The Effects of Pre-Pregnancy Body Mass Index and Gestational Weight Gain on the Risk of Preeclampsia at a Tertiary Referral Hospital, Northern Tanzania

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Abstract

Background: Pre/eclampsia and other hypertensive disorders of pregnancy contributed to 18% of the maternal mortality reported in Northern Tanzanian. There is increasing prevalence of obesity in Tanzania which is related to excessive weight gain in pregnancy. Both high BMI and excessive gestation weight gain are identified to increase risk of PE and subtypes, however this is still inconclusive and little is known about the joint effect of pre-pregnancy BMI and GWG on risk of PE and its subtypes in Africa.

We evaluated the independent and joint effects of pre-pregnancy BMI and GWG on the risk of pre-eclampsia and its subtypes among women who delivered at Kilimanjaro Christian Medical Center (KCMC) from October 2018 to May 2019, Northern Tanzania.

Methods: We performed a retrospective birth cohort study from October 2018 to May 2019 at KCMC, Tanzania. Pre-pregnancy BMI was categorized using WHO categories into Underweight (18.5kg/m²), Normal weight (18.5-24.9kg/m²), Overweight (25-29.9kg/m²) and Obese (≥ 30kg/m²). Gestational Weight Gain (GWG) was categorized using the 2009 Institute of Medicine (IOM) guidelines into Inadequate, Adequate and Excessive weight gain in pregnancy. Multinomial logistic regression analysis was used to adjust for confounders using relative risk, 95% confidence interval for the risk ratios (RR) that did not cross 1 and $p<0.05$ were regarded statistically significant.

Results: Among the 1309 women analysed, 5.3% were Underweight, 51.1% Normal weight, 26.9% Overweight and 16.7% were Obese. About 43.5% had excessive GWG. Women with PE were 9.5%. Both obesity and excessive GWG independently increased risk of PE with adjusted RR=2.42, 95%CI: 1.48-3.96 and RR=1.77, 95%CI: 1.16-2.69 when compared to normal BMI and adequate GWG respectively. Jointly, Obesity and Excessive GWG had the highest risk of PE (ARR=4.95, 95%CI: 2.21-11.10). The increased risk was similar for Mild PE (MPE), Severe PE or eclampsia (SP/E) and Late Onset PE (LOPE). No association was found for Early Onset PE (EOPE).

Conclusion: Pre-pregnancy Obesity and Excessive GWG independently and jointly increases risk for PE and the risk varies by PE subtype.

Background

Preeclampsia (PE) is a serious and life-threatening complication of pregnancy which is characterized by a new onset hypertension and either proteinuria or end organ damage occurring after 20 weeks of gestation. Eclampsia (E) is the development of convulsions in a woman with PE. This pregnancy syndrome is associated with a large burden of maternal and foetal morbidity and mortality with substantial contributions to prematurity of the foetus and long term maternal cardiovascular and renal disease (1). Preeclampsia (PE) is estimated to affect 2–10% of pregnancies worldwide (2). PE and eclampsia are estimated to cause over 50,000 annual maternal deaths globally (3). At a tertiary hospital in Northern Tanzania, PE and other hypertensive disorders of pregnancy contributed to 18% of maternal deaths. (4). After obstetric haemorrhage, PE is the second leading cause of pregnancy related intensive care unit admissions (5). In many African countries, it continues to be a major public health challenge being a leading cause of prematurity and foetal growth restriction. It has a perinatal mortality rate five times higher than that among babies born to healthy mothers (6).

There is wide geographic and regional variation in the incidence of PE with the USA reporting an estimated incidence of 5.9% (1). The World Health Organization (WHO) estimates the incidence of PE to be seven times

higher in developing countries (2.8% of live births) than in developed countries (0.4% of live births), with Africa reporting ranges from 1.8%-16.7%. Nigeria reported the highest incidence at 16.7% (2). The incidence rates from other African countries such as South Africa, Egypt, Tanzania and Ethiopia vary from 1.8% -7.1% (2). The incidence for Tanzania was reported at 1.7% (7).

Women with PE in one pregnancy have a substantially increased risk of recurrence in subsequent pregnancies with an absolute recurrence risk of 25% reported in Northern Tanzania (8).The underlying pathogenesis of PE remains unclear. However it is characterized by defective placentation, placental ischaemia, abnormal spiral artery remodeling and oxidative stress at the maternal foetal interface. Other factors include angiogenic imbalance in the maternal circulation with resultant endothelial and end - organ damage (9). The disease can be understood in terms of both placental and maternal dysfunctions. Several studies have suggested PE as a heterogeneous disease with two stages, namely, Early Onset or placental disease (EOPE) and Late Onset or maternal disease (LOPE) with different epidemiology, clinical presentation and associated morbidity (10).

Early Onset Preeclampsia (EOPE) occurs before 34 weeks of gestation and it involves abnormal placentation with shallow trophoblastic invasion, insufficient spiral artery remodeling leading to reduced placental perfusion. It is associated with increased risk for intrauterine growth restriction and a 3–25 fold increased risk of severe maternal complications. These include abruptio placenta, disseminated intravascular coagulation, pulmonary oedema and aspiration pneumonia (1, 6, 11) and a 20 fold higher risk of maternal mortality (6).

Late Onset PE or maternal disease occurs at or after 34 weeks of gestation and it involves maternal systemic inflammation and oxidative stress which results in vascular endothelial dysfunction leading to multi organ failure. It is frequently associated with maternal obesity, larger placental volume, normal foetal growth, normal birth weight and more favorable maternal and neonatal outcomes.

Preeclampsia (PE) is also subcategorized into severe (SP/E) and mild (MPE) disease. Severe P/E has a blood pressure ≥ 160/90 mmHg with or without proteinuria, and or evidence of end organ damage, such as thrombocytopenia, impaired liver function with persistent severe right upper quadrant pain or epigastric pain. Others are new onset renal failure, pulmonary oedema or new onset cerebral or visual disturbances. Mild PE has a blood pressure 140/90 ≥ BP 160/110 mmHg, and no features of severe disease (12).

A wide range of factors are associated with PE such as parity, placental factors, multifoetal gestation and excessive weight gain during pregnancy. Others are some pre-pregnancy maternal factors like age, race, pre-pregnancy overweight and obesity, diabetes mellitus and chronic hypertension (6).

Pre-pregnancy Body Mass Index (BMI) and gestational weight gain (GWG) are two modifiable risk factors implicated in the development of PE. Obese women who become pregnant and their foetuses are predisposed to various adverse pregnancy related complications. Infants and later adults of obese mothers have correspondingly increased rates of morbidity, mortality and obesity (13). In Tanzania, the prevalence of obesity among women of reproductive age has increased progressively from 6% in 2010 to 10% in 2015 (14) with Kilimanjaro region reporting an increase in obesity from 10.8% in 2010 to 19.7% in 2015 (14).

The association between GWG and the risk of PE is still inconclusive with some studies reporting a positive association (6) while others found no association (15).

Studies which evaluated the association between BMI, GWG and the risk of PE by different subtypes in low resource settings like ours are limited. More so, there are very few studies investigating the joint effect of pre-pregnancy BMI and GWG on risk of PE and its subtypes.

The current study therefore, aimed to evaluate the independent association of pre-pregnancy BMI, GWG and their combined effect on the risk of developing PE and its subtypes in a low resource setting.

Methods

Study design, setting and period

We conducted a hospital based retrospective cohort study from October 2018 to May 2019 at Kilimanjaro Christian Medical Centre (KCMC), a zonal referral hospital in Northern Tanzania located in Moshi urban district. The hospital caters for about 15 million people and it has over 3,000 deliveries annually. It also receives patients from the surrounding districts in the northern zone including Kilimanjaro, Tanga, Arusha, Manyara and neighboring districts of Kenya. Obstetric assessments, vital signs check, weight measurements at booking and every Antenatal clinic (ANC) visit thereafter, height measurement at booking, screening for pregnancy complications, health education on nutrition and pregnancy danger signs, counseling and testing for HIV are done regularly.

Study population and eligibility

Eligible study participants were all women who delivered at KCMC between October 2018 and May 2019 at gestational age ≥ 28 weeks. All women with history of chronic hypertension, multiple pregnancies, first ANC visit gestational age ≥ 20 weeks, missing information on the following, blood pressure measurements,, proteinuria, admission weight, first ANC visit weight (kg) and height (m) measurements were excluded from the study.

Data collection procedure

The hospital registration numbers from the birth register book were used to trace patient admission files and antenatal clinic records from medical records or post-natal ward. Patient files were then reviewed and all important variables were obtained. These variables were socio-demographic data, anthropometric measurements of the mother, conditions, diseases and complications during the current pregnancy, maternal obstetric history, and medical history of the mother. WHO BMI guidelines were used to categorize participants' BMI into Underweight (18.5), Normal weight (18.5–24.9), Overweight (25.0-29.9) and Obese (≥ 30) categories (16). Pre-pregnancy BMI for this study was calculated using the first ANC visit weight (kg) divided by the square of height (m^2) when the gestational age recorded in the ANC record at first visit was ≤ 20 weeks (The last normal menstrual period was used to calculate the gestational age at first ANC visit). The pre-pregnancy weight (kg) was the recorded ANC weight at first visit when the gestational age was ≤ 20 weeks.

The 2009 Institute of Medicine (IOM) recommendations for gestational weight gain were used to categorize GWG into Adequate, Inadequate and Excessive categories based on the respective BMI categories (17). Gestational Weight Gain was calculated by subtracting the pre-pregnancy weight (kg) from the weight (kg) at delivery. The ranges for underweight, normal weight, Overweight and obese were 12.5–18.0 kg, 11.5–16.0 kg, 7.0-11.5 kg and

5.0-9.1 kg respectively. BMI and GWG with their respective categories were the main independent variables in this study. PE and its subtypes were the outcome of interest in this study.

A total of 2,305 deliveries were recorded in the delivery book between October 2018 and May 2019. There were 34 missing patient files that could not be traced. The remaining 2,271 patient files were therefore reviewed. Of these, 962 patient files were excluded due to exclusion criteria (619 lacking records for BMI, blood pressure and proteinuria; 58 history of chronic hypertension; 65 multiple pregnancies and 220 files due to having the gestational age at first booking recorded in the antenatal record more than 20 weeks of gestation). We ended up with 1,309 singleton deliveries for final analysis. A total of 125 PE/E participants with their respective BMIs and GWG and 1,184 with no PE/E participants with their respective BMIs and GWG were analyzed (Fig. 1). The 125 PE participants were sub categorized into MPE (45), SPE (80), EOPE (34) and LOPE (91) subtypes (Fig. 1).

Pre-eclampsia was identified as BP ≥ 140/90 mmHg measured on two separate occasions at least four hours apart with ≥ 1 + proteinuria on dipstix occurring after 20 weeks of gestation. Mild preeclampsia was identified when BP ≥ 140/90 mmHg and < 160/110 mmHg, proteinuria (≥ 1 + and < 2 + on dipstix) without symptoms of severity. Severe pre/eclampsia was identified as BP ≥ 160/110 mmHg and proteinuria (≥ 2 + on dipstix) with additional symptoms of severity i.e. headache, blurred vision, epigastric pain, decreased urine output and convulsions. Early onset preeclampsia (EOPE) was identified with onset of PE before 34 weeks of gestation and late onset preeclampsia (LOPE) was identified with onset of PE at 34 weeks or more of gestation. PE and subtypes where the outcome variables in the study.

Data analysis

Data was analyzed using Stata Version 13.0 after adequate data cleaning process. Numerical data was summarized using mean and standard deviations while categorical variables were summarized using frequency and proportions. Chi-square and Fisher's tests were used to compare the maternal characteristics by BMI categories and PE with their corresponding p-values. P value < 0.05 was regarded as statistically significant. Multinomial logistic regression analysis was employed to compute risk ratios (RR) for PE and its subtypes by BMI and GWG. Both crude and adjusted RR was employed to identify significant association between exposures and the outcome of interest (PE and its subtypes). All noted risk factors for PE in this study were adjusted to control possible confounders and effect modifiers. 95% confidence interval was used to identify the significant risk of PE and its subtypes. Further analysis was done for the joint effects of BMI and GWG on the risk of PE and subtype. Adjusted RR for PE and its subtypes and the probability for interactions between BMI and GWG was estimated using test of homogeneity. The findings of the study were presented using tables and figure.

Results

Out of the 1,309 singleton birth deliveries analyzed, the majority of participants were in the age group 20–34 years (80.2%), with a mean age of 28.3 years and standard deviation of 5.6 years. The ages ranged from 15 to 47 years old. The median gestation age at first ANC visit was 15 weeks with Inter-quartile range (IQR) of 12 to 17 weeks. The mean pre-pregnancy BMI was 25.5 kg/m² with a standard deviation of 4.6 kg/m^2. Underweight women were 5.3%, normal weight women 51.1%, overweight women 26.9% and obese women 16.7%.

Majority of the study participants were married (85.4%), multiparous (65.2%), unemployed (64.9%), non-smokers and non-alcohol users, 98.4% and 96.6% respectively; with good antenatal visit attendance (67.8%) and had at

least a secondary school education (71.9%). A high proportion of women (52.1%) were from an urban residence and were self-referred from home for delivery. Participants with Gestational Diabetes Mellitus (GDM) were only 0.5% (Table 1). The highest proportion of obesity was noted in women with age 35 years and above, with secondary school and above education, employed, married, urban dwelling, non-alcohol drinking, non-smoking, with 4 or more ANC visits, multiparous, self-referred from home and in those with GDM (Table 1).

Table 1
The characteristics of the participants by BMI categories (N = 1309)

Variables	All Participants	Pre-pregnancy BMI (Kg/m^2)				
		Underweight (n = 69)	Normal weight (n = 669)	Overweight (n = 352)	Obese (n = 219)	P-value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Maternal age, years						
15–19	57(4.4)	2(3.5)	38(66.7)	15(26.3)	2(3.5)	**< 0.0001***
20–34	1050(80.2)	63(6.0)	550(52.4)	278(26.5)	159(15.1)	
≥ 35	202(15.4)	4(2.0)	81(40.1)	59(29.2)	58(28.7)	
[Mean, SD]	[28.3, (5.6)]					
Education						
Primary/below	367(28.1)	19(5.2)	205(55.9)	91(24.8)	52(14.2)	0.362
Secondary	668(51.0)	39(5.8)	330(49.4)	182(27.2)	117(17.5)	
College/University	274(20.0)	11(4.0)	134(48.9)	79(28.8)	50(18.)	
Employment status						
Unemployed	850(64.9)	50(5.9)	449(52.8)	222(26.1)	129(15.2)	0.067
Employed	459(35.1)	19(4.2)	220(47.9)	130(28.3)	90(19.6)	
Marital status						
Married	1118(85.4)	64(5.7)	545(48.7)	306(27.4)	203(18.2)	**< 0.0001**
Unmarried	191(14.6)	5(2.6)	124(64.9)	46(24.1)	16(8.4)	
Residence						
Rural	627(47.9)	24(3.8)	335(53.4)	182(29.0)	86(13.7)	**0.002**
Urban	682(52.1)	45(6.6)	334(49.0)	170(24.9)	133(19.5)	
Alcohol						
No	1265(96.6)	68(5.4)	645(51.0)	340(26.9)	212(16.8)	0.825*
Yes	44(3.4)	1(2.3)	24(54.5)	12(27.3)	7(15.9)	
Smoke						
No	1288(98.4)	69(5.4)	652(50.6)	349(27.1)	218(16.9)	**0.047**

*χ^2 tests for categorical variables with expected count not less than 5, otherwise *Fisher's test was used*

Variables	All Participants	Pre-pregnancy BMI (Kg/m^2)				
		Underweight (n = 69)	Normal weight (n = 669)	Overweight (n = 352)	Obese (n = 219)	P-value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Yes	21(1.6)	0(0.0)	17(81.0)	3(14.3)	1(4.8)	
Antenatal visit						
≥ 4	887(67.8)	49(5.5)	463(52.2)	224(25.3)	151(17.0)	0.457
1–3	282(21.5)	12(4.7)	141(48.8)	81(30.3)	48(16.2)	
None	140(10.7)	8(5.3)	65(51.1)	47(26.9)	20(16.7)	
Parity						
Primiparous	455(34.8)	26(5.7)	261(57.4)	125(27.5)	43(9.5)	**< 0.0001**
Multiparous	854(65.2)	43(5.0)	408(47.8)	227(26.6)	176(20.6)	
GDM						
No	1302(99.5)	69(5.4)	667(51.2)	352(27.0)	214(16.4)	**0.001***
Yes	7(0.5)	0(0.0)	2(28.6)	0(0.0)	5(71.4)	
Referral status						
Self-referred from home	814(62.2)	37(4.5)	416(51.1)	213(26.2)	148(18.2)	0.152
Referred from other facilities	495(37.8)	32(6.5)	253(51.1)	139(28.1)	71(14.3)	

*χ^2 tests for categorical variables with expected count not less than 5, otherwise *Fisher's test was used*

The distribution of the participants GWG as per the 2009 Institute of Medicine guidelines for GWG were 21.2%, 35.3% and 43.5% for Inadequate, Adequate and Excessive GWG respectively (Table 2). Of the total birth cohort, 125 (9.5%) of the women had PE. Amongst those with PE, 45 (36%) had MPE, 80 (64%) had SPE, 34 (27.2%) had EOPE and 91 (72.8%) had LOPE. Women with PE were more likely to be younger, with at most a secondary school education, primiparous, from a rural residence, with no antenatal care, overweight and obese, had excessive weight gain during pregnancy, and were mostly referred from other facilities (Table 2).

Table 2
The maternal characteristics associated with preeclampsia (N = 1309)

Variables	N (%)	Preeclampsia (n = 125) n (%)	P-value
Maternal age, years			
15–19	57(4.4)	11(19.3)	**0.003**
20–34	1050(80.2)	87(8.3)	
≥ 35	202(15.4)	27(13.4)	
Education			
Primary/below	367(28.1)	41(11.2)	**0.017**
Secondary	668(51.0)	49(7.3)	
College/University	274(20.9)	35(12.8)	
Employment status			
Unemployed	850(64.9)	84(9.9)	0.577
Employed	459(35.1)	41(8.9)	
Marital status			
Married	1118(85.4)	105(9.4)	0.639
Unmarried	191(14.6)	20(10.5)	
Residence			
Rural	627(47.9)	73(11.6)	**0.013**
Urban	682(52.1)	52(7.6)	
Alcohol			
No	1265(96.6)	120(9.5)	0.677
Yes	44(3.4)	5(11.4)	
Smoke			
No	1288(98.4)	123(9.5)	0.997
Yes	21(1.6)	2(9.5)	
Antenatal visit			
≥ 4	887(67.8)	66(7.4)	**< 0.0001**
1–3	282(21.5)	36(12.8)	
None	140(10.7)	23(16.4)	

*χ^2 tests for categorical variables with expected count not less than 5, otherwise *Fisher's test was used*

Variables	N (%)	Preeclampsia (n = 125) n (%)	P-value
Pre-pregnancy BMI (kg/m^2)			
Underweight: <18.5	69(5.3)	3(4.3)	**0.010***
Normal: 18.5–24.9	669(51.1)	55(8.2)	
Overweight: 25.0-29.9	352(26.9)	34(9.7)	
Obese: ≥ 30	219(16.7)	33(15.1)	
GWG in kg by IOM			
Adequate	462(35.3)	34(7.4)	**< 0.0001**
Inadequate	277(21.2)	14(5.1)	
Excessive	570(43.5)	77(13.5)	
Parity			
Primiparous	455(34.8)	54(11.9)	**0.037**
Multiparous	854(65.2)	71(8.3)	
GDM			
No	1302(99.5)	123(9.4)	0.138*
Yes	7(0.5)	2(28.6)	
Referral status			
Self-referred from home	814(62.2)	62(7.6)	**0.002**
Referred from other facilities	495(37.8)	63(12.7)	

*χ^2 tests for categorical variables with expected count not less than 5, otherwise *Fisher's test was used*

The effect of pre-pregnancy BMI on the risk of development of PE

Compared to normal weight mothers, pre-pregnancy overweight was associated with increased risk of PE with (RR = 1.13, 95%CI: 0.69–1.84) although this was not statistically significant. Pre-pregnancy Obesity was associated with a 2.42 increased risk of PE, (RR = 2.42, 95%CI: 1.48–3.96) as compared to normal pre-pregnancy BMI. Pre-pregnancy underweight was however protective against risk of pre-eclampsia, (RR = 0.81, 95%CI: 0.25–2.58) when compared to pre-pregnancy normal weight. This was not statistically significant (Table 3).

Table 3
The effect of pre-pregnancy BMI on the risk of development of PE (N = 1309)

Variables	No PE (n = 1184)	PE (n = 125)	Crude RR (95%CI)	Adjusted RR (95%CI)*	P-value
Pre-pregnancy BMI					
Underweight	66(95.7)	3(4.3)	0.51(0.15–1.67)	0.81(0.25–2.58)	0.264
Normal weight	614(91.8)	55(8.2)	1.00		
Overweight	318(90.3)	34(9.7)	1.19(0.76–1.87)	1.13(0.69–1.84)	0.439
Obese	186(84.9)	33(15.1)	1.98(1.25–3.14)	2.42(1.48–3.96)	0.004
* adjusted by parity, number of antenatal visits, Education, Residence, GDM and Referral status					

The effect of pre-pregnancy BMI on the risk of development of PE subtypes

Compared to normal pre-pregnancy BMI, overweight was associated with increased risk of MPE (RR = 1.15, 95%CI: 0.55–2.37), SPE (RR = 1.21, 95%CI: 0.70–2.09) and LOPE (RR = 1.27, 95%CI: 0.75–2.14). These associations were all however not statistically significant. Pre-pregnancy obesity was on the other hand statistically significantly associated with increased risk of MPE (RR = 2.05, 95%CI: 1.01–4.19), SPE (RR = 1.82, 95%CI: 1.03–3.23) and LOPE (RR = 2.14, 95%CI: 1.26–3.63) compared to normal pre-pregnancy BMI. Underweight pre-pregnancy BMI when compared to normal pre-pregnancy BMI was protective for SPE and LOPE, (RR = 0.82, 95%CI: 0.25–2.75) and (RR = 0.75, 95%CI: 0.23–2.51) respectively. These relationships were not statistically significant (Table 4).

Table 4
The effect of pre-pregnancy BMI on the risk of development of PE subtypes (N = 1309)

Variables	All participants	MPE (n = 45)		SP/E (n = 80)		EOPE(n = 34)		LOPE(n = 91)	
		n	RR(95%CI)	n	RR(95%CI)	n	RR(95%CI)	n	RR(95%CI)
PP BMI									
Underweight:	69	0	-	3	0.82(0.25–2.75)	0	-	3	0.75(0.23–2.51)
Normal	669	20	ref	35	ref	17	ref	38	ref
Overweight	352	12	1.15(0.55–2.37)	22	1.21(0.70–2.09)	9	1.01(0.44–2.28)	25	1.27(0.75–2.14)
Obesity	219	13	2.05(1.01–4.19)	20	1.82(1.03–3.23)	8	1.45(0.62–3.42)	25	2.14(1.26–3.63)
PP BMI*									
Underweight:	69	0	-	3	1.13(0.34–3.71)	0	-	3	1.66(0.48–5.75)
Normal	669	20	ref	35	ref	17	ref	38	ref
Overweight	352	12	1.09(0.49–2.40)	22	1.14(0.63–2.09)	9	0.95(0.41–2.20)	25	1.21(0.68–2.13)
Obesity	219	13	2.38(1.05–5.42)	20	2.35(1.28–4.28)	8	1.37(0.55–3.42)	25	3.05(1.70–5.47)

PP BMI: Pre-pregnancy body mass index (maternal body weight in first trimester)

***** adjusted by parity, number of antenatal visits, Education, Residence, GDM and referral status

The effect of GWG on the risk of development of PE and its subtypes

Overall, when compared to adequate GWG, excessive GWG was significantly associated with an increased risk of pre-eclampsia (RR = 1.77, 95%CI: 1.16–2.69) after adjusting for confounding factors. Inadequate GWG on the other hand was noted to be protective against risk of pre-eclampsia, (RR = 0.48, 95%CI: 0.24–0.98). This association was statistically significant. When GWG was assessed by pre-pregnancy BMI category, the underweight mother with excessive GWG had an increased risk of pre-eclampsia, (RR = 3.3, 95%CI: 0.28–38.77) when compared to the mother with adequate GWG. This association was not significant statistically. No association for risk of PE was appreciated for the underweight mother with inadequate GWG when compared to the underweight mother with adequate GWG. The Normal weight mother with excessive GWG was found to have a

slightly increased risk of PE when compared to the normal weight mother with adequate GWG, (RR = 1.03, 95%CI: 0.23–1.10). The association was not statistically significant.

Normal weight with inadequate GWG was found to be protective against risk of PE development when compared to the normal weight mother with adequate GWG (RR = 0.25, 95%CI 0.08–0.83). This association was statistically significant. Overweight pre-pregnancy BMI with excessive GWG had a two folds increased significant risk of PE when compared to the pre-pregnancy overweight mother with adequate GWG, (RR = 2.58, 95%CI: 1.03–6.43). Conversely the pre-pregnancy overweight mother with inadequate GWG had a reduced risk of PE development when compared to the pre-pregnancy overweight mother with adequate GWG (RR = 0.9, 95%CI: 0.22–3.36), but this was not statistically significant. The pre-pregnancy obese mother with excessive GWG had nine fold increased risk of PE development when compared to the obese pre-pregnancy mother with adequate GWG and this was statistically significant, (RR = 9.40, 95%CI, 1.91–46.23) (Table 5).

Table 5
The effect of GWG for the risk of PE (N = 1309)

GWG	No PE (n = 1184)	PE (n = 125)	Crude RR (95%CI)	Adjusted RR (95%CI)*	P-value
Overall					
Inadequate	263(94.9)	14(5.1)	0.67(0.35–1.27)	0.48(0.24–0.98)	0.0391
Adequate	428(92.6)	34(7.4)	Ref		
Excessive	493(86.5)	77(13.5)	1.97(1.29-3.00)	1.77(1.16–2.69)	0.0073
Underweight					
Inadequate	13(100)	0(0.0)	-		
Adequate	33(97.1)	1(2.9)	Ref		
Excessive	20(90.9)	2(9.1)	3.30(0.28–38.77)	3.06(0.19–48.87)	0.4035
Normal weight					
Inadequate	175(95.1)	9(4.9)	0.50(0.23–1.10)	0.25(0.08–0.83)	0.0138
Adequate	232(90.6)	24(9.4)	Ref		
Excessive	207(90.4)	22(9.6)	1.03(0.56–1.89)	0.69(0.32–1.45)	0.3200
Overweight					
Inadequate	44(93.9)	3(6.4)	0.90(0.22–3.36)	-	
Adequate	92(92.9)	7(7.1)	Ref		
Excessive	182(88.3)	24(11.7)	1.73(0.72–4.17)	2.58(1.034–6.43)	0.0347
Obesity					
Inadequate	31(93.9)	2(6.1)	2.29(0.31–17.01)	1.47(0.18–11.82)	0.7134
Adequate	71(97.3)	2(2.7)	Ref		
Excessive	84(74.3)	29(25.7)	12.56(2.82–53.16)	9.40(1.91–46.23)	0.0007
* adjusted by parity, number of antenatal visits, Education, Residence, GDM and Referral status					

Excessive GWG had a significantly increased risk of MPE (RR = 2.59, 95%CI: 1.23–5.46) and LOPE (RR = 1.78, 95%CI: 1.08–2.92) when compared to normal GWG. Excessive GWG was also found to have an increased risk for SPE (RR1.42, 95%CI: 0.85–2.36) and EOPE (RR = 1.62, 95%CI: 0.76–3.44) but these associations were not statistically significant. Inadequate GWG reduced the risk of development of SPE (RR = 0.32, 95%CI: 0.12–0.82), EOPE (RR = 0.60, 95%CI: 0.15–2.39) and LOPE (RR = 0.45, 95%CI: 0.20–1.03) when compared to adequate GWG. However, these associations were not statistically significant. On the contrary inadequate GWG was associated with increased risk of MPE (RR = 1.11, 95%CI O.39-3.17). This association was not statistically significant (Table 6).

Table 6
The effect of GWG for the risk of PE subtypes (N = 1309)

Variables	All Participants	MPE(n = 45)		SP/E(n = 80)		EOPE(n = 34)		LOPE(n = 91)	
		n	RR(95%CI)	n	RR(95%CI)	n	RR(95%CI)	n	RR(95%CI)
GWG									
Adequate	277	9	ref	25	ref	9	ref	25	ref
Inadequate	263	6	1.11(0.39–3.17)	8	0.52(0.23–1.17)	4	0.74(0.22–2.42)	10	0.65(0.31–1.38)
Excessive	493	30	2.80(1.31–5.95)	47	1.57(0.95–2.59)	21	1.92(0.87–4.24)	56	1.90(1.17–3.10)
GWG *									
Adequate	277	9	ref	25	ref	9	ref	25	ref
Inadequate	263	6	1.03(0.37–2.84)	8	0.32(0.12–0.82)	4	0.60(0.15–2.39)	10	0.45(0.20–1.03)
Excessive	493	30	2.59(1.23–5.46)	47	1.42(0.85–2.36)	21	1.62(0.76–3.44)	56	1.78(1.08–2.92)

***** adjusted by parity, number of antenatal visits, Education, Residence, GDM and referral status

The joint effects of pre-pregnancy BMI and GWG on the risk of development of PE and its subtypes

Mothers with both pre-pregnancy obesity and excessive GWG had a close to 5 fold increased risk of PE when compared to normal weight mothers (RR = 4.95, 95%CI: 2.21–11.10), this association was statistically significant. Mothers with pre-pregnancy overweight and excessive GWG also had an increased risk of PE (RR = 1.40, 95%CI: 0.71–2.74), this was not statistically significant. Pre-pregnancy Underweight and excessive GWG was also associated with a close to 4 fold increased risk of PE (RR = 3.96, 95%CI: 0.60- 25.98) but was not statistically significant. Women who did not have excessive GWG irrespective of BMI category were not at risk for PE and subtypes development when compared to normal BMI. There was significant interaction between BMI and GWG in PE, MPE and LOPE ($P < 0.05$). This finding illustrates that, there is a joint effect between BMI and GWG on risk of PE, MPE and LOPE. We found no significant interaction between BMI and GWG on risk of SPE and EOPE ($P > 0.05$) (Table 7).

Table 7
The joint effects of pre-pregnancy BMI and GWG on the risk of development of PE and its subtypes (N = 1309)

Total GWG by IOM								
Variables	**N**	**Not Excessive (n = 739)**			**Excessive (n = 570)**			**Pinteract**
		No PE n = 691	**PE n = 48**	**ARR (95%CI)**	**No PE n = 493**	**PE n = 77**	**ARR (95%CI)**	
BMI by All PE	440							0.0046
Normal		407	33	ref	207	22	ref	
Underweight	47	46	1	0.27(0.04–2.01)	20	2	3.96(0.60-25.98)	
Overweight	146	136	10	0.91(0.44–1.89)	182	24	1.40(0.71–2.74)	
Obesity	106	102	4	0.48(0.17–1.40)	84	29	4.95(2.21–11.10)	
BMI by MPE								0.0073
Normal	420	407	13	ref	207	7	ref	
Underweight	46	46	0	-	20	0	-	
Overweight	137	136	1	0.23(0.03–1.75)	182	11	2.98(0.89–9.99)	
Obesity	103	102	1	0.31(0.04–2.42)	84	12	8.97(1.52–52.84)	
BMI by SP/E								0.3711
Normal	427	407	20	ref	207	15	ref	
Underweight	47	46	1	0.46(0.06–3.48)	20	2	6.02(0.75–48.43)	
Overweight	145	136	9	1.38(0.61–3.10)	182	13	0.93(0.40–2.16)	
Obesity	105	102	3	0.61(0.18–2.10)	84	17	3.50(1.50–8.17)	
BMI by EOPE								0.9677
Normal	415	407	8	ref	207	9	ref	
Underweight	46	46	0	-	20	0	-	
Overweight	141	136	5	1.91(0.62–5.95)	182	4	0.68(0.22–2.12)	

ARR adjusted by parity, number of antenatal visits, Education, Residence, GDM and referral status

				Total GWG by IOM				
Obesity	102	102	0	-	84	8	2.34(0.73–7.53)	
BMI by LOPE								0.0046
Normal	432	407	25	ref	207	13	ref	
Underweight	47	46	1	0.36(0.05–2.73)	20	2	12.43(1.37-113.04)	
Overweight	141	136	5	0.59(0.22–1.57)	182	20	1.93(0.84–4.40)	
Obesity	106	102	4	0.65(0.22–1.91)	84	21	8.30(2.57–26.82)	
ARR adjusted by parity, number of antenatal visits, Education, Residence, GDM and referral status								

Discussion

This hospital based retrospective birth cohort study revealed a prevalence of PE among our study population to be 9.5%. This is higher than the previously reported prevalence of 3.3% from our center (18). Both obesity and excessive GWG independently increased the risk of PE when compared to normal BMI and adequate GWG respectively. Jointly Obesity and Excessive GWG had the highest risk of PE. The increased risk was similar for Mild PE (MPE), Severe PE (SPE) and Late Onset PE (LOPE). However, there was no association for Early Onset PE (EOPE).

From our study, the results further demonstrated the independent, positive and dose dependent relationship between increasing BMI and excessive GWG on the risk of PE and subtypes. Statistical significance of this association was more noted with obese women. The combined effect of pre-pregnancy obesity and excessive GWG on increased risk of PE, MPE and LOPE was also demonstrated in this study. The findings of this study reflect the rising trend and growing burden of high BMI and PE in Tanzania, specifically in Kilimanjaro region.(18). In addition, the results reflect figures which are above the national figures of 18% and 10% for overweight and obesity respectively reported in the TDHS 2015/2016. They are also higher than those reported for Kilimanjaro region, overweight 24.1% and obesity 10.8% in the 2010/2011 TDHS. Despite this, our findings are consistent with results reported in many other African countries (19–21).

The increased prevalence of PE as observed in this study highlights the increased contribution of hypertensive disorders of pregnancy including PE to the alarmingly high maternal mortality ratios, of 12% reported by Bergsjø *et al.*, (2010) and 18% reported by Maro *et al.*, (2016) for the same institution (4, 22). This trend is attributable to the increasing rates of urbanization with associated sedentary lifestyles, increased consumption of high fat, high sugar, highly refined and highly processed foods. Sadly, there is a concomitant decrease in the consumption of fruits, vegetables, nuts and legumes which are believed to prevent obesity and thus PE. This is consistent with the

finding by Endeshaw *et al* which reported an association between increased risk for PE in obese young rural Ethiopian obstetric patients and reduced dietary intake of folate, fruit and vegetables (21).

Excessive GWG was also associated with increased risk of PE which is consistent with findings as reported by some authors (19). They however did not find any association between overweight, obesity and risk of PE. This was likely due to the small sample size (N = 462) of their retrospective cohort among Cameroonian women. Our findings were also comparable to the findings of a meta-analysis performed by Zabih and colleagues (23) which explored the association between high BMI and risk of PE and subtypes (24). The authors further reported that BMI was appreciated to rise within each BMI category and noted that women with BMI ≥35 had a triple risk of PE compared to women with BMI of 30 or 31.

Our study further showed that Obesity was associated with significantly increased risk of PE and its subtypes, MPE, SPE and LOPE. This was in keeping with findings by other researchers (6, 25, 26). The variations in observed risk by PE subtypes can be explained by the fact that PE subtypes may have different clinical and biochemical features and different haemodynamic states. Early onset PE for instance, is typically linked to abnormal placentation with resultant placental insufficiency and is postulated to have a genetic component. This would then cause foetal growth restriction and other adverse maternal and neonatal outcomes. Maternal mortality is reported to be twenty fold higher in women who develop PE women at ≤ 32 weeks of gestation (6). Late Onset PE on the other hand is more likely to be related to maternal factors and typically involves normal foetal growth, larger placental volume, normal birth weight and more favorable maternal and neonatal outcomes. Maternal obesity has been identified as a crucial risk factor in both scenarios (27). Other similar studies have also observed increased risk of PE with maternal overweight and obesity.(6, 18, 28–30).

Furthermore, we found that overall excessive GWG was associated with a twofold increased risk of PE. Specifically, excessive GWG in the pre-pregnancy overweight and obese mothers was significantly associated with increased risk of PE. This is in keeping with the findings reported by previous works (31, 32). This finding was also appreciated for MPE and LOPE (6, 33). Inadequate GWG on the other hand was noted to be protective for SPE across the different BMI categories. Interestingly, Saftlas and co-workers (15) reported that higher than expected gestational weight gain did not increase the risk of PE and therefore was not associated with PE. The difference between their study and this present one is most likely explained by variations in study populations (different ethnic/racial distribution) and sources of GWG data (self-reported vs. medical records).

In addition, we also found that inadequate GWG in the normal weight mothers was associated with a significantly reduced risk of PE, which is consistent with findings reported by Fouelifack et al. (19). Most other studies consistently reported a reduced risk of PE and subtypes in the normal weight and underweight sub categories with inadequate GWG.

The joint effects of BMI and GWG on risk of PE and subtypes from this index study, indicates that pre-pregnancy obesity and excessive GWG were jointly associated with a significantly increased risk of PE, MPE, SPE and LOPE. This was contrary to the study done by Shao et al., (2017) which found no such significant interactions .These differences in findings could be explained by the fact that the Chinese study had a smaller proportion of obese women in their cohort when compared to our study. However, the mechanism through which obesity and excessive GWG affect hypertensive disorders is still unclear. It may be related to excessive adiposity acquisition and endothelial dysfunction resulting from inflammation associated with obesity (34).

We also reported on the heterogeneity of PE subtypes and this may be the explanation for the variations in the effect of pre-pregnancy BMI and GWG on risk of PE subtypes. Our findings are consistent with those reported from Western and Asian populations (6, 24, 34) although very few assessed this joint effect by PE subtypes (6). To the best of our knowledge, there are no studies which assessed these joint effects of pre-pregnancy BMI and GWG on risk of PE and subtypes in the African population, particularly in low resource settings, thus this study.

A main strength of our study was that although it was conducted at a single tertiary level hospital, the large sample size which included participants from several districts and the neighboring districts of Kenya served to increase the statistical power of the study. This may allow for generalization to the reproductive aged women in Kilimanjaro region, Tanzania.

Furthermore, potential disease misclassification was minimized by the use of hospital records which were readily available to us. Detailed information on demographic factors, medical histories and lifestyle factors as well as the exclusion of participants with potential confounders was another strength of our study. There was however no adjustment for unmeasured confounding variables such as diet, physical activity before pregnancy as well as maternal and paternal genetic factors which may have biased the results.

However, potential BMI exposure misclassification is a limitation of our study because of weight gained in early pregnancy. The average gestational age at first booking was 14.5 weeks of gestation. Analysis was restricted to first ANC visit gestational age $\leq$ 20 weeks for study participants. Another limitation of the study was that the weight of patients at onset of PE was weight on admission for delivery; it should have been weight of onset of PE. The small distributions in the PE subtype categories made it challenging to compute effect estimates for the GWG subcategories and risk of PE subtypes. Total GWG was used instead to compute the statistical estimates.

Conclusions

Our findings showed high proportions of overweight and obesity among obstetric women who delivered at KCMC. Pre-pregnancy overweight and obesity are critical modifiable factors associated with increased risk of PE. Notably, excessive GWG may magnify this effect. The independent and joint effects of High BMI and excessive GWG on risk of PE were supported by our findings. This makes overweight and obesity in reproductive age women a major health concern and especially a priority for maternal and child health.

Community sensitization and mobilization to raise awareness on the risks of overweight and obesity on development of PE should be vigorously pursued. Also, lifestyle modification campaigns which will target women of reproductive age and promoting nutritional education, healthy eating habits, preconception normalization of weight and exercise are necessary.

Future multi Centre studies with larger sample sizes that can study the heterogeneous nature of PE subtypes in relation to pre-pregnancy BMI and GWG and hopefully confirm our findings and improve the certainty of our statistical estimates are recommended.

List Of Abbreviations

BMI Body Mass Index

BP Blood Pressure

CDC Centers for Disease Control and Prevention

EOPE Early onset preeclampsia

GWG Gestational weight gain

IOM Institute of Medicine

KCMC Kilimanjaro Christian Medical Center

LOPE Late onset preeclampsia

MPE Mild preeclampsia

PE Preeclampsia

SP/E Severe pre/eclampsia

TDHS Tanzania Demographic and Health Survey

US United States

USA United States of America

WHO World health organization

Declarations

Ethics approval and consent to participate

Ethical clearance was obtained from the Kilimanjaro Christian Medical University College Research and Ethics Committee with certificate number 2348. Permission was also sought from the Head of department of the department of Obstetrics and Gynaecology. Confidentiality was observed with the use of participant identification numbers. All data was stored under lock and key, unlinked to patient identifiers.

Consent for publication

Not applicable

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests

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Authors' contributions

Nelago Tukondjeni Amagulu; the main author of the manuscript; the writer of the manuscript

Bariki Mchome; co-supervisor, assisted with proof reading of the manuscript

Julius Pius Alloyce; statistician, assisted with data quality management and analysis

Eusebious Maro; the main supervisor; assisted with research design and proof reading of manuscript

Kingsley U Tobi: assisted with proof reading and editing of manuscript

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Figures

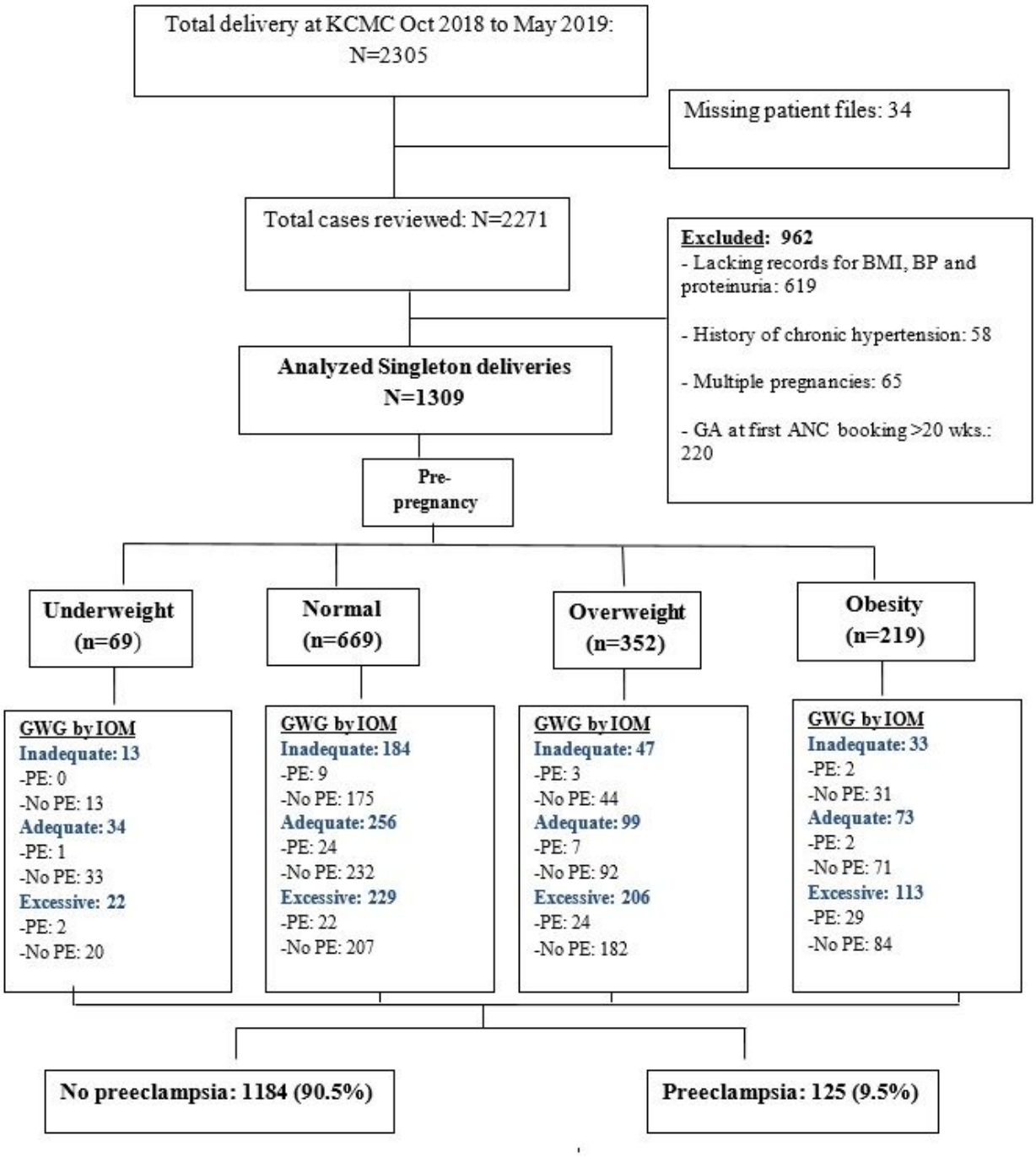

Figure 1

Schematic presentation of the study participants

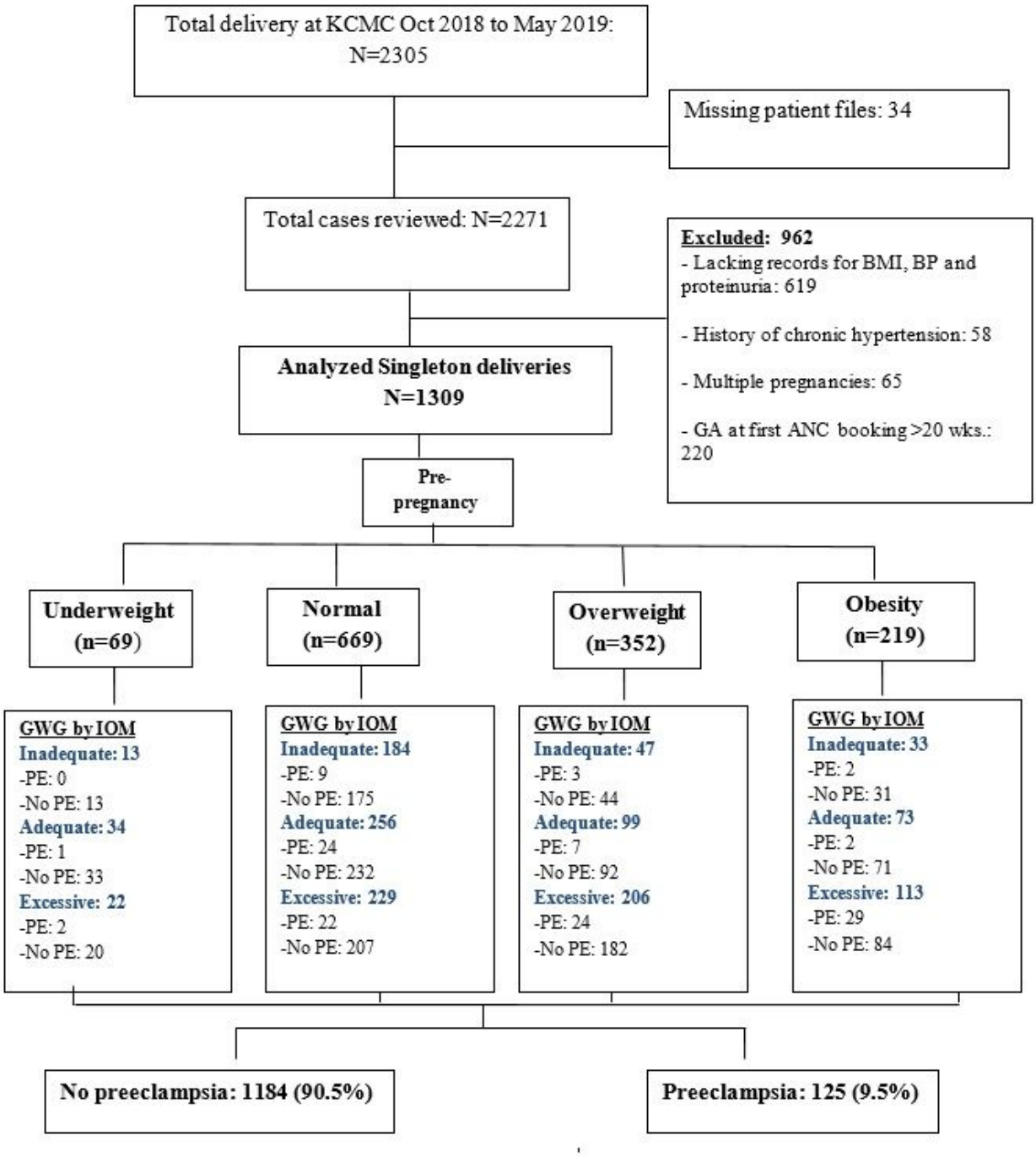

Figure 1

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