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Severe Pregnancy Induced Hypertension, a Dreaded Complication in Semi-Urban Area in Fako Division, Cameroon? A Case – Control Study

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Authors' contributions

This work was carried out in collaboration between all authors. Authors GEHE and MC designed the study, wrote the protocol, and the first draft of the manuscript. Authors NNB, TEO and PFN managed the literature searches, data entry and made important contributions in the first draft of the manuscript. Authors JA and DSN analyzed the data. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Severe pregnancy-induced hypertension (severe pre-eclampsia and eclampsia) is a major cause of fetal and maternal morbidity and mortality. Pregnancy induced hypertension occurs in 7.7 – 8.2% of pregnancies and causes 17.5% of maternal deaths in Cameroon. However, few descriptive studies have been published in the last decade to demonstrate the gravity of adverse maternal and perinatal outcomes of these disorders in the Fako Division of the South West Region, Cameroon.
Objectives: This study was aimed at determining the prevalence, risk factors and the maternal

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and perinatal outcomes associated with severe PIH in the two Regional Hospitals in the South West Region of Cameroon.

Methods: This was a cross-sectional and case-control study conducted at the maternities of the two Regional Hospitals of the South West region. Of the 2112 files of parturients that had childbirth in these hospitals between 16th July 2013 and 16th January 2015, 94 case files were selected. These files were classified according to the National High Blood Pressure Education Program Working Group (2000) as severe preeclampsia (64 files) or eclampsia (30 files). A reference group of 188, age, gravidity and parity-matched parturients files with normal blood pressures (BPs) was also selected. Structured questionnaires were used to obtain demographic data, risk factors, gestational age, symptoms and signs of severity, neonatal and maternal morbidity and mortality. Data was analyzed using Epi Info™ 7.0.8.3, odds ratios and their 95% confidence intervals were recorded and $p<0.05$ was considered statistically significant.

Results: The prevalence of severe PIH was 5.02%. Parturients aged 21 – 25 years 30.9% (29) and primiparous 57.5% (54) were most affected. Severe PIH was associated with family history of chronic HBP [44.7% (42) versus14.9% (28)] and pre-tertiary level of education [62.8% (59) versus 44.2% (83)] both with $p<0.001$ and $p\leq0.031$ respectively. The maternal mortality ratio in cases was 1887/100,000 live births but no maternal death occurred in the reference population. Severe PIH was associated with certain maternal outcomes, the most frequent being caesarean delivery [68.1% (64) versus 16.5% (31)], $p<0.001$. Others included visual impairment [11.7% (11) versus 0.0% (0)] and Placenta abruptio [5.3% (5) versus 0.0% (0)]. Similarly, severe PIH was associated with perinatal outcomes; low birth weight [50.0% (47) versus 10.6% (20)], prematurity [46.8% (44) versus 9.6% (19)] and perinatal death [27.7% (26) versus 5.3% (10)] all $p\leq0.001$.

Conclusion: The prevalence of severe PIH was high (5.02%). It was common in age group 21-25, primiparous and women with family history of chronic HBP and low level of Education. Parturients with a severe PIH had significantly more maternal and perinatal complications. These data suggest a gap in maternal health in Cameroon. Hence there is need to do complete evaluation (clinical and laboratory) to better assess patients; encourage early patient referral and prompt management of complications; more mid- wives and creation of adult and neonatal intensive care units in the Buea and Limbe Regional Hospitals.

Keywords: Severe; pregnancy-induced hypertension; maternal and perinatal outcomes; Cameroon.

ABBREVIATIONS

AGA : Appropriate-for-gestational age
ALT : Alanine transaminase
ANC : Antenatal clinic
AST : Aspartate transaminase
BP : Blood Pressure
CI : Confidence interval
DBP : Diastolic Blood Pressure
ELBW : Extreme low birth weight
FHS IRB : Faculty of Health Sciences Institutional Review Board
HBP : High blood pressure
HDP : Hypertensive disorders of pregnancy
ICU : Intensive care unit
IUFD : Intra-Uterine Foetal Death
IUGR : Intra-Uterine Growth Restriction
LBW : Low birth weight
MDG : Millennium Development Goals
MMR : Maternal Mortality Ratio
NHBPEP : National High Blood Pressure Education Program
PIH : Pregnancy Induce Hypertension
SBP : Systolic Blood Pressure
UNFPA : United Nations Population Fund
VLBW : Very low birth weight
VLBW : Very low birth weight

1. INTRODUCTION

Hypertensive disorders of pregnancy (HDP) account for 100,000 maternal deaths yearly worldwide. They are the leading cause of maternal mortality in the India [1], and the third in Cameroon [2-6]. These disorders affect 10-30% of all pregnancies [7-9]. However, no study has been carried out in the Buea and Limbe health district and the South West Region as a whole to determine the prevalence and the maternal and perinatal outcomes of HDP.

Cameroon is one of the 189 countries that signed the Millennium Declaration and is required to meet the Millennium Development Goals (MDGs) by September 2015 deadline. The MDGs are the world's time-bound goals and quantified targets to address the problems of extreme poverty, promote gender equality; education and environmental sustainability by 2015 [10,11]. This study focuses on goals MDGs4 and 5. To achieve the above MDG, it is estimated that an annual decline in maternal mortality of 5.5% is needed. However, between 1990 and 2013, the global maternal mortality ratio (i.e the number of maternal deaths per 100,000 live births) declined annually by 2.6% with a disproportionate decline in in sub-Saharan region [2]. According to the WHO's Trends in Maternal Mortality: 1990 to 2013, Cameroon has made no progress towards achieving MDG 5 as MMR [2]. The deadly obstetric triad of hemorrhage, infection and pregnancy-induced hypertension were responsible for 75% of the deaths; 17% of which were due to pregnancy-induced hypertension alone [12].

The UNFPA 2013 report also implied that eighteen neonates die daily in Cameroon (Neonatal Mortality of 42 deaths per 1000 live births). Preterm delivery and low birth weight, which are both frequent complications of hypertensive disorders of pregnancy, accounted for 30% of these deaths according to the same report [2].

Despite the fact that hypertensive disorders of pregnancy are the third most frequent cause of maternal morbidity and mortality, and their perinatal complications are responsible for one third of neonatal deaths, very few and mainly descriptive studies have been published on the subject in Cameroon since the year 2000 [3,13]. The number of these disorders is apparently increasing over the years in Fako Division, Cameroon according to unpublished data obtained from the hospital statistics of Obstetrics and Gynecology units of hospitals in this area [14]. This case-control hospital based study was carried out to determine the prevalence of severe pregnancy-induced hypertension, risk factors, and maternal and perinatal outcomes associated with these disorders in two Regional Hospitals in Buea and Limbe, South West Region of Cameroon.

2. METHODS

2.1 Study Design

This was a cross sectional and case-controlled hospital based study.

2.2 Study Setting

The study was carried out between 16th July 2013 and 16th January 2015 in the Buea and Limbe Regional Hospitals which are the two public tertiary referral health care institutions in the South West Region of Cameroon.

Both hospitals have obstetrical and gynecological units, blood banks and surgical theatres. The Buea Regional Hospital's Obstetrics and Gynecology department is made up of a labor room with four delivery beds and wards with nineteen bed capacity. This unit is headed by a Gynecologist assisted by a General practitioner, three mid-wives, nine nurses and four para-clinical staff. The latter group of personnel is not trained in offering specialize obstetric care but is mainly involved in the cleanliness of the units, taking samples and obtaining results from the laboratory.

The Obstetrics and Gynecology Unit of the Limbe Regional Hospital has a twenty bed capacity. The staff strength, facilities and methods of documentation are similar to those of the Buea Regional Hospital but is managed by two gynecologists. In both hospitals laboratory technicians also work in shifts like nurses but during weekends only a limited number of investigations are carried out.

2.3 Study Population and Sampling Method

The target population for this study was parturients who delivered at the Maternity units of both Hospitals. A non-probability convenience sampling method was used to select files. For every parturients' file (case) selected in the study

group, two (2) corresponding parturients files matched for age group, parity and gravity were selected.

2.4 Sample Size Calculation

The sample size was calculated using the formula for comparing two proportions $N = \frac{[\mathrm{Zcrit}\sqrt{2\mathrm{P}(1-\mathrm{p})}}{D^2} \frac{+\mathrm{Zpwr}\sqrt{\mathrm{P1}(1-\mathrm{P1})+\mathrm{P2}(1-\mathrm{P2})]^2}}{D^2}$ [15]. For a confidence level of 95%, Z_{crit} = 1.96, $Z_{pwr=}$ standard normal deviation for the desired statistical power of 90% = 0.90. The pre-study prevalence of adverse outcome in participants with preterm delivery in women with hypertensive disorders in pregnancy, =28.8%= 0.29 [1] while those with preterm deliveries in normotensive women in pregnancy, = 3% = 0.03[1]. A minimum sample size of 61 pregnant women was required. However, ninety four case files and 188 case files for the reference group (referred to as 'controls') were enrolled to make our results more justifiable.

2.5 Ethical Issues

Ethical approval was issued by the Faculty of Health Sciences Institutional Review Board of the University of Buea, followed by administrative approval from the Regional Delegation of Public Health of the South West Region and directors of both institutions. Furthermore, personal and demographic data collected during the study were coded to ensure confidentiality and the data was only accessible to the principal investigator

2.6 Study Procedure

During the study period, two thousand one hundred and twelve files were exploited from the maternities of both hospitals amongst which 127 were identified with severe hypertension (HTN) in pregnancy. We excluded 21 files of chronic HTN paturients and 12 files in which only the severity of PIH was specified. Consequently the medical records of ninety four (94) parturients with severe hypertensive disorders in pregnancy were retained for detailed analysis. One hundred and eighty eight (188) participants matched for age-group, gravidity and parity with consistently normal BPs were selected as the controls.

Parturients' files with sustained intrapartum BP measurement of ≥ 160/110 mmHg, a urine dipstick with proteinuria of ≥1+ and any of the following features; severity symptoms (headache, blurred vision, dyspnoea, right upper quadrant pain), severity signs (grand mal seizure, reduced visual acuity, bibasilar inspiratory crackles, anasarca, oliguria/anuria), serum creatinine>12 mg/l, platelet count <150,000 /$mm^{3,}$ Aspartate Amino Transferase (AST) ≥ 40 U/l and Alanine Amino Transferase (ALT) ≥ 40 U/l, Lactate Dehydrogenase (LDH) ≥ 600 U/l were selected. Files were grouped by age, parity and gravity. The age groups were < 20 years, 21 – 25, 26 - 30, 31 – 35 and > 35 years and the antepartum parity and gravidity groups were 0, 1 – 4 and > 4.

For each case file studied with paturient blood pressure ≥ 160/110 mmHg, or convulsions, or coma and with an elevated blood pressure, they were further evaluated to make sure she fulfilled all the other inclusion criteria listed above. The reference population (controls) were, two corresponding age-group, gravidity and parity matched control files with normal BPs before, during and after pregnancy enrolled in the same hospital not more than two weeks apart.

The files of following potential participants were excluded as cases; those with Systolic Blood Pressure (SBP) = 140-159 mmHg and Diastolic Blood Pressure (DBP) = 90-109 mmHg after 20 weeks gestation, a pre-20 weeks gestation SBP > 140 mmHg and DBP > 90 mmHg, on pharmacological treatment for chronic hypertension prior to or during pregnancy, with a negative proteinuria after 20 weeks gestation.

2.7 Data Management and Analysis

Data was collected from 1st November 2014 to 28th February 2015, coded, keyed and analyzed using the Epi Info™ 7.0.8.3. The categorical variables were presented as percentages and continuous variables as mean and standard deviation. The associations between two categorical variables were tested using chi-square test and T test where appropriate. Odds ratios and their 95% confidence intervals were considered. ANOVA (Analysis of variance) was used to test the association between continuous variables. A *p value* < 0.05 between two categorical or continuous variables was considered statistically significant.

3. RESULTS

The prevalence of severe pregnancy-induced hypertension (severe pre-eclampsia and eclampsia) was 5.2% (106). The prevalence of severe pre-eclampsia was 3.3% (69) while that of eclampsia was 1.8% (37).

3.1 Risk Factors of Developing Severe PIH

The mean age of cases was 27.2+/-6.0 and controls 27.1+/-6.3% years, these were not statistically significantly different from the control group (p value =0.83) as they were matched. The percentage of married women who developed PIH was 65.1% (62), higher than in single women with the difference not being significant (P value=0.34). It was also noted that women who were unemployed had almost the same chances of developing PIH compared to those who were employed (p value = 0.55). However, those who had had tertiary education were twice unlikely to develop PIH compared to those who had had just pre-tertiary education (OR 0.47, 95%CI: 0.28-0.78, P value=0.03). All these are represented on Table 1.

3.2 Clinical Characteristics of Cases

As shown in Table 2, comparing the gravidities and parities of our cases with the normal subjects, there was no significant difference (p-value =0.87 and p-value =0.66 respectively). Meanwhile, cases with family history of hypertension in first degree relatives had higher SBP and DBP and were more likely to develop PIH than the control (p-value <0.001).

3.3 Maternal Outcomes of Severe PIH

Two eclamptics died after caesarean delivery. The maternal mortality ratio among parturients with severe pregnancy-induced hypertension (pre-eclampsia and eclampsia) was 1887 per 100,000 live births. Other maternal outcomes observed in this study were; apparently uncomplicated caesarean delivery 64 (68.1%) and visual impairment 11 (11.7%) with statistical significant difference between PIH cases and normotensive parturients, meanwhile the cases of placenta abruption 5 (5.3%) in severe PIH was statistically insignificant compared to normotensive parturients (P-value=0.76). (Table 3).

3.4 Perinatal Outcomes of Severe PIH

The perinatal outcomes of parturients with PIH were significantly different from those who were normotensive. In which case, outcome worsened in terms of gestational age at delivery, birth weight, early neonatal deaths, intrauterine fetal deaths and perinatal deaths in PIH mothers compared to normotensive parturients. Early neonatal death was 6 times more frequent in cases as compared to the reference group. Furthermore, cases were seven times more likely to have perinatal deaths as shown in Table 4.

Table 1. Risk factors of developing severe PIH

	Cases (PIH) %	Control (normotensive)%	P value	OR, 95% confidence	CI
Educational level					
Pre-tertiary	59 (62.8)	83 (44.2)	0.03	0.47	0.28 – 0.78
Tertiary	35 (37.2)	105 (55.9)			
Marital status					
Married	62 (65.9)	113 (60.1)	0.34	1.29	0.77 – 2.16
Not married	32 (34.0)	75 (39.9)			
Occupation					
Unemployed	49 (52.1)	91 (48.4)	0.55	0.86	0.52 – 1.41
Employed	45 (47.9)	97 (51.6)			

Table 2. Clinical characteristics of cases

Clinical characters	PIH cases	Control	P-value
Means of BPs			
DBPs	115.3+/-9.5	74.9+/-9.8	<0.001
SBPs	176.7+/-17.0	119.4+/-12.1	<0.001
Mean Gravidity	2.2+/-2.7	2.2+/-1.7	0.87
Mean Parity	0.9+/- 1.3	0.9+/-1.3	0.66
Family history of HTN in first degree relatives (OR 4.61, 95% CI:2.61 – 8.17)			
Present (%)	42 (44.7)	28 (14.9)	P-value <0.001
Absent	52 (55.3)	160 (85.1)	

Table 3. Comparing maternal outcomes among cases and controls

Maternal outcome	Severe PIH cases (%)	Controls (%)	P-value	O.R, 95% confidence	CI
Caesarean sections					
Yes	64 (68.1)	31 (16.5)	<0.001	10.81	6.05 – 19.29
No	30 (31.9)	157 (83.5)			
Visual impairment					
Yes	11 (11.7)	0	<0.001	5.32	2.30-15.72
No	83 (89.3)	188 (100)			
Placenta abruptio					
Yes	5 (5.3)	8 (4.3)	0.76		0.12-1.02
No	89 (94.7)	180 (95.7)			
Maternal deaths					
Yes	2 (2.1)	0 (0)	0.9	4.12	3.21-7.19
No	92 (97.9)	188 (100)			

Table 4. Comparing perinatal outcomes in cases and controls

Perinatal outcome	PIH mothers (%)	Normotensive mothers (%)	P-value	OR	CI
Gestational age at delivery					
Preterm	44 (46.8)	19 (9.6)	<0.001	0.12	0.07-0.22
Term	50 (53.2)	169 (90.4)			
Birth weight					
Low	47 (50.0)	20 (10.6)	<0.001	0.12	0.06-0.22
Normal	47 (50.0)	168 (89.4)			
Early neonatal deaths					
Yes	21(22.3)	8 (4.3)	<0.001	6.47	2.74-15.27
No	73 (77.7)	180 (95.7)			
IUFD					
Yes	5 (5.3)	2 (1.1)	0.03	5.22	0.99-27.46
No	89 (94.7)	186 (98.9)			
Perinatal deaths					
Yes	26 (27.7)	10 (5.3)	<0.001	6.80	3.12-14.86
No	68 (72.3)	178 (94.7)			

4. DISCUSSION

4.1 Prevalence of Severe Pre-eclampsia and Socio-Obstetrical Factors

The prevalence of severe pregnancy induced hypertension (severe pre-eclampsia and eclampsia) was 5.02%.This value is similar to what was obtained in a similar recent study in India where severe PIH had a prevalence of 4.16% [16]. Two similar studies carried out in Yaoundé Cameroon, documented higher values of severe PIH in 7.7% and 8.2% of pregnancies respectively [17,18]. The variations in prevalence may be due to the difference in the settings, geographical locations and study designs. It was also noted that, 65.1% (69) had severe pre-eclampsia and 34.9% (37) eclampsia (with an overall prevalence of 3.3% and 1.8% respectively). This is similar to the study carried out in Yaoundé, where 60% had severe PIH and 40.0% eclampsia [18].

Furthermore, the age group most affected was that of 21 – 25 years. This was similar to the age group of 20 – 24 years reported by Adisso et al. in a study in Benin [19]. Primiparous women were most affected (57.5%), this finding was similar to the 60% obtained in a study by Kongnyuy et al. [3]. However, higher values were obtained of 41.34% and 45% were reported by Motaze [17] and Ayuk [18] respectively. In Dempouo's study [20] which was also carried out in Yaoundé Cameroon, primiparous parturients accounted for 75% of cases. The difference was probably because the studies were carried out in tertiary hospitals in Yaoundé using different study designs and at different years and periods

because this disorder has also been shown to have seasonal variations [17].

Moreover, family history of high blood pressure (HBP) in first degree relative(s) was a risk factor for severe PIH in 44.7% of cases, much higher than 4% reported in previous studies carried in Yaoundé Cameroon [20]. Most parturients in case group had had at most secondary level of education (62.8%) which is similar to trends in Cameroon (61.0%) [20] but higher than the study carried out by Motaze (41.4%) [17] in 2007. This may be because most girls in Cameroon now reach child bearing age while in secondary school. Hence, pregnancy-induced hypertension is associated with lower educational level [OR = 0.47 (95% CI = 0.28 – 0.78), p <0.05] a finding similar to that of Baeta et al. in Lome, Togo were the risk of PIH increased with lower educational level [21].

More so, more parturients with PIH were married (65.9%) which is a similar to findings elsewhere in Cameroon [4,17,18] where more parturients with PIH were married. Fifty two percent of parturients with PIH were unemployed. This trend is similar to that obtained by Motaze (59.0%) [17], but lower than those obtained by Naoussi (73.5%) [4] and Dempouo (89.0%) [20]. The difference in values is probably due to the recent decrease in job opportunities nationwide.

4.2 Maternal Outcomes of Severe Pre-eclampsia

In this study, the maternal mortality rate of severe pregnancy-induced hypertension was 1.89% giving maternal mortality ratio (MMR) of 1887 per 100,000 live births. A similar rate of 1.8 was reported by Ayuk in Yaoundé, Cameroon [18] but a lower rate (1.2%) was reported in Turkey [22]. However, higher proportions were reported in Nigeria where a case fatality of 5.8% was documented [23]. The high MMR in this study was probably due to late referral and inadequate resources for expeditious management in the labor ward, theatre and absence of intensive care units in these institutions. Also caesarean delivery was performed in 68.1% of cases. This is higher than what was obtained in Nigeria (55.2%) [23] and Turkey (58.8%) [22], and doubles 26% obtained in a previous study in Cameroon by Dempouo [20]. The higher caesarean rate in the present study was probably because of late referral from primary and secondary health care facilities in the environs. Also it could be due to the use of caesarean section kits provided by the government which made the procedure affordable. Maternal complications like visual impairment occurred in 11.7% of cases which was lower than in a study by Ayuk in Yaoundé where 17.1% of cases had this complication [18]. Abruptio placenta occurred in 5.3% of cases which is similar to the 5% obtained in Yaoundé [20].

4.3 Perinatal Outcomes of Severe Pre-eclampsia

In this study, the mean birth weight was 2.47±0.84 kilograms with the range 0.90 – 4.20 kilograms in cases. This was statistically significantly different (p value <0.05) from controls, similar conclusions were made by Ayuk in Yaoundé [18]. The frequency of low birth weight in our study was 50.0% similar to a recent study carried out in Indian where this was 56.3% [16] but higher than previous studies in Cameroon 24.3% [18] and 20.0% [20]. This difference was probably due to the presence of qualified personnel who better managed premature labor in the tertiary care institutions in Yaoundé. Furthermore, the mean gestational age was 36.18±3.49 weeks which was statistically significantly lower in cases than controls (p< 0.05). Similarly to a Pakistani case-control study by Fatemeh, gestational age was significantly lower in the case group (p< 0.001) [24].

In this study, prematurity rate was 46.8% much higher than 28.8% and 21.5% reported in India [1] and Yaoundé [18] respectively. The higher rate of prematurity in this study compared to the study by Ayuk may be due to better management of premature labor in tertiary hospitals in Yaounde which have neonatal ICU with more and better trained health personnel. The perinatal death rate of 27.7% recorded, is similar to the perinatal mortality rate of 20.9% reported in Nnewi, Nigeria by Mbachu II et al. [23]. Lower perinatal rates were reported by Yadav et al. in India (14.8%) [1], Yücesoy et al. in Turkey (14.4%) [22], Buga and Lumu in South Africa (14.0%) [25]. Higher rates were reported by Dempouo in Cameroon (32%) [20]. The lower perinatal mortality rate in this study compared to that reported by Dempouo was probably because the study focused on cases of severe preeclampsia and eclamptic. Moreover, the IUFD rate was 5.32%, higher rates were reported by Buga and Lumu, in Umtata, South Africa (11.2%) [25] and Yücesoy et al. in Kocaeli, Turkey (9.4%) [22]. Higher still birth rate of 12.8% occurred in cases compared to controls. Lower rates were found in a Turkish study by Yücesoy (3.9%) [22]

and Yadav et al. in India 4.8% [1]. While higher rates were reported by Mbachu II et al. in Nigeria (17.4%) [23] and in a recent study in Indian by Sachan (16.9%) in paturients with PIH [16]. This regional variability is probably linked to the study designs and the level of health care that is provided in these countries.

An early neonatal death rate of 9.6% was found in this study, lower values were documented by Buga and Lumu, in South Africa (3.8%) [25] and Prakash et al. in India (5.55%) [26].This higher stillbirth rate may be due to the fact that, the study was carried out in tertiary health facilities in this locality were most cases were referral cases with delayed time and poor logistics for referral. It might also reflect the level of care offered to this group of patients as there were no intensive care facilities

4.4 Limitations of the Study

Documentation in the medical records was poor; this rendered the exploitation of information very difficult with a lot of missing data especial on the laboratory investigations. Limited investigations were carried out in both hospitals so the prevalence of certain fetal and maternal complications were probably underestimated. Furthermore, the short duration of follow up of the cases rendered it impossible for the late complications to be determined. The study had a limited scope because it was carried in only two hospitals in the region. It however, fairly represents the situation in other hospitals which have less personnel, infrastructure and facilities in this area.

5. CONCLUSION

The prevalence of severe pregnancy-induced hypertension (severe pre-eclampsia and eclampsia) was high (5.02%). Also, severe pregnancy-induced hypertension was common among the 21-25 years age group, primiparous parturients with a family history of chronic hypertension and paturients of low educational level irrespective of their occupation, or marital status.

Severe PIH was also associated with adverse maternal outcomes (caesarean delivery, placenta abruption, and visual disturbances) and perinatal complications (low birth weight, intrauterine growth restriction, IUFD, stillbirths and early neonatal death). Finally we had a high maternal mortality ratio (1887 maternal deaths per 100,000 live births). These findings suggest a gap in mother and child health care in the South West Region of Cameroon and failure to achieve MDG goals 4 and 5. Sensitization and amelioration of the health care services provided will greatly reduce the maternal and fetal, morbidity and mortality associated with this complication.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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