiteracy of mother (AOR: 52.8, 95% CI: 6.4-434.9), not visited by health worker (AOR=8.4, 95% CI: 2.1-33.3), not referred (AOR=25.3, 95% CI: 4.9-131.7); not visited by doctor (AOR=4.6, 95% CI: 1.4-15.2) and did not received salt restriction advice (AOR=4.9, 95% CI: 1.1-21.4) more likely to develop adverse pregnancy outcome. However who went for last ANC within one month before delivery (AOR=0.3, 95% CI: 0.1-0.8) and mothers with adequacy of antenatal care score > 2 (AOR=0.1, 95% CI: 0.01-0.3) were at lower risk to develop adverse outcome (Table 4).

Discussion

Factors including low adequacy of antenatal care utilization, illiteracy, rural residence, poor economic status and non-awareness of risk were significantly associated with adverse pregnancy outcome.

We identified from our study result that women with better adequacy of prenatal care utilization are likely to have lower risk of adverse outcome. Antenatal care utilization is associated with socio-economic and demographic conditions and is interrelated. Poor quality of care is also a cause of less antenatal care utilization. Access to health care is a problem of rural India. Studies in India showed that antenatal care in poor and disadvantageous group helps in improving pregnancy outcome. The poor pregnancy outcome in north as compared to south India is due to inadequate antenatal care[30]. Antenatal check ups during 2nd and 3rd trimester of pregnancy will help in early detection and prevent adverse outcome. However, in our study, the majority of pregnant mothers did not avail this facility beyond 32 weeks. Urinary protein estimation, regular blood pressure monitoring are essential for detection of

pre-eclampsia, however, majority of pregnant ladies of our study were from rural areas either had poor access(sub centre situated at a distant place) or no facility for doctors check up, no facility for urinary protein estimation or blood test at subcentre. They were not diagnosed or referred. Socio-economic differentials and quality of care and utilization of services in rural areas were significantly related[31].

In our study result, adverse outcome were more common among rural resident illiterate mothers. Studies in India indicated better utilization of antenatal services amongst young, literate, urban, and primipara mothers as compared to others. Further, the services of the treating physicians were found to be better in urban setting[32 33]. District Level Health Survey (DLHS) shows weighing of 58% of women, blood pressure check up to 60%, abdominal examination in 71%, urine test in 59% were recorded. However, these figures differed significantly in rural and urban set up[34]. Our study findings were similar to the above observations. Purulia survey findings by DLHS also found to be similar to our study[35]. Illiteracy and knowledge are complimentary. In our study, we detected that illiterate mother without knowledge of risk in pregnancy was at more risk of adverse outcome. The mothers of our study who were not advised about institutional delivery were also had more adverse outcome. Studies in India showed awareness about danger signs and benefit of institutional delivery reduces adverse outcome among pregnant mothers[36]. Poor interpersonal communication, as less time spent for examination by ANM and irregular home visit by health worker might attribute to poor awareness about danger signs and referral etc.

We identified that the mothers who are from economically backward section were at higher risk for poor outcome. Poverty is related to poor nutrition. Those who are eating non-vegetarian more are at lower risk. Maternity benefit scheme is in place to support poor backward mothers. This monetary support is meant for nutritional support. But we observed in or study that 90% of the eligible mothers had not received that money in pregnancy period. This might have changed the picture significantly. In India, health workers house visit (once in three months) is around 10 percent both in national as well as in the context of West Bengal[37] support our study findings.

Bias and limitations

As it was a hospital-based study, population was not representative of the community. High-risk pregnancy prevalence among admitted mothers in a district referral hospital was more. The proportion of urban residents was more among our study participant was more than the community and this population was supposed to have better access to health care and hospital facilities. We could not obtain response from those who were referred out due to complication could not be obtained. This led to selection bias and might have underestimated the risk ratio. There might be recall bias at the time of interview leading to differential misclassification. We crosschecked the information with review of prescription to minimize the bias. We used close-ended questionnaire. We engaged two people simultaneously for an interview to control interviewer bias.

Conclusions

In conclusion our study showed a significant association between utilization of ANC service with pregnancy outcome among mothers suffering from toxemia. Simple intervention like estimation of proteinuria by dipstick method along with regular blood pressure monitoring can detect pre-eclampsia early and can be referred in time and ultimately help in reduction of morbidity/mortality. As we are not in a position to prevent development of toxemia or pre-eclampsia, the only alternative to address the problem is by providing quality antenatal care to the mothers of district.

Health workers house visit as per schedule, spending some time for interpersonal communication will might improve the knowledge of mother about pregnancy related risk and in turn reduce the adverse outcome. Residents of remote areas with poor economic status are less likely to have access to medical services. Visit by a doctor can improve the quality of antenatal services to reduce adverse outcome. The money in maternity benefit scheme can facilitate access to nutrition and other health care services. Illiteracy and lack of knowledge related to risk in pregnancy are complimentary to each other. Proper IEC can improve the conditions.

There should be an effort to develop antenatal-care systems that allow close vigilance and easy referral for all pregnant women at risk. Greater attention should be made to identify

patients with risk factors, optimuum antenatal care and timely increased use of obstetrician interventions.[38] Under India's National Rural Health Mission (NRHM), launched in 2005, district health administration should lay greater emphasis on improving the quality of antenatal care, among other things, to increase utilization of antenatal care and achieve better maternal health outcomes.[39]

Recommendations

Our study suggest that there are opportunities to prevent adverse pregnancy outcome in toxemia in pregnancy by providing improved quality antenatal care and further by making it more accessible to poor illiterate mothers of rural area.

On the basis of our finding we want to propose a number of specific recommendations to the local health managers. Improve the quality of antenatal care by providing test for proteinuria at sub centre level. Ensure regular recording of blood pressure, weighing and par abdominal check-up. The antenatal check up should be well spaced with at least one at each trimester. Regular house visit by health worker should be ensured. Regular evaluation of ANC services will help in specific planning and measures thereof. Provide out reach services in difficult to reach areas by doctors and encourage referral. Utilize available financial resources like JSY fund and referral transport money. Plan target IEC to improve knowledge of mothers about risk in pregnancy and danger signs of pre-eclampsia to reduce the adverse outcome.

Table-1: Selected characteristics of women with toxemia, Deben Mahato district hospital, Purulia, West Bengal, India, 2007

Characteristics		#	Total	%
Demographics	Age below 19 yrs[iii]	70	295	24
	Scheduled caste & tribe	174	295	59
	Resident of rural area	231	295	78
	Muslim religion	44	295	15
	Joint family	235	295	80
	Number of family member>4	176	295	60
Socioeconomic status	BPL card holder[iv]	160	295	54
	Economic status < grade 5[v]	229	295	78
	Mother working outside of home	123	295	42
	Husband part time worker	103	295	35
	Eat non-vegetarian > 4 days a wk	190	295	64
Education	Mother illiterate	110	295	37
	Father illiterate	59	295	20
Risk factors	Used tobacco during pregnancy	118	295	40
	Not taken rest after lunch	104	295	35
	Knew about conception within 4 weeks	94	295	32
	Nullipara	219	295	74
Access to maternal and child health care	No ANC one month before delivery[vi]	124	295	62
	Not examined at subcentre	72	295	24
	Not examined at government hospital	198	295	67

[iii] 19 year is the minimum accepted age of child birth as per legislation
[iv] BPL card: Card issued to familes who are below poverty line by state government
[v] Idex based on household belongings, graded from 0 to 10
[vi] Last ante natal check up at least within one month before delivery increases chance of referral

Characteristics		#	Total	%
	Not examined at private clinic	164	295	56
	Not examined by ANM[vii]	67	295	23
	Not examined by doctor	86	295	29
	Examined by quack	20	295	7
	Examined by other	17	295	6
	No 3-BP check up[viii]	45	295	15
	No 3-weight measurement	28	295	10
	Not consumed 100 IFA tablet	91	295	31
	Urinary protein not estimated	140	295	48
	No ultra sonogram done	234	295	79
	Not received salt restriction advice	129	295	44
	No referral advice given	133	295	45
	No institutional delivery advice given	73	295	25
	Distance of sub-center > 2 km	99	295	34
	Not visited by health worker at house	194	295	66
	Health worker visited < 3 times	29	81	12
	Not received JSY money[ix]	180	199	90
	Adequacy of prenatal care index > 2[x]	105	295	36
Danger signs	Oedema	200	295	68
	Blurring of vision	102	295	35
	Severe headache	97	295	34
Knowledge	Awareness about risk in this pregnancy	133	295	45

[vii] Auxilliary nurse midwife in government set up
[viii] Three blood pressure check up is minimum as per Government of India guideline
[ix] Money given to mothers in maternity benefit scheme to support and encourage institutional delivery
[x] Based on KOTELCHUK Index

Table-2: Incidence of adverse outcome according to selected characteristics, Deben Mahato district hospital, Purulia, West Bengal, India, 2007

Characteristics		Incidence of adverse outcome						Relative risk	95% confidence interval
		Among exposed			Among unexposed				
		#	Total	%	#	Total	%		
Demographic	Scheduled tribe and caste	110	140	79	89	155	57	1.4	1.2-1.6
	Muslim	22	44	50	177	251	71	0.7	0.5-0.9
	Rural residence	165	231	71	34	64	53	1.3	1.1-1.7
	Joint family	152	235	65	47	60	78	0.83	0.7-1
	Family member>4	107	176	61	92	119	77	0.8	0.7-0.9
	BPL card holder[xi]	117	160	73	82	135	61	1.2	1 -1.4
Socioeconomic	Economic status < grade 5[xii]	171	229	75	28	66	42	1.8	1.3-2.4
	Working outside of home	93	123	76	106	172	62	1.2	1.1-1.4
	Husband part time worker	125	192	65	77	103	75	1.15	1-1.3
	Eating non-vegetarian > 4 days a wk	113	190	60	86	105	82	0.7	0.6-0.8
Education	Mother illiterate	96	110	87	103	185	56	1.6	1.4-1.8
	Father illiterate	56	59	95	143	234	61	1.57	1.4-1.8
Risks	Used tobacco during pregnancy	92	118	78	107	177	61	1.3	1.1-1.5
	Not taken rest after lunch	81	104	78	118	191	62	1.3	1.1-1.5
	Knew pregnant within 4 weeks	53	94	56	146	201	73	0.8	0.6-0.9
	Nulliparity	159	219	73	40	76	53	1.3	1.1-1.7
Prenatal care	Not examined at subcentre	35	72	18	164	223	82	0.7	0.5-0.9
	Not examined at private clinic	132	164	81	67	131	34	1.6	1.3-1.9
	Not examined by ANM	34	67	51	165	228	83	0.7	0.6-0.9
	Not examined by doctor	75	86	38	124	209	59	1.5	1.3-1.7

[xi] Card issued to families below poverty line by government

[xii] Economic status of families ascertained by methods used in RCH surveys

Characteristics		Incidence of adverse outcome						Relative risk	95% confidence interval
		Among exposed			Among unexposed				
		#	Total	%	#	Total	%		
	Examined by quack	17	20	85	182	275	66	1.3	1.1-1.6
	No 3-BP check up	54	66	27	145	229	73	1.3	1.1-1.5
	No 3-weight measurement	127	194	66	72	101	36	0.9	0.8-1.1
	No blood test done	86	14	86	113	195	58	1.5	1.3-1.7
	Urinary protein not estimated	114	140	81	85	155	55	1.5	1.3-1.8
	Not examined par abdominally	40	51	78	159	244	65	1.2	1-1.4
	No ultra sonogram done	168	234	72	31	61	51	1.4	1.1-1.8
	ANC one month before delivery	42	77	55	78	124	63	0.9	0.7-1.1
	Health worker visited < 3 times	186	266	70	13	29	45	1.6	1-2.4
	Not received salt restriction advice	110	129	85	89	166	54	1.6	1.4-1.9
	Not referred	121	133	91	78	84	48	1.9	1.6-2.2
	APNCU Index > 2[xiii]	106	190	56	93	105	87	0.6	0.5-0.7
Knowledge	No institutional delivery advice given	66	7	90	133	222	60	1.5	1.3-1.7
	No awareness of risk	70	133	10	129	162	65	1.5	1.3-1.8
	Not received JSY[xiv]	146	186	79	3	10	23	3.4	1.3-9.2

[xiii] Based on Kotekchuk index model

[xiv] JSY: Money in maternity benefit scheme Janani Suraksha Yojana

Table 3: Risk of adverse outcome of pregnancy according to increasing gradient of exposure variables, district Purulia, West Bengal, India, 2007

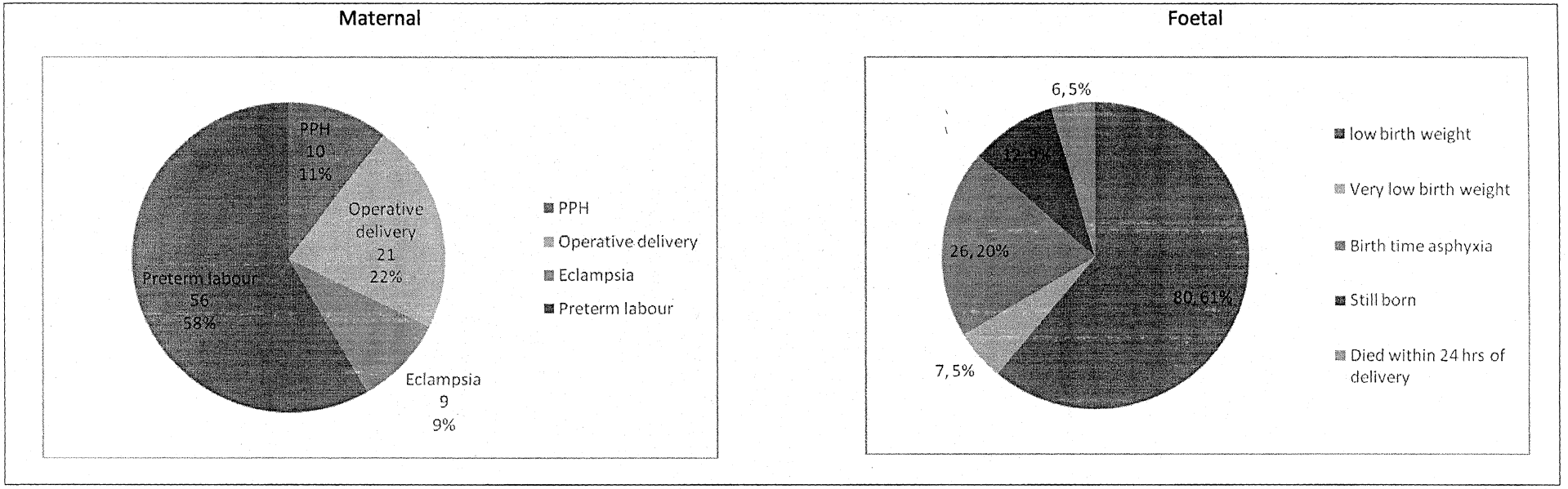
Exposure		Adverse outcome		No adverse outcome			
	Level	#	%	#	%	RR	95% CI
Adequacy of prenatal care [a]	Score 4	61	46.2	71	53.8	1	Reference
	Score 3	45	77.6	13	22.4	1.68	1.3-2.1
	Score 2	60	88.2	8	11.8	1.91	1.6-2.3
	Score 1	33	89.2	4	10.8	1.93	1.6-2.4

[a] Chi-square for trend: 44.3; P-value: 0.0000

Table 4: Factors associated with adverse pregnancy outcome in multiple logistic regressions, Deben Mahato district hospital, Purulia, West Bengal, India, 2007

Characters	Crude OR	Adjusted Odds ratio	
		Estimate	95% C. I.
Illiteracy of mother	5.5	52.8	6.4-435
Health worker house visit < 3 times	2.9	8.4	2.1-33.3
Not referred	10.9	25.3	4.9-131.7
Not advised for salt restriction	5	4.9	1.1-21.4
Not visited private doctors	3.9	4.6	1.4-15.2
Last ANC within one month before delivery	0.7	0.3	0.1-0.8
Adequacy of prenatal care index score > 2	0.2	0.1	0.01-0.32

Chart 1: Maternal and foetal outcome among study population group in Deben Mahato district, Purulia, West Bengal, India, 2007



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APPENDIX – I : Identifier collection sheet

(To ensure confidentiality, identifiers will not be collected in the paper questionnaires)

ID Number	Name	Husband's name	Village	Block

APPENDIX – II : INFORMED CONSENT FORM

Consent form for the investigation of the risk factors for out come of toxemia in pregnancy in Purulia district of West Bengal, India in 2007

Namaskar,

I _____ and am working with the Deben Mahato district hospital, Purulia to look into factors that may put you at risk for outcome of toxemia in pregnancy or protect you from them. We are doing this research as a response to high maternal mortality (XX) due to eclampsia in Purulia between XX month and XX month in the year XX. Since toxemia in pregnancy is a health problem and also commonly occurs in Purulia, it is also being looked at. The National Institute of Epidemiology, Chennai is also working with us on this investigation.

To find out what modifies the outcome of toxemia in pregnancy, we need to ask questions to mothers who had toxemia in pregnancy. Thus, between _____ and _____, we will be asking the same questions to mothers with toxemia admitted and delivered in district hospital. We would like to confidentially ask these few questions to you once. Answering these questions should take about 25 minutes of your time.

For all the subjects: For this study, we will ask the same questions. However, we will not mention any medical information about you and we will not mention that we come and see them because there was any problem with you.

Taking part in this survey is voluntary. No compensation will be paid to you for taking part in this study. You can choose not to take part. You can choose not to answer a specific question. You can also stop answering these questions at any time without having to provide a reason. This will not affect your rights to health care in the district hospital, Purulia, or any other rights. There is no specific benefit for you if you take part in the survey. However, taking part in the survey may be of benefit to the community, as it may help us to understand the problem, its causes and potential solutions. When the results will have been analyzed, a report will be shared with all the participants and the local health officials concerned with public health, so that the right measures can be taken to prevent poor outcome related to toxemia in pregnancy in the district Purulia.

The information we will collect in this survey will remain between you and the doctor. We may ask questions about various specific things you do. This does not mean that we think that these things you do would put you at risk for poor outcome. We will not write your name on this form. We will only use a code instead. Only the doctor will know the key to this code. It will be kept under lock and key. It will be destroyed after the project.

If you wish to find out more about this survey before taking part, you can ask me all the questions you want. You can also contact Dr.Sobhan De MAE-FETP Scholar (VI Cohort) and principal investigator of this survey attached to the National Institute of Epidemiology, Chennai, at the district hospital, Purulia or Dr.M.De, obstetrician attached to the district hospital at Purulia, who will be happy to give you more details. If you are OK to take part, we will go ahead now.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this study and understand that I have the right to withdraw from the study at any time without in any way it affecting my further medical care.

Name of the study participant

Signature/thumb impression of the study participant

Name of the witness

Signature of the witness

Name of the interviewer

Signature of the interviewer

APPENDIX – III : DEFINITIONS USED

Prenatal Care: Women who received full antenatal care, (that is, at least three antenatal check-ups, and at least one tetanus toxoid injection and supplementary iron in the form of iron folic acid tablets/syrup daily for 100 days. We will use Kotelchuk prenatal care index to grade the care in three subgroups.

Kotelchuck M. An evaluation of the Kessner Adequacy of Prenatal Care Index and a proposed Adequacy of Prenatal Care Utilization Index. Am J Public Health 1994;84:1414-20.

Quality of prenatal care was measured by use of the Kotelchuck Adequacy of Prenatal Use Index, which quantifies the adequacy of care use according to the timing of enrollment into prenatal care, the number of prenatal visits, and gestational age at delivery. Four levels of use were defined: inadequate, intermediate, adequate, and adequate plus. In our study, the latter two groups were combined and defined as adequate for analysis purposes.

Adverse maternal outcomes were classified according to the International Classification of Diseases, tenth revision (ICD-10). Eclampsia. Third-trimester bleeding included placenta previa with hemorrhage. Placental abruptio. Cesarean delivery. Operative vaginal delivery. Premature rupture of membranes. Postpartum hemorrhage. Maternal death was defined as the death of a woman while pregnant or (during hospital stay or within 42 days) after delivery from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.

Peri-natal outcomes evaluated were LBW (live infant weighting < 2500 g at birth), very LBW (live infant weighting <1500 g at birth), pre-term delivery (live infant delivered at <37 weeks' gestation), very pre-term delivery (live infant delivered at < 32 weeks' gestation), SGA (live infant with birth weight below the 10th percentile for the gestational age and gender, according to the Williams et al6 reference curve), fetal death (delivery of a dead infant at or after 20 weeks' gestation), early neonatal death (neonatal death occurring during the first 7 days of life), and low Apgar scores at 5 minutes (< 7).

Gestational age will be determined by the best obstetric estimate on the basis of the information on menstrual history and physical examination as well as early ultrasound examination when available. If the gestational age determined from the self-reported menstrual history was within 10 days of that derived from the physical examination and ultrasound, the gestational age was based on self-reported menstrual history. If these two measures differed by >10 days, the date determined from the earliest ultrasound estimate was used as the actual gestational age.

Preeclampsia was present if the patient had high blood pressure (>140/90 mm Hg), abnormally urinary protein (+1 by dipstick methods), and symptoms of edema during pregnancy.

Hypertensive complications (pre-eclampsia and gestational hypertension) defined in accordance with International Society for the Study of Hypertension in **Pregnancy.** Hypertension is defined as one diastolic blood pressure reading of greater than or equal to 110 mm Hg or two consecutive diastolic blood pressure readings of greater than or equal to 90 mm Hg at least four hours apart. Significant proteinuria is defined as 1+ proteinuria by dipstick. Gestational proteinuric hypertension (pre-eclampsia) is defined as hypertension in

combination with proteinuria developing after 20 weeks' gestation in a previously normotensive, non-proteinuric woman.

Anemia: We defined, as hemoglobin concentration below 10 gm/dl. When the hemoglobin concentration was below 8 gm/dl, severe anemia was diagnosed. According to monitoring procedures, the hemoglobin level of each pregnant woman will measured at admission to hospital.

Age: in completed years, if more than 6 month take next completed year

Caste: 'Others' include general and other backward class (OBC)

Urban: Includes district, subdivision, and block headquarter towns

Type of family: House holds with 3 or more related adults are assumed to have an extended/joint structure (coded as 1), while households with two related adults of opposite sex are assumed to have a nuclear family structure (coded as 2)

Husband's occupation: Part time work means work less than 4 hrs a day/seasonal; Full time work means more than 4 hrs a day/throughout the year

Economic status: of the household is measured by a composite score of several indicators of household possessions. The questions were asked whether the household had such items and facilities as piped water, toilet, non-dirt floor, electricity, radio, television, telephone, bicycle, motorcycle, and cooking gas. Affirmative responses to ten items are counted and a composite scale ranging from 0 through 10 is created. The higher the score, the higher is the economic status of the household. Households are graded as below scale 2, between 2 and 4, between 5 and 8, and above 8.

Antenatal check up: It will be ascertained by review of documents available with the study subjects. If could not be documented, we will consider her as defaulter. Documents entertained will be ANC card / prescription.

Literature Review

Factors associated with adverse pregnancy outcome in mothers suffering from toxemia in pregnancy.

Introduction:

Toxemia in pregnancy includes gestational hypertension and or pre-eclampsia. Pre-eclampsia is said to be present when hypertension arises in pregnancy (pregnancy-induced hypertension) in association with significant protein in the urine. Its cause remains unclear, although the principal cause appears to be a substance or substances from the placenta causing endothelial dysfunction in the maternal blood vessels.[i] While blood pressure elevation is the most visible sign of the disease, it involves generalized damage to the maternal endothelium and kidneys and liver, with the release of vasopressive factors only secondary to the original damage.

Pre-eclampsia may develop at varying times within pregnancy and its progress differs among patients; most cases are diagnosed pre-term. It has no known cure apart from ending the pregnancy (induction of labor or abortion). It may also occur up to six weeks post-partum. It is the most common, dangerous complication of pregnancy and it may affect both the mother and the fetus.[1]

Diagnosis:

Pre-eclampsia is usually symptomless, hence its detection depends on signs or investigations. Nonetheless, one symptom is crucially important because it is so often misinterpreted. The epigastric pain, which reflects hepatic involvement and is typical of the HELLP syndrome, may easily be confused with heartburn, a very common problem of pregnancy. However, it is not burning in quality, does not spread upwards towards the throat, is associated with hepatic tenderness, may radiate through to the back, and is not relieved by giving antacids. It is often very severe, described by sufferers as the worst pain that they have ever experienced. Affected women are not uncommonly referred to general surgeons as suffering from an acute abdomen, for example acute cholecystitis.

In general, none of the signs of Pre-eclampsia is specific; even convulsions in pregnancy are more likely to have causes other than eclampsia in modern practice. Diagnosis, therefore, depends on finding a coincidence of several preeclamptic features, the final proof being their regression after delivery.

Pre-eclampsia is diagnosed when a pregnant woman develops high blood pressure (two separate readings taken at least 6 hours apart of 140/90 or more) and 300 mg of protein in a 24-hour urine sample (proteinuria). A rise in baseline BP of 20 systolic or 15 diastolic, while not meeting the absolute criteria of 140/90 is still considered important to note but no longer diagnostic. Swelling, or edema, (especially in the hands and face) was originally considered an important sign for a diagnosis of pre-eclampsia, but in current medical practice only hypertension and proteinuria are necessary for a diagnosis. However, unusual swelling, particularly of the hands, feet, or face, notable by leaving an indentation when pressed on, can be significant and should be reported to your health-care provider.

Some women develop high blood pressure without the proteinuria (protein in urine); this is called Pregnancy-induced hypertension (PIH) or gestational hypertension. Both Pre-eclampsia and PIH are regarded as very serious conditions and require careful monitoring of mother and baby.

Epidemiology of Toxemia in pregnancy:

Pre-eclampsia occurs in 6% of pregnancies, usually in the second or third trimester, and after the 32nd week. Some women will experience pre-eclampsia as early as 20 weeks, though this is rare. It is much more common in women who are pregnant for the first time.[ii]

Pre-eclampsia is also more common in women who have preexisting hypertension, diabetes, autoimmune diseases like lupus, various inherited thrombophilias like Factor V Leiden, or renal disease, in women with a family history of Pre-eclampsia, and in women with a multiple gestation (twins, triplets, and more). The single most significant risk for developing Pre-eclampsia is having had Pre-eclampsia in a previous pregnancy.

Pre-eclampsia may also occur in the immediate post-partum period or up to 6-8 weeks post-partum. This is referred to as "postpartum Pre-eclampsia." The most dangerous time for the

mother is the 24-48 hours postpartum and careful attention should be paid to Pre-eclampsia signs and symptoms

Global:

The hypertensive disorders of pregnancy affect up to 8% of all gestations and remain major causes of maternal and neonatal mortality and morbidity in the United States and worldwide.

The reported rate of eclampsia in the Western world is 1 in 2000 to 1 in 3000 deliveries.[iii] The rates are significantly higher in the nonindustrialized countries.[5, 6] Eclampsia is associated with increased risks of maternal and perinatal mortality and morbidity.7 Thereported maternal mortality rates from eclampsia range from 0.5% in some centers in the United States8, 9 to as high as 14% in Mexico.[6]

Developing Countries:

Study among a cohort of pregnant mother in Saudi Arabia shows Pre-eclampsia was encountered at a high percentage (40.0%) in women at the extreme of their reproductive age (< 20 and >40 years), and more women with PE delivered prematurely (30.2%) as compared to healthy controls (13.5%).[iv] A study in West Africa (Burkina Faso, Cote d'Ivoire, Mali, Mauritania, Niger, Senegal) in a sample of 2522 pregnant mother 9.6% mother suffered from toxemia in pregnancy.

India:

In a study in Mumbai over a 36-month period, a total of 29562 deliveries were recorded, of which 1238 patients developed Pre-eclampsia (4.18%) and 34 developed eclampsia (0.11%).[v] The maternal mortality rate associated with eclampsia ranges from 100 to 6000 per 100,000, and the perinatal mortality rate ranges from 150 to 400 per 1000. Both eclampsia and its preceding condition, pregnancy-induced hypertension, occur in varying degrees in different parts of India.[vi]

Factors associated with toxemia in pregnancy:

Public health importance of toxemia in pregnancy:

It is associated with an increased risk for maternal and fetal morbidity and mortality. Possible maternal complications include placental abruption, operative vaginal delivery and cesarean section, eclamsia and even mortality. Foetal complication includes prematurity, intra uterine growth retardation, birth time asphyxia and stillbirth.[vii] The reported rate of eclampsia in the Western world is 1 in 2000 to 1 in 3000 deliveries. The rates are significantly higher in the non-industrialized countries. Eclampsia is associated with increased risks of maternal and perinatal mortality and morbidity. The maternal mortality rate associated with eclampsia ranges from 100 to 6000 per 100,000, and the perinatal mortality rate ranges from 150 to 400 per 1000.[viii]

Biological:

Pre-eclampsia is thought to be caused by a shallowly implanted placenta which becomes hypoxic, leading to upregulated inflammatory mediators secreted by the placenta and acting on the vascular endothelium. If severe, it progresses to fulminant pre-eclampsia, with headaches, visual disturbances, and epigastric pain, and further to HELLP syndrome and eclampsia. Placental abruption is associated with hypertensive pregnancies. These are life-threatening conditions for both the developing baby and the mother. The current understanding of the disease is as a two-stage process, with a variable first stage which predisposes the placenta to hypoxia, followed by the release of soluble factors which result in many of the other observed phenomena. Many of the older theories can be subsumed under this umbrella, as the soluble factors have been shown to cause, for example, endothelial cell injury, altered vascular reactivity, the classic lesion of glomerular endotheliosis, decreased intravascular volume, etc. Underlying maternal susceptibility to the damage is likely implicated as well.

The literature on eclampsia has long been unsatisfying because even after reviewing dozens of articles, it is not possible to say very much about causation, which is why toxemia has been called the disease of theories.[ix] Even now this remains a topic full of questions and theories, so much so that the World Health Organization (WHO) Reproductive Health Library

[x]made the following statement about anticonvulsants, which were used for >80 y to prevent Pre-eclampsia from progressing to eclampsia: "At the present time, there is no clear evidence either in favor of or against the use of anticonvulsants..." Hypotheses about toxemia have proposed causal roles for placental abnormalities, immunologic dysfunction, coagulation abnormalities, endothelial damage, endocrine abnormalities, genetic factors, and dietary factors.[xi] Narrowing the focus to dietary factors, there are many alleged culprits, including the consumption of too little protein, magnesium, calcium, or zinc, and the consumption of too much sodium or fatty acids.[xii]

Low dietary intake of protein and calcium:

Although each theory has, or has had, its proponents, there is contradictory evidence on the causal roles of these dietary components. Moreover, because toxemia is a complex disease— involving a variety of organ systems and functions—it is not clear whether the abnormalities that occur represent causes or effects.

Presently, one of the more popular hypotheses is the belief that a lack of calcium is a precipitating factor in the incidence of toxemia and that calcium supplementation can lower the incidence of this condition. Again, there is conflicting evidence. Several clinical trials have suggested that calcium supplementation may prevent toxemia,[xiii] whereas other trials have not shown positive results.[xiv] Moreover, researchers at the National Institute of Child Health and Human Development in Bethesda, MD, found that methodological problems and differences in study designs made the positive studies inconclusive.[xv]

Treatment and prevention

The only known treatment for eclampsia or advancing Pre-eclampsia is delivery, either by induction or Caesarean section. However, post-partum Pre-eclampsia may occur up to 6 weeks following delivery even if symptoms were not present during the pregnancy. Post-partum pre-eclampsia is dangerous to the health of the mother since she may ignore or dismiss symptoms as simple post-delivery headaches and edema. Hypertension can sometimes be controlled with anti-hypertensive medication, but any effect this might have on the progress of the underlying disease is unknown.

Magnesium sulphate

In some cases women with Pre-eclampsia or eclampsia can be stabilized temporarily with magnesium sulphate intravenously to forestall seizures while steroid injections are administered to promote fetal lung maturation. Magnesium sulp SM Khedun, J Moodley, T Naicker and B Maharaj, Drug management of hypertensive disorders of pregnancy, Pharmacol Ther 74 (1997), pp. 221–228.hate as a possible treatment was considered at least as far back as 1955,[xvi] but only in recent years did its use in the UK replace the use of diazepam or phenytoin.[xvii] Evidence for the use of magnesium sulphate came from the international MAGPIE study.[xviii] When induced delivery needs to take place before 37 weeks gestation, it is accepted that there are additional risks to the baby from premature birth that will require additional monitoring and care.

Other investigated treatments

Studies into supplementation with antioxidant vitamins C and E found no change in Pre-eclampsia rates.[xix] Drs. Padayatty and Levine with NIH in a "Letter to the Editor" stated that the studies and another "Letter to the Editor" overlooked a key reason for the lack of vitamin C on the prevention of Pre-eclampsia. Because plasma ascorbate concentrations were not reported, we estimated them from known data; the placebo and treatment groups in the study probably had similar plasma and tissue ascorbate concentrations. Doses of 1 g per day have little effect on plasma or intracellular ascorbate concentrations[xx]. Calcium supplementation in women with low-calcium diets found no change in Pre-eclampsia rates but did find a decrease in the rate of severe preeclamptic complications.[xxi] Aspirin supplementation is still being evaluated as to dosage, timing, and population and may provide a slight preventative benefit in some women, however significant research has been done on aspirin and the results thus far are unimpressive.[xxii] There is insufficient evidence to recommend either exercise [xxiii]or bed rest[xxiv] as treatments. Studies of protein/calorie supplementation have found no effect on Pre-eclampsia rates, and dietary protein restriction does not appear to increase Pre-eclampsia rates.[xxv]

Effects of smoking

Smoking may also interfere with development of Pre-eclampsia.[xxvi] A plausible mechanism of action may be the nicotine in tobacco smoke acting as an anti-inflammatory agent and interfering with the disease process.[xxvii] This reported minor reduction in risk of pre-eclampsia is far outweighed by the general risks of smoking to both mother and fetus.

Primary prevention of Pre-eclampsia

The best way to cope with human disease, by preventing it happening, is only achievable if the cause is understood and if it is feasible to avoid or manipulate those causes. Shallow endovascular cytotrophoblast invasion in the spiral arteries, an exaggerated inflammatory response, and inappropriate endothelial-cell activation are key features in the pathogenesis of Pre-eclampsia.[xxviii] But the mechanisms behind these features are unknown. Thus contraception is currently the only way to avoid Pre-eclampsia. However, several risk factors have been identified,[xxix] and manipulation of some of these risk factors might allow primary prevention.

Secondary prevention of Pre-eclampsia

Secondary prevention of a disease is only possible if the following three requirements are met: knowledge of pathophysiological mechanisms (pathogenesis and genetics of Pre-eclampsia were reviewed in the first part of this series); availability of methods of early detection; and means of intervention and correction of the pathophysiological changes.

Availability of methods of early detection

Many tests have been proposed to predict later development of the disease. Some of these methods are already used or could be easily introduced in most hospitals in more-developed countries. Measuring blood pressure or second trimester mean arterial pressure is not useful for early diagnosis of Pre-eclampsia.[xxx] If an increased diastolic blood pressure or second trimester mean arterial pressure predicts anything, it is gestational hypertension, not the real disease Pre-eclampsia with its associated perinatal morbidity and mortality.[xxxi] Also weight gain cannot be used to predict development of pregnancy-induced hypertensive disorders, and excess weight gain alone imparts no adverse prognosis to perinatal outcome.[xxxii] Most women with a pregnancy-induced hypertensive disorder are symptomless, which is an important part of the rationale for frequent antenatal visits in late pregnancy. Laboratory tests have been used for prediction, diagnosis, and monitoring of disease progress. The diagnosis of Pre-eclampsia is even based on a laboratory test. Uric acid clearance drops disproportionately in Pre-eclampsia compared with creatinine and urea clearance. The explanation for this specific decrease in urate clearance lies in the biphasic pattern of renal involvement in Pre-eclampsia. Tubular function is the first to be involved and later in the disease process glomerular function is impaired. Uric acid is used as an indicator of disease severity in established Pre-eclampsia and has been reported to be a

better predictor for adverse perinatal outcome than blood pressure.[xxxiii] In most patients the increase in urate concentrations seems to coincide with the increase in blood pressure, and precedes development of the proteinuric stage (a sign of glomerular damage) of the disease. Uric acid concentrations have been used for early diagnosis of Pre-eclampsia, but not for hypertension as such. The low sensitivity found in most studies renders uric acid measurement unhelpful for widespread use.[xxxiv]

Proteinuria is a late sign of pregnancy-induced hypertensive disorders, and HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome and eclampsia could occur in the absence of proteinuria. After blood pressure measurement, dipstick proteinuria analysis is the most common screening test for Pre-eclampsia.

Tertiary prevention

Without a doubt, proper antenatal care is the most important part of tertiary prevention. The decrease in maternal mortality and serious morbidity since the 1950s resulted not from the management of acute hypertension but mainly from the screening and intervention (such as timed delivery) that comes with organised antenatal care. There should be an effort to develop antenatal-care systems that allow close vigilance and easy referral for all pregnant women at risk. Greater attention should be made to identify patients with risk factors.

New developments

Low-dose aspirin does correct the prostacyclin/ thromoxane-A2 imbalance, so why is it not the wonder drug we all hoped for? The most likely explanation is that such an imbalance is not the only, and certainly not the major, pathogenic biochemical pathway.[xxxv] Other investigators have stressed that the dose of aspirin should be high enough to inhibit placental synthase and thus a major part of placental lipid peroxide production, and to allow for other anti-inflammatory effects of aspirin.[xxxvi] The importance of a higher dose of aspirin is supported by several studies using biochemical or clinical endpoints.[xxxvii] Some of the larger trials could have looked at the wrong dose of aspirin used at the wrong time of pregnancy.[xxxviii] Thus it is unclear whether aspirin given in early pregnancy in an appropriate dose is effective in Pre-eclampsia. A multicentre trial to address that question is in progress in France. Low-dose aspirin has been studied in combination with other antiplatelet drugs. In a South African study, addition of ketanserin to aspirin was associated with a substantial

decrease in the frequency of superimposed pre-eclampsia and an improvement in pregnancy outcome among patients with mild to moderate midtrimester hypertension.[xxxix] The aim of treating a pregnant woman with Pre-eclampsia is the prevention of complications (tertiary prevention). What are we treating? There is a consensus that drug treatment of severe hypertension in pregnancy is required and beneficial.[xl] The more controversial issues are the role of pharmacological treatment for conservative management in severe pre-eclampsia aimed at prolongation of pregnancy, the ability of such treatment to modify the course of the underlying systemic disorder, and the effect on fetal and maternal outcome.

Summary:

Purulia district have higher MMR (248). Eclampsia a sequel of toxemia is the major cause of MMR (33%) in the district. There are modifiable risk factors (Regular antenatal check up with detection of proteinuria in pregnancy, dietary practice modification, campaign against tobacco addiction, birth spacing, referral advice, health worker house visit, utilization of maternity benefit schemes), which can improve pregnancy outcome significantly.

In Purulia district Reproductive and Child Health programme II is being implemented with a primary goal to reduce the MMR. Certain steps have already been taken to improve coverage and quality of prenatal care services. Maternity benefit scheme is also in place to support the financially and socially backward community. We in district liked to know the association between modifiable risk factors and outcome among mothers suffering from toxemia in pregnancy.

Our research question was to identify risk factors that may be associated with adverse pregnancy outcome among women with toxemia in pregnancy in district.

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