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ORIGINAL ARTICLE

Frequency of Pre-Eclampsia in Obese pregnant Females taking Metformin During Pregnancy

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ABSTRACT

Background: It has been shown that obesity takes its roots in the womb. Maternal obesity has an association with macrosomia and the risk of obesity late in life.Obese women who have weight loss before pregnancy may have better pregnancy outcomes if excessive weight gain is avoided during pregnancy.
Aim: To determine the frequency of pre-eclampsia in obese pregnant females taking metformin during pregnancy.
Methods: It was a Descriptive case series conducted at Unit 1, Department of Obstetrics & Gynecology, Lady Willingdon Hospital, and Lahore from 16-11-21 to 16-5-2022. Non-probability, consecutive sampling was done.165 females fulfilling the selection criteria were included in the study. Informed consent in written form was obtained. If BP was 140/90mmHg, a urine sample was obtained and proteinuria was detected by dipstick method. If proteinuria was present with high blood pressure, then pre-eclampsia was labeled (as per the operational definition). All patients were followed till delivery.Proformas were used for collecting data which was analyzed statistically using SPSS version 20.
Results: Participants had a mean age of 28.73±6.71 years, 53(24.65%) females were nulliparous. The mean gestational age of the females was 29.91±5.86 weeks.
The mean BMI of the females was 33.12±1.75 kg/m^2. In our study, preeclampsia was found in 18(8.37%) obese pregnant females using metformin.
Practical implications the correction of diabetes would help in the prevention of preeclampsia in our population.
Conclusion: According to this study approximately one-tenth (8.4%) of obese females developed preeclampsia taking metformin during pregnancy.
Keywords: Metformin, Pregnancy, Obese, and Preeclampsia, nulliparous, macrosomia

INTRODUCTION

A very commonly encountered problem, obesity has its originbefore birth. There is evidence of a correlation between maternal obesity, macrosomia, andthe risk of having obeseoffspring later on. Obesewomen duringpregnancy have agreater risk of adverse outcomes, including gestational diabetes and stillbirth. The exact way this is caused is not yet known,although hyperglycemia and resistance to insulinare considered to be strong culprits[1].

The idea that metformin administered during pregnancy can decrease birth weight in high-risk, obese pregnant women is one of the considerations. Others suggestedmetformin benefited mothers. Pregnant females who used metformin had significantly reducedmarkers like C-reactive protein and interleukin 6, which lead to hypertension in pregnancy[2].

Metformin is responsible for maternal and neonatal weight gain in gestational diabetes mellitus but, this effect remains unclear in non-diabetic women[3]. Metformin belongs to a biguanide class and is taken orally. Itenhances tissue insulin sensitivity and inhibits hepatic gluconeogenesis without affecting normal glucose levels[4].

One study reported that in obese females taking metformin for weight control, preeclampsia also developed in a negligible number of females i.e. 3.0%.[5]In another study, obese females taking metformin for weight control, preeclampsia developed in 3% of females.[6] While a different study showed that the prevalence ofpreeclampsia was 7.4% in the metformin group,[7]one more study showed a double rate of preeclampsia with metformin i.e. 13.9%[8].
The rationale for doing this research is to study the frequency of pre-eclampsia in obese pregnant females taking metformin during pregnancy. Literature has shown conflicting evidence regarding the relationship of metformin with pre-eclampsia in obese pregnant. This creates a dispute about whether to alter the dosage of metformin in obese pregnant females or add some other medicines to avert preeclampsia. Moreover, no local data is available in this regard. So we want to conduct this study in a search for the local data and in the future, we will be in a position to recommend metformin alone in obese pregnant females. This will help to improve our practice as well as the local guidelines for use of metformin during pregnancy.

The objective of the study was to determine the frequency of pre-eclampsia in obese pregnant females taking metformin during pregnancy.

Operational Definitions:
Obesity: It is defined as BMI>30kg/m^{2}before pregnancy or during the first three months of pregnancy.
Preeclampsia: Moreover, some reports indicated that an elevated BMI elevates the risk of pre-eclampsia

MATERIALS AND METHODS

It was a case seriesconducted at Unit 1, Department of Obstetrics & Gynecology, Lady Willingdon Hospital, and Lahore from 16-11-21 to 16-5-2022.The sample size for this study was 215 which was calculated with a level of confidence at 95%, and a 3.5% margin of error taking the expected percentage of preeclampsia i.e. 7.4% in obese pregnant females taking metformin.[7]Non probability, consecutive sampling wasdone**.** Females of age 18-40 years, parity<5, presenting at gestational age > 20 weeks (on LMP) taking metformin during pregnancy due to pre-pregnancy obesity (as per Operational definition) were included in the study. Females with PT>20sec, APTT>15sec, INR>2, Females with polycystic ovarian syndrome (on medical record),Females with anemia (Hb<10g/dl), TSH>5 IU/m and those withthe abnormal placenta (increta, percreta, previa, accrete, or abruption assessed on ultrasound) were excluded from the study.

165 females who met the selection criteria were included through OPD of the Department of Obstetrics & Gynecology, Lady Willingdon Hospital, Lahore. Informed written consent was obtained before including females in the study. Demographic profile (name, age, BMI, parity, gestational age, **dose,** and duration of taking metformin) was noted at each follow-up visit, then blood pressure was noted by using a sphygmomanometer. If BP was 140/90mmHg, a urine sample was obtained in a sterile container and proteinuria was detected by dipstick method. If proteinuria was present with high blood pressure, then preeclampsia was labeled (as per the operational definition). All patients were followed till delivery. Pre-eclamptic patients were

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managed according to hospital policy. All this information was recorded on proforma;

The collected data was entered and analyzed statistically by using SPSS version 20. Quantitative variables like age, gestational age, BMI, and duration of metformin use were presented in form of mean+S.D. Qualitative variables like preeclampsia werepresented in frequencies and percentages. Frequency was calculated for parity. Data was divided into strata basedon age, gestational age, parity, duration of metformin use, and BMI. Post-stratification, the chi-square test wasutilized to compare preeclampsia in stratified groups considering a p-value of less than 0.05 as significant.

RESULTS

The mean age of the females was 28.73±6.71 years (Table 1). Among 215 females, there were 53(24.65%) females were nulliparous, 61(28.37%) females had parity 1, 54(25.12%) females had parity 2, 34(15.81%) females had parity 3, and 13(6.05%) females had parity 4 (Fig 1). The mean gestational age of the females was 29.91±5.86 weeks (Table 2). The mean BMI of the females was 33.12±1.75 kg/m^2 (Table 3). The mean duration of metformin use was 4.18±1.802 months (Table 4). In our study, the mean diastolic BP of the females was 85.17±4.70 mmHg and the mean systolic BP of the females was 128.22±7.33 mmHg.(Table 5). In our study, the mean proteinuria value of the females was 0.77±0.24 mg/dl with minimum and maxim proteinuria values of 0.30 & 1.30 mg/dl respectively (Table 6). The study results showed that preeclampsia was found in 18(8.37%) obese pregnant females using metformin (Fig. 2).)According to this study among patients aged ≤30 years preeclampsia was noted in 11(8.9%) patients while in patients having an age >30 years preeclampsia was noted in 7(7.7%) patients (p-value=0.758). Similarly in nulliparous & primary parity patients,preeclampsia was noted in 9(7.9%) patients while in multiparty patients preeclampsia was noted in 9(8.9%) patients (p-value=0.788) (Table 7). According to this study among patients having gestational age ≤30 weeks preeclampsia was noted in 10(8.5%) patients while in patients having gestational age >30 weeks preeclampsia was noted in 8(8.2%) patients (p-value=0.919). Similarly in patients having BMI ≤33 kg/m^2 preeclampsia was noted in 11(10.5%) patients while in patients having BMI >33 Kg/m^2 preeclampsia was noted in 7(6.4%) patients (p-value=0.276) (Table 8). In this study in patients duration of use of metformin ≤4 months preeclampsia was noted in 13(9.5%) patients while in patients having a duration of metformin >4 months the preeclampsia was noted in 5(6.4%) patients (p-value=0.433) (Table 9).

Table 1: Summary statistics of age (years)

Age (years)	n	215
	Mean	28.73
	Std. Deviation	6.71
	Minimum	18
	Maximum	40

Fig 1: Frequency distribution of parity

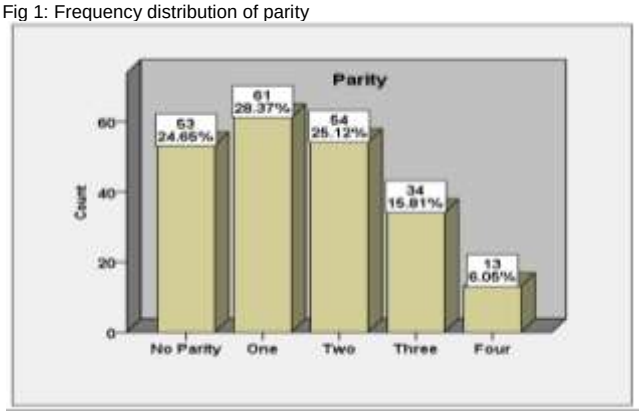

Table 2: Summary statistics of the age of gestation (weeks)

Gestational age (weeks)	n	215
	Mean	29.91
	Std. Deviation	5.86
	Minimum	21
	Maximum	40

Table 3: Summary statistics of BMI (kg/m^2)

BMI (kg/m^2)	n	215
	Mean	33.12
	Std. Deviation	1.75
	Minimum	30.01
	Maximum	35.94

Table 4: Summary statistics of duration of metformin use (months)

Duration of metformin use (months)	n	215
	Mean	4.18
	Std. Deviation	1.802
	Minimum	1
	Maximum	8

Table 5: Summary statistics of blood pressure (mmHg)

		Diastolic	**Systolic**
Blood Pressure (mmHg)	n	215	215
	Mean	85.17	128.22
	Std. Deviation	4.70	7.33
	Minimum	80	120
	Maximum	100	150

Table 6: Summary statistics of proteinuria

Proteinuria (mg/dl)	n	215
	Mean	0.77
	Std. Deviation	0.24
	Minimum	0.30
	Maximum	1.30

Fig 2: Distribution frequency of preeclampsia

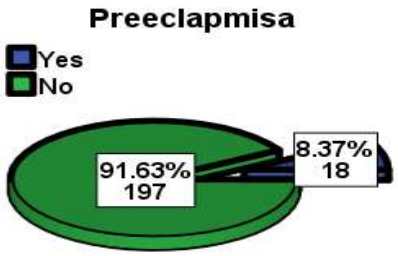

Table 7: Comparison of preeclampsia between age and parity

		Preeclampsia		**Total**	**P-value**
		Yes	**No**		
Age (years)	≤30	11	113	124	0.758
		8.9%	91.1%	100.0%	
	>30	7	84	91	
		7.7%	92.3%	100.0%	
Parity	Null & primary	9	105	114	0.788
		7.9%	92.1%	100.0%	
	Multiple	9	92	101	
		8.9%	91.1%	100.0%	

Table 8: Comparison of preeclampsia between gestational age and BMI

		Preeclampsia		**Total**	**p-value**
		Yes	**No**		
Gestational age (weeks)	≤30	10(8.5%)	107(91.5%)	117(100%)	0.919
	>30	8(8.2%)	90(91.8%)	98(100%)	
BMI	≤33	11(10.5%)	94(89/5%)	105(100%)	0.276
	>33	7(6.4%)	103(93.6%)	110(100%)	

Table 9: Comparison of preeclampsia between duration of metformin use

Duration of metformin use	Preeclampsia		Total	p-value
	Yes	No		
≤4	13(9.5%)	124(90.5%)	137(100%)	0.433
>4	5(6.4%)	73(93.6%)	78(100%)	
Total	18(8.4%)	197(91.6%)	215(100%)	

DISCUSSION

Obesity is a nutritional and metabolic lifelong hazard, and it isan important public health problem. It has repercussionsfor the well-being of both mother and child in the case of a pregnant female. Traditionally considered a problem infirst-world countries, maternal obesity has received greater attention in 2nd and 3rd world countries in recent years. Metformin has been used substantiallyto treat gestational diabetes mellitus, and there has been no evidence of an increase in incidence of birth defects associated with its use[9-11].

In our study, the frequency of pre-eclampsia in obese pregnant females taking metformin during pregnancy was 8.4%. In a screening study involving 120,492 primigravida females,in one study population, the incidence of preeclampsia was 2.2%, and in the subgroup of 7152 women (5.9%) with a BMI over 35, the incidence was 5.5%[12].

Another study showed that Preeclampsia prevalence was 7.4% in those using metformin.[7] One more study showed a double rate of preeclampsia with metformin i.e. 13.9%[8.]

Different studies came up with the results that women with T2DM have high rates of maternal morbidity, including gestational hypertension and preeclampsia (17–19%)[13-16]. Moreover, some reports indicated that a raisedBMI multiplies the risk of pre-eclampsia, and obesity is a crucial risk factor for preeclampsia[17-18]. One study reported that in obese females taking metformin for weight control, preeclampsia also developed in a negligible number of females i.e. 3%.[5] Inanother study, 3% of obese females who took metformin for weight control, developed pre-eclampsia[6.]

A study by Argyro Syngelaki et al[19] resulted in their findings that the median weight gain in women during pregnancy was lower in those taking metformin(4.6 kg [interquartile range, 1.3 to 7.2], p<0.01) than those who took the placebo 6.3 (kg [interquartile range, 2.9 to 9.2], p<0.01), as was the incidence of preeclampsia (3% compared to 11.3%; odds ratio, 0.24; 95% confidence level, 0.10 to 0.61; P=0.001).

A study by Charles J Glueck et al[20]documented in their findings thatin pregnancy Metformin has no association with pre-eclampsia in those women who also havethe polycystic ovarian syndrome, and appears to cause no harmtothe mother and fetus. Some systematic reviews revealed a direct relationship between pre-eclampsia and obesity showing that obese women are 10 times more prone to develop it[21.]

Women who had BMI above 35 kg/m2 and gave birth beyond 24 weeks gestationhad a prevalence of 5%. Among those, 2% were class III obese and 0.2% weresuper-morbid obese. An increase in the incidence of gestational hypertension, pre-eclampsia, and severe eclampsia was found in women with higher BMI categories[22].

With an increase of 3 kg/m^2 in BMI, the risk of pregnancy-induced hypertension (relative risk 2.24) and pre-eclampsia (relative risk 1.64) increases[23].

On the contrary, one trial involving 40 women who received metformin at a dose of 1.7 g per day or inert pills showed that metformin did not alter neonatal birth weight or the incidence of preeclampsia or maternal gestational diabetes mellitus.[24]

CONCLUSION

According to this study approximate one-tenth (8.4%) of the obese females taking Metformin developed preeclampsia during pregnancy

Conflict of interest: Nil

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