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Inter-Pregnancy Interval Effect on Preeclampsia Recurrence

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Introduction

Interpregnancy interval defined as the period between delivery of the previous infant and conception of the current pregnancy[1] has been shown to influence fetomaternal outcomes in many earlier studies.[2] Maternal compli cations associated with short interpregnancy interval include increased risk of operative deliveries, anaemia, uterine rupture, placenta abruptio, placenta praevia and puerperal sepsis[3] while fetal complications include intrauterine growth restriction, prematurity, low birthweight, and neonatal jaundice. Various direct and indirect factors that have been noted to contribute to high prevalence of short interpregnancy interval especially in developing countries include desires for male child due to certain cultural recognition like land allocation and the belief that it is only the male child that immortalizes the family lineage. Other factors that contribute to SIPI include poor educational background, poverty, advance maternal age and poor utilization of family planning services.[4]

Pre-eclampsia (PE) is a multisystem disorder that typically affects 2%–5% of pregnant women and is one of the leading causes of maternal and perinatal morbidity and mortality, especially when the condition is of early onset.[5] Preeclampsia and eclampsia account for greater than 50,000 maternal deaths yearly worldwide. Like hypertensive disorders, the incidence of preeclampsia is correlated to ethnicity and race, most prevalent among African-American and Hispanic patients, making up around 26% of maternal death among this population.[6]

There are several risk factors and predeterminants of preeclampsia. These include nulliparity, multi-gestation pregnancy, advanced maternal age greater than 35 years old, in-vitro fertilization or other forms of assisted reproductive technology, maternal comorbidities (chronic hypertension, chronic kidney disease, diabetes mellitus, thrombophilia, obstructive sleep apnea, obesity with pre-pregnancy BMI greater than 30), family history, history of placental abruption or preeclampsia in a previous pregnancy, or intrauterine fetal growth restriction.[6,7,8] Women with a history of pre-eclampsia have a higher risk of developing pre-eclampsia in subsequent pregnancies.[9–11] This risk of recurrent pre-eclampsia varies from 7 to 65 % depending on factors such as gestational age at the onset or delivery of the initial pregnancy, severity of the disease and women's pre-existing medical disorders.[11] The relationship between birth interval and maternal and perinatal outcomes has been studied extensively.[12,13] Short inter-pregnancy intervals (< 18 months) may be associated with adverse pregnancy outcomes due to depletion of maternal nutrients and to the failure to treat existing comorbidities.[14,15] Whereas longer inter-pregnancy intervals might allow more complete recovery of the mother, they are associated with reduced fertility, older age, maternal disorders and partner change that

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are also linked with higher risk of pre-eclampsia.[16] This study was conducted to explore the effect of inter-pregnancy interval on the risk of recurrent preeclampsia or eclampsia.

Material and Methods:

Study design and participants: This is a observational prospective study to know the effect of inter-pregnancy interval on recurrence of preeclampsia and eclampsia conducted in the department of Obstetrics and Gynecology at a tertiary health centre. Study period was from first of March 2018 to 31st of january 2022. Patients admitted in Labor room emergency with second pregnancy onwards and history of preeclampsia in previous pregnancy were included in the study. The sample size was calculated from the formula $n=Z^2 P(1-2 P)/d^2$ using the prevalence of preeclampsia from a previous study[17] making total number of cases > 800 during the study period.

Data sources and management: All the records of patients included in the study were reviewed. Primi patients, patients with no prior history of preeclampsia, patients with gestational age < 20 weeks, cases with incomplete records and other co-morbidities like diabetes, immunocompromised health, heart disease and other severe medical illness were excluded from the study.

Definitions and Measurements: WHO technical report recommendation of normal interpregnancy interval (NIPI) of 24 months and short interpregnancy interval (SIPI) of less than 24 months was used in this study.

The study adopted the definition of Preeclampsia as proposed by the International Society for the Study of Hypertension in Pregnancy (ISSHP). According to the ISSHP, Preeclampsia is defined as systolic blood pressure at ≥140 mm Hg and/or diastolic blood pressure at ≥90 mm Hg on at least two occasions measured 4 hours apart in previously normotensive women and is accompanied by one or more of the following new-onset conditions at or after 20 weeks of gestation: 1. Proteinuria (i.e. ≥30 mg/mol protein : creatinine ratio; ≥300 mg/24 hour; or ≥2 + dipstick); 2. Evidence of other maternal organ dysfunction, including: acute kidney injury (creatinine ≥90 μmol/L; 1 mg/dL); liver involvement (elevated transaminases, e.g. alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain; neurological complications (e.g. eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata); or hematological complications (thrombocytopenia–platelet count <150 000/μL, disseminated intravascular coagulation, hemolysis); or 3. Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth). Eclampsia was diagnosed as the presence of new-onset grand- mal seizures in women with preeclampsia.

Data analysis: Data were analyzed using SPSS statistical package version 22, (IBM Corp, Armonk, NY).

Statistic tests used were Chi-square and ODDs Ratio.

Results:

Overall number of total admissions during the study was 34,215 while cases with pregnancy > 20 weeks were 33,205. Primi cases were 55% (18,263/33205), Multipara cases 45% (14942/33205) and total number of cases with preeclampsia and eclampsia were 5.59% (1859/33205). 46.4% (855/1859) of preeclampsia cases were multigravida while 54% (1004/1859) were primigravida. Multigravida preeclampsia cases constituted by Multigravida with history of preeclampsia in prior pregnancy as 86% (735/855) and with normotensive prior pregnancy as 14%(120/855).

Table 1: Showing Multigravida Cases and Incidence of preeclampsia in current pregnancy (chi-square statistic is 2431.5, p<0.00001)

Group	Number of Cases [N]	Incidence of Preeclampsia
Multigravida with history of preeclampsia in prior pregnancy	(16.4%) 2450/14942	30% (735/2450)
Multigravida with normotensive prior pregnancy	(83.6%) 12492/14942	1% (120/12492)

Table 2: Showing recurrence of Gestational Vascular Complications (60%) [1470/2450] in Multigravida Cases with history of preeclampsia in prior pregnancy

Preeclampsia	50% [735/1470]
Gestational hypertension	35% [515/1470]
Abruptio placentae	3% [44/1470]
HELLP syndrome	8% [118/1470]
Others	4% [58/1470]

Table 3: Showing Risk of Recurrence of preeclampsia by Interpregnancy interval in multigravida with history of preeclampsia in prior pregnancy

Inter-Pregnancy Interval	N= no. of cases	Recurrence of Preeclampsia
<24 months	527	28% [150/527]
2 to 3 years	1012	29% [300/1012]
3 to 5 years	585	31% [181/585]
5 to 6 years	208	32% [66/208]
>6 years	118	32% [38/118]

Odds Ratio for Risk of Recurrence of Preeclampsia with Inter-pregnancy interval >24 months compared to short interval was 1.0989 (95%CI 0.8883 to 1.3593).

Table 4: Age wise distribution in each interpregnancy interval within multigravida cases with history of preeclampsia in previous pregnancy

Inter-Pregnancy Interval	N= total no. of cases (2450)	>18-21 years	21-30 years	30-35 years	>35 years
<24 months	527	301/527 [57%]	163/527 [31%]	42/527 [8%]	21/527 [4%]
2 to 3 years	1012	142/1012 [14%]	600/1012 [59%]	245/1012 [24%]	25/1012 [2.5%]
3 to 5 years	585	81/585 [14%]	251/585 [43%]	203/585 [35%]	50/585 [8.5%]
5 to 6 years	208	19/208 [9.1%]	42/208 [20%]	129/208 [62%]	18/208 [9%]
>6 years	118	-	10/118 [8%]	20/118 [17%]	88/118 [75%]

Discussion:

In this study we found the prevalence of preeclampsia 5.9% similar to the previous study done in Indian setting.[17] Preeclampsia is primarily regarded as a disease of first pregnancy. In our study, 54% were primigravidas and 46.4 % were multigravidas. Several other authors have reported primiparity in 52-73% patients of preeclampsia. In our study, both primigravida and multigravida were equally affected with eclampsia. But literature indicates that eclampsia is a disease of primigravida. According to Hellman incidence of eclampsia in primigravida and multigravida was in the proportion of 3:1.[18]

The incidence of preeclampsia was much higher in multigravida group with history of preeclampsia in previous pregnancy (30%) than with the normotensive history group (1%) p<0.00001. This finding was slightly different from one of the previous study[8] but it gives robust finding that preeclampsia in previous pregnancies are important risk factor for recurrence of preeclampsia in subsequent pregnancy very similar to one of the previous survey.[19]

Of all the recurrence of gestational vascular complications, Preeclampsia contributed 50%, Gestational hypertension 35%, abruptio placentae 3% and HELLP syndrome 8% similar to the findings of the french study.[20]

Hernandez-Díaz et al. included a cohort of pregnancies from the first antenatal visit (usually at 8 to 12 weeks'gestation) with diagnosis of pre-eclampsia or eclampsia and a subsequent pregnancy between January 1987 and December 2004.[21] The study reports a 14.7 % risk of recurrent pre-eclampsia. For those women with a history of pre-eclampsia in the first pregnancy the risk of recurrence was 13.1 % if they became pregnant within 2 years and 15.8 % if the next pregnancy was after 8 years or later. But in our study overall risk of recurrence was 30%, for short inter-pregnancy interval (<24 months) 28% and 32% for inter-pregnancy interval >6 years, different results can be attributed to different population composition, literacy rate and socioeconomic status.

Age has an important influence on the incidence of hypertensive disorders of pregnancy. In our study highest incidence of the hypertensive disorders occurred among those aged 18 to 22 years and also this was the largest age group in short (<24 months) inter-pregnancy interval. This could be because the majority of conceptions take place in this age group in our country. In our study majority of preeclampsia patients were between the ages of 18 to 22 years. This may have confounding effect on the study.

In our study there was no significant increased risk of recurrence of preeclampsia due to difference in inter-pregnancy interval as suggested by Odds Ratio (for Risk of Recurrence of Preeclampsia with Inter-pregnancy interval >24 months) 1.0989 (95%CI 0.8883 to 1.3593) which was similar to previous studies.[22,23] However there was slight increased risk in larger inter-pregnancy interval >6 years.

In addition, even though among the risk factors for recurrent pre-eclampsia, inter-pregnancy interval may be regarded as a minor contributor, it is nonetheless, together with weight control, a modifiable factor through which to intervene before conception.

Conclusion:

Patients with a history of preeclampsia or HELLP syndrome during the index pregnancy are at increased risk for obstetric complications in subsequent pregnancies.

The recurrence of an obstetric vascular accident is experienced with fear by the practitioner and the patient. Our study aimed to highlight predictive factors of recurrence.

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