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ORIGINAL ARTICLE

Maternal complications in women presenting with first trimester threatened miscarriage.

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ABSTRACT… Objective: To determine the frequency of miscarriage, hypertensive disorder of pregnancy, placental abruption and preterm birth in women with first trimester threatened miscarriage. **Study Design:** Cross-sectional study. **Setting:** Department of Obstetric & Gynaecology, Sir Syed Hospital and Pakistan Naval Ship Shifa Hospital (Karachi). **Period:** April, 2021 to March, 2022. **Material & Methods:** Ninety two women 18-40 year old, diagnosed as threatened miscarriage at ≤ 13 weeks based on history, examination and ultrasound were included in the study after informed consent and followed till delivery. Women with genital infection, other form of miscarriage and multiple pregnancy were excluded. Data recorded from hospital documents. Maternal age, parity and Gestational age assessed. Miscarriage, hypertensive disorder of pregnancy, placental abruption, preterm birth and PPROM expressed as frequency and percentages. Logistic regression analysis performed. Chi square test (x^2) used and P-value ≤ 0.05 taken as significant. **Results:** Mean age of women was 29.21±3.49 years. Mean parity was 2.65±1.15. Mean Gestational age at presentation was 7.96±1.78 weeks. 11.11%. (10/90) cases had miscarriage. 88.88% (80/90) women continued their pregnancy. 42.5% (34/80) had hypertensive disorder of pregnancy. 20% had pregnancy induced hypertension and 22.5% had pre-eclampsia. Preterm birth was seen in 26.3% (21/80). Frequency of PPROM and placental abruption was 6.3% (5/80) each. Women of 21-25 yr age were more at risk of hypertensive disorder of pregnancy than other age groups. There was no significant affect of maternal age and parity on preterm birth and placental abruption. Frequency of Preterm birth was 38.4% in women with hypertensive disorder, more than 2 times higher than non-hypertensives (17.4%) and found significant (P-value=0.043). **Conclusion:** Hypertensive disorder of pregnancy was the most common maternal complication observed in women who had threatened miscarriage in first trimester. Preterm birth had significant association with hypertensive disorder of pregnancy.

Key words: Hypertensive Disorder of Pregnancy, Miscarriage, Pretermbirth, PPROM (preterm pre- labour rupture of membranes), Placental Abruption, Threatened Abortion.

INTRODUCTION

Primary embryonic circulatory system is developed in early pregnancy. About one third of human pregnancies are affected by abnormal placental development. Miscarriage and pre-elcampsia are the two major maternal complications related to abnormal placental development.[1] One fourth human pregnancies are affected by miscarriage and its the commonest maternal complication of pregnancy.[2] In two third miscarriages, pregnancy loss is due to improper development of circulatory system in early pregnancy. Focal bleed from a developing placenta in first trimester may be a manifestation of placental dysfunction. Bleed in placenta can extend further in the form of subchorionic haematoma which impair blood flow to the developing fetus.[2] vaginal bleeding during pregnancy before 24 weeks gestation with closed cervical os and embryo having fetal cardiac activity on ultrasound is threatened miscarriage by which 14-27% pregnancies[3] are affected. Various studies done in the past on threatened miscarriage showed conflicting results of miscarriage ranging from 9.3% by john et al[4] to 25.9%[5] in Asian women. Rate of miscarriage depend on the age of the couple, parity, gestational age at presentation, amount of bleed, presence or absence of sub chorionic

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haematoma and other co morbid of the women.[5]

Around 10% pregnancies are complicated by a hypertensive disorder of pregnancy including 3-5% cases complicated by pre eclampsia.[6] In pre eclampsia, initiating event could be defective trophoblastic invasion due to oxidative stress that could result in incomplete conversion of spiral arteries into low resistance channels. Inflammatory markers produced from the damaged placenta due to chronic hypoxia disturb the maternal angiogenic balance leading to multi organ involvement.[7] Improper embryonic circulatory system development in early pregnancy could be the common initiating factors in threatened miscarriage and hypertensive disorders of pregnancy like pre-elcampsia.[2,7] This could explain, the pregnancies which survived after threatened miscarriage are at risk of adverse outcome later which include pre-eclampsia, preterm birth, preterm pre-labour rupture of membranes, intrauterine growth retardation and placental abruption.[8] Various frequencies of hypertensive disorder of pregnancy were observed in women with threatened miscarriage. There was zero to 1.5 times high risk of pre-elcampsia at one end[8,9] and more than 6 times higher risk of hypertensive disorder of pregnancy at other end by S.M.S.G Gunarathna[10] Placental Abruption a disorder related to placental dysfunction. Literature showed that pregnancies complicated by threatened miscarriage had more than 3 times increased risk of placental abruption than controls.[8,11] Frequency of preterm birth was 9.6% in USA[12] and usually one third cases (3-4%) of preterm births got complicated by pre-labour rupture of membranes but frequency of PPROM was found 14% in women who had threatened miscarriage i.e. 3 to 4 times higher than controls.[9] One possible reason could be chronic inflammatory reaction due to sub-chorionic haematoma that weaken the membranes making them more prone to rupture before term. Frequency of preterm birth and PPROM was significantly higher in pregnancies survived after threatened miscarriage.[4,8,11]

Preventive strategies to reduce the rate of miscarriage, hypertensive disorder of pregnancy including pre eclampsia, placental abruption and preterm birth are required in order to improve fetomaternal outcome. Identification of "high risk" population is important for fetomaternal surveillance in pregnancy. Very few Studies related to above mentioned maternal complications in women who had threatened miscarriage are available from Pakistan. Rationale of this study was to find the frequency of maternal complications in women who had threatened miscarriage. It will provide a road map to improve maternal outcome by the use of preventive strategies and timely interventions.

MATERIAL & METHODS

This cross sectional, prospective study was carried out in the Obstetrics and Gynaecology departments of two Hospitals of Karachi i.e. Sir Syed hospital and Pakistan Naval Ship, Shifa hospital during one year, from 1st April 2021 till 31st March 2022.

Data was Collected from 92 patients who presented with threatened miscarriage prior to 13 completed weeks of gestation. Sample size was calculated by WHO sample size calculator. Approval of the study was taken from the ethical committee (023 SSMS-Ethics/2021) of hospitals. Women presenting to the outdoor or emergency departments of above mentioned hospitals with episode of vaginal bleeding had ultrasound by sonologist after history and clinical examination. Women with closed cervix on examination and positive fetal cardiac activity on ultrasound were included in the study after informed consent. Women with other types miscarriage like inevitable, incomplete or complete miscarriage, ectopic pregnancy, molar pregnancy and multiple pregnancy were excluded.

Detailed history about personal biodata, past obstetric details, gestational age at presentation and co morbid like chronic hypertension, diabetes or thyroid disorder were taken. Their relevant clinical examination and ultrasound by sonologist got done .Pre designed proforma was filled to record the findings after informed consent. Patients were managed according to the hospital protocol. They were followed till delivery. Maternal

complications including miscarriage, pregnancy induced hypertension, pre-eclampsia /eclampsia, placental abruption, preterm birth, preterm pre-labour rupture of membranes were managed as per protocol of institution. Relevant information was recorded in hospital documents at the time of admission and delivery of the woman. Data was filled in the proforma for record.

Following maternal complication were noted:-

1. miscarriage, defined as loss of pregnancy before 24 weeks gestation.
2. Hypertensive disorder of pregnancy, including

α. Pregnancy induced hypertension defined as new onset of Systolic Blood pressure ≥140mmHg or Diastolic Blood pressure ≥90mmHg, 2 readings at 2 different occasions at least 6 hours apart after 20 weeks gestation in a previously normotensive woman.

β. Pre-elcampsia is defined as pregnancy induced hypertension with significant proteinuria++, ≥30mg/24hour excretion of albumin, Severe pre-elcampsia ≥300mg/24hr excretion of albumin

χ. Eclampsia is occurrence of fits with pre-eclampsia.

3. Placental Abruption defined as premature separation of a normally situated placenta .It present with vaginal bleeding anytime after 24 weeks and before delivery called Antepartum haemorrhage.
4. Preterm birth defined as delivery of the baby before 36^{+6} completed weeks of gestation.
5. Preterm pre- labour rupture of membranes (PPROM) defined as rupture of fetal membranes before 3^{6+6} completed weeks of gestation. It presents with watery vaginal discharge before 3^{6+6} weeks gestation.

Above mentioned data was entered and analyzed by SPSS version 25. Age of the women, parity and gestational age at presentation were presented as mean± SD. Maternal complications including miscarriage, hypertensive disorder of pregnancy including pregnancy induced Hypertension / pre-eclampsia/ eclampsia, placental abruption, preterm birth and preterm pre-labour rupture of membranes were expressed as frequencies and percentages. Chi square test X^2 used for comparison between groups of categorical data. Binary logistic regression analysis performed with age and parity and results expressed as OR with 95% confidence interval (CI). P-value ≤ 0.05 considered statistically significant.

RESULTS

92 women who presented with threatened miscarriage in first trimester were included in the study. Two patients were lost from follow up. Demographic variables of women i.e. age categories with mean age of women, various number of parity with mean parity and their gestational age at presentation with mean gestational age were shown in Table-I.

Age (Years)	**Mean± SD**
	29.20±3.49
	Frequency (n=90) (%)
21-25	11 (12.2%)
26-30	54 (60.0%)
31-35	23 (25.55%)
> 35	2 (2.22%)
Parity	**Mean± SD**
	2.65±1.15
	Frequency (n=90) (%)
1	18 (20.0%)
2	20 (22.22%)
3	30 (33.33%)
4	16 (17.77%)
5	6 (6.66%)
Gestational Age	**Mean± SD.**
	7.96±1.78
	Frequency (n=90) (%)
6-8	60 (66.66%)
8 – 10	22 (24.44%)
10 – 12	6 (6.66%)
>12	2 (2.22%)

Table-I. Demographics variables of the study

Frequency of various maternal complications in women included in the study were shown in Table-II.

Maternal Complications	Frequency (%)
Miscarriage	10/90 (11.1%)
Hypertensive disorder in pregnancy	34/80 (42.5%)
PIH	16/80 (20%)
Preeclampsia	18/80 (22.5%)
Placental Abruption	5/80 (6.3%)
Preterm Birth	21/80 (26.3%)
PPROM	5/80 (6.3%)

Table-II. Maternal complications in women with threatened miscarriage in first trimester

10/90 women (11.11%) had miscarriage. More than 60% miscarriages were in women who presented with threatened miscarriage at earlier age i.e. at 6-8 weeks gestation. Maternal age and parity had no significant association with miscarriage in these cases.

80/90(88.9%) women continued their pregnancy beyond 24 weeks gestation. Most common maternal complication was Hypertensive disorder of pregnancy recorded and managed in 34/80 (42.5%) women. 20% women had pregnancy induced hypertension and 22.5% had pre eclampsia. 4/80 (5%) cases had severe-pre-elcampsia. None of our patient suffered eclampsia, renal failure or maternal death. Data analysis revealed that women in the age group of 21-25 yrs were more at risk of development of hypertension in pregnancy. (p-value = 0.038) shown in Table-III.

Preterm birth was found in 21/80 (25.9%) women in our study. 17/21 (80%) of preterm births were after 35 weeks gestation. PPROM was seen in 5/80 (6.3%) cases. Placental abruption was found in 5/80 (6.3%) cases. Logistic regression analysis revealed that age and parity had no statistically significant association observed with preterm birth (p value =0.184) and placental abruption. (P-value =0.200). Preterm birth had significant association with hypertensive disorder of pregnancy (P-value=0.043) whereas placental abruption had no statistically significant association with hypertensive disorder. (P-value=0.157), shown in Table-IV.

There were some women who had more than one maternal complication. 13/80 (16.25%) women developed hypertensive disorder of pregnancy and delivered preterm. 4/80 (5%) cases were complicated by three maternal complications which include hypertensive disorder of pregnancy, placental abruption and preterm birth. 59/80 (73.8%) women included in the study delivered at term. About one third of term deliveries, 21/59 (35.5%.) had hypertensive disorder of pregnancy and 2/3rd term patients 37/59 (64.40%) did not develop any maternal complication during pregnancy.

Maternal Age (Years)	Hypertensive Disorder of Pregnancy		Total (n=80)	P-Value
	No (n=46)	Yes (n=34)		
21-25	3 (6.5%)	7 (20.6%)	10 (12.5%	0.038
26-30	30 (65.2%)	18 (52.9%)	48 (60.0%)	
31-35	12 (26.1%)	8 (23.5%)	20 (25.0%)	
> 35	1 (2.2%)	1 (2.9%)	2 (2.5%)	
Total	46 (100.0%)	34 (100.0%)	80 (100.0%)	

Table-III. Hypertensive disorder in pregnancy in various age groups.
***Chi-square test was applied to see the significance at P-value ≤ 0.05**

		Hypertensive Disorder in Pregnancy		Total (n=80)	P-Value
		No (n=46)	Yes (n=34)		
Placental Abruption	No Placental Abruption	45 (97.8%)	30 (88.2%)	75 (93.8%)	0.157**
	Placental Abruption	1 (2.2%)	4 (11.8%)	5 (6.3%)	
Preterm Birth	Term Birth	38 (82.6%)	21 (61.8%)	59 (73.8%)	0.043*
	Preterm Birth	8 (17.4%)	13 (38.2%)	21 (26.3%)	

Table-IV. Association of placental abruption and preterm birth with hypertensive disorder in pregnancy
***Chi-square test was applied to see the significance at P-value ≤ 0.05**
****Fischer exact test was applied to see the significance at P-value ≤ 0.05**

DISCUSSION

Development of hypertension during pregnancy put the life of mother at great risk and it was the third leading cause of maternal mortality.[6] Compared to pregnancy induced hypertension, pre-elcampsia was associated more with life threatening maternal complications including eclampsia, HELLP syndrome, cerebral haemorrhage, placental abruption and renal failure.[13] Under developed countries affected more by hypertensive disorder of pregnancy than developed ones. Highest frequency was found in south Asia, western sub Saharan Africa, Eastern sub-Saharan Africa whereas lowest frequency was observed in Australia and Europe.[6] The reason could be poverty, lack of health education, poor health services at peripheral areas, pregnancies at extremes of maternal age and genetic factor.

Commonest maternal complication in our study was hypertensive disorder of pregnancy found in 34/80 (42.5%) women. Frequency of pregnancy induced hypertension (20%)and pre-eclampia (22.5%) was almost same. 4/80 i.e. 5% of total cases had early onset of pre-elcampsia before 28wks gestation, later developed severe pre-elcampsia with marked urinary proteins and required high doses of anti hypertensives for blood pressure control. However, none of the case progressed to eclampsia possibaly due to early termination of pregnancy decided on clinical grounds. Incidence of hypertensive disorder of pregnancy with threatened miscarriage was 64% by Gunarathna et al in Sri Lanka where 56% had Gestational hypertension and 44% had pre eclampsia[10] In Lahore, 57%cases of hypertensive disorder of pregnancy were found in women with threatened miscarriage.[14] The reason of less number of hypertensive disorder of pregnancy in our study could be early booking and antenatal care provided.

Prevalence of preterm birth in Pakistan was 21.64% by Hanif A. et al[15] ≥ 2 times higher than USA (9.6%).[12] 21/80 i.e. 26.3% women among those who continued pregnancy delivered preterm in our study. Systemic review by Saraswat et al concluded that pregnancies complicated by threatened miscarriage had 1.5 -4.5 times increased risk of preterm birth than controls. Almost 3 times higher frequency of pretermbirth[12] found in our study was in accordance with Saraswat et al, Nwafor et al and weiss et al.[8,11,16] In a study on threatened miscarriage by Haleema et al preterm birth frequency was 17.1% that was lower than our results.[17] The discrepancy could be related to variation in other factors like difference in age, parity, social factors, co morbid, blood loss and sub chorionic haematomas in the two study groups.

Its evident that women who had threatened miscarriage were at high risk of preterm birth although majority (17/21) of preterm births were at ≥35 wks of gestation. Hypertensive disorder were found in 13 (38.09%), a highest contributor of preterm birth followed by PPROM in 5 (23%) cases. This was not in accordance with other studies, where PPROM was the main contributor of preterm birth.[8,11,16]

Another life threatening maternal complication observed was placental abruption which was seen in 5 (6.3%) cases. Placental abruption in peripheral areas of Sindh was found in 2.7% population with high maternal morbidity and perinatal mortality.[18] Higher incidence of hypertensive disorder, more grand multiparas, poverty, lack of health education could be the factors for its high prevalence in Pakistan. Increased frequency of placental abruption as found in our study was in accordance with the findings of Nwafor et al in Nigeria.[11] In our study, 4/34 i.e 11.76 % women with hypertensive disorder of pregnancy had placental abruption where as Saba et al found it in 29.4% cases of hypertensive disorder of pregnancy.[19] Lower frequency of placental abruption in our hypertensive patients could be due to differences in social and demographic variables of the two study groups and better antenatal care services provided to our patients.

Frequency of miscarriage in our study was 11.1%. Our results were in accordance with the results of czajkowski et al[7] and johns et al.[4] Contrary to Fawzy Ahmed who found 22% miscarriage rate[9], we had lower rate of miscarriage probably due to progesterone supplements and antenatal

support provided in early pregnancy. To prevent miscarriage, NICE recommended progesterone in cases of threatened miscarriage.[20] Oral Dydrogesterone or oral micronized progesterone 400mg in two divided doses lowered the rate of miscarriage, improved fetal circulation and was found safe(non teratotenic).[21,22,23]

To prevent hypertensive disorder of pregnancy and its squeal, women with threatened miscarriage need evaluation of risk factors for hypertension development and vigilant monitoring during pregnancy. History of chronic hypertension, chronic renal disease, auto-immune diseases in family, anti-phospholipid antibody syndrome, BMI 35kg/m^2, previous history of pre-eclampia were the indicators for the start of aspirin for prophylaxis of pre-eclampsia and its sequlae.[24] Low dose aspirin 100mg initiated before 16 weeks gestation to high risk women and oral calcium supplementation in low intake population provided better outcome (15% reduction in pre eclampsia). However, the role of rest, exercise, low salt intake, anti-oxidants, nitric oxide and diuretics to lower the risk of hypertensive disorder of pregnancy is not proved.[25]

Limitation of our study was that we have not correlated the hypertensive disorder of pregnancy with various risk factors of hypertension development in history like chronic hypertension, APLA syndrome, auto-immune diseases in family, shorter marriage to pregnancy interval, previous miscarriages etc. in these cases. Early initiation of prophylactic management based on the clinical risk assessment can reduce the burden of hypertensive disorder of pregnancy later.

Another limitation of our study was that we have not assessed the amount of blood loss light or heavy, single or repeated episodes and its impact on adverse feto-maternal outcome.

CONCLUSION

Women with threatened miscarriage in first trimester of pregnancy have high risk of miscarriage, hypertensive disorder of pregnancy, preterm birth and placental abruption. The commonest maternal complication was hypertensive disorder of pregnancy (42.5%) with almost equal frequency of pregnancy induced hypertension (20%) and pre-eclampsia (22.5%). Preterm birth had statistically significant association with hypertensive disorder of pregnancy. Early antenatal care, feto-maternal surveillance and vigilant monitoring is required to improve feto maternal outcome in these cases.

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2	Bushra Iftikhar	Data collection, Literature search.	
3	Mukhtiar Begum Noonari	Literature search.	
4	Farzana Nasir	Editing & Revision of manuscript.	
5	Nazia Hashim	Revision of manuscript.	
5	Sonia Naqvi	Study design & Ethical review.	