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25th March, 2024

Dr O.O Ogunbode

Department of Obstetrics and Gynaecology

University College Hospital,

Ibadan.

Dear Sir,

LETTER OF ACCEPTANCE

This is to inform you that your manuscript titled: **PREGNANCY OUTCOMES IN WOMEN WITH SICKLE CELL DISEASE AT A TERTIARY HOSPITAL IN NIGERIA: A FIVE YEAR RETROSPECTIVE STUDY**, of which you are an author, has been accepted for publication in Annals of Ibadan Postgraduate Medicine.

The manuscript is scheduled for August 2024 edition, Volume 22 and issue 2.

Thank you for your interest in or Journal.

Yours sincerely,

Dr. K.I .Egbuchulem

Editor-in-Chief

TITLE PAGE

1. Original article

Title: Pregnancy outcomes in women with sickle cell disease at The University College Hospital, Ibadan: a five-year retrospective study

Running Title: Pregnancy outcomes in sickle cell disease women at the University College Hospital, Ibadan, Nigeria.

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9. This manuscript has been read and approved by all the authors.

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PREGNANCY OUTCOMES IN WOMEN WITH SICKLE CELL DISEASE AT A TERTIARY HOSPITAL IN NIGERIA: A FIVE-YEAR RETROSPECTIVE STUDY

ABSTRACT

Background: Sickle cell disease (SCD) in pregnancy constitutes a high-risk pregnancy, associated with increased risk of adverse outcomes.

Objective: To describe the outcome of pregnancy in SCD women managed at the University College Hospital, Ibadan, Nigeria.

Materials and Methods: A retrospective review of the health records of sixty-three SCD pregnant women managed between January 1, 2016, and December 31, 2020. The information extracted included sociodemographic and obstetric characteristics, clinical presentations, mode of delivery, maternal and fetal outcomes. The data was analyzed using the IBM Statistical SPSS Statistics for Windows, version 23.0. The test of association was done using Chi-square and level of significance was $p<0.05$.

Results: Prevalence of SCD in pregnant women was 0.65%. Mean age was 28.8±4.1years, 63.5% were haemoglobin SS while 36.5% were haemoglobin SC. Most of the women had tertiary education (61.8%) and booked for antenatal care (ANC) (60%). About 72.4% delivered at term while 46.1% had caesarean delivery. Most common complication was anaemia (79.4%) while vaso-occlusive crisis was the most common type of crisis (55.6%). Most of the women (92.5%) had live-birth with 15.2% of neonates requiring Neonatal Intensive Care Unit (NICU) admission. Maternal death rate was 6.3%. Good maternal and fetal outcomes occurred in 71.4% and 61.9% of participants respectively. Good maternal outcome was significantly associated with tertiary education($p=0.01$). Good fetal outcome was associated with tertiary level of education($p=0.04$) and multigravida status($p=0.03$).

Conclusion: SCD pregnant women have good fetal-maternal outcomes, however not receiving ANC and lower level of education were associated with poor pregnancy outcomes. Health education, access to ANC, prompt diagnosis, treatment of complications and multi-disciplinary team management will improve the pregnancy outcomes.

Keywords: Fetal outcome, Maternal outcome, Haemoglobinopathy, Sickle cell disease in Pregnancy.

INTRODUCTION

Sickle cell disease (SCD) in a pregnant woman constitutes a high-risk pregnancy, with associated increased risk of adverse fetal and maternal outcomes. SCD is a single gene disorder with point mutation that affects the globin chain of the red blood cell[1,2]. SCD is most prevalent in malaria endemic areas in the tropics where outcomes are often poor due to resource constraints[3].

Globally, an estimated 3.2 million people are living with SCD, and an additional 43 million are estimated to have sickle cell trait[3,4]. About 5-7% of the world population carries an abnormal haemoglobin gene and SCD is found in one in every 500 Africans[5]. A study done in Benin city, Nigeria, revealed a SCD prevalence of 2.39% and a carrier rate of about 23%[6]. It is estimated that over 80% of over 300,000 annual births of children with SCD occur in sub-Saharan Africa, with largest burden from Central Republic of Congo[4.]

The term SCD comprises of a spectrum of disorders such as haemoglobin SS(HbSS), haemoglobin SC(HbSC) and haemoglobin S beta thalassemia (HbS beta^{o} or Hb S beta^{+}). Haemoglobin AS (HbAS) or haemoglobin AC (HbAC), are benign conditions that have no specific antenatal sequelae[1]. The polymerization of the abnormal haemoglobin in low-oxygen conditions in a SCD patient leads to the formation of rigid and fragile sickle-shaped red cells, and eventually resulting in myriads of clinical complications[1,2].

In Nigeria, the prevalence of SCD among pregnant women is 0.14-1.16%[7] and in newborns about 20-30 per 1000 live births[6,8]. Low- and middle-income countries (LMIC) are resource poor countries with documented high maternal and perinatal morbidity and mortality, which are also much higher in association with SCD. These have been attributed to the poor health seeking behaviors, low literacy rate, widespread poverty as well as poor infrastructure and dysfunctional health care service delivery[6,8].

Pregnancy in SCD women is associated with increased risk and incidence of complications due to the stress posed by the pregnancy and the aggravated physiological changes of pregnancy[4,7]. These complications may be maternal or fetal or both and could occur during the antenatal, intrapartum, or postpartum period. Commonly documented complications include anaemia, vaso-occlusive crisis, malaria infection, acute chest syndrome, pseudo- toxaemia, haemolytic crisis, aplastic crisis, pre-eclampsia, miscarriage, intrauterine growth restriction (IUGR), low birth weight (LBW) infants, stillbirths, and increased risk of operative delivery among others[7,9].

With improved care of the individuals living with SCD, women with HbSS and HbSC constitute an increasing population of pregnant women attending antenatal care (ANC). These women now live longer than in time past due to improved knowledge of the disease, newer therapies and multi-disciplinary care, therefore periodic review to assess the presentation, risk factors or complications in pregnancy, outcomes in pregnancy and identification of areas for improvement is imperative. The University College Hospital (UCH), Ibadan, Nigeria, is a tertiary health facility, staffed with multi-disciplinary specialist and a referral centre for SCD patients including pregnant women.

This study was therefore designed to review the clinical presentation, complications, maternal and fetal outcomes in pregnant SCD women.

MATERIALS AND METHODS

Study design and site: This was a 5-year retrospective study conducted amongst pregnant women managed at the UCH, Ibadan, Nigeria, between January 1, 2016, and December 31, 2020. The UCH, Ibadan, Nigeria, is the foremost and one of the largest teaching hospitals in Nigeria. It is situated in the metropolitan city of Ibadan, in the south-west region of Nigeria, and provides in-patient and out-patient care to people from neighboring states and other regions in Nigeria.

Pregnant women with SCD are managed in a multi-disciplinary approach involving midwives, obstetricians, haematologists, internal medicine physicians, anesthetists, paediatricians, and physiotherapists among others.

Study participants: Pregnant women with SCD managed at UCH, Ibadan, Nigeria, within the study period were identified using the admission register at the obstetrics out-patient unit, obstetrics lying-in wards, labour ward, gynaecological emergency unit and from coding unit at the medical records department. Thereafter, the health records were retrieved from the medical records department.

Inclusion and exclusion criteria: All SCD pregnant women were included in the study while those SCD pregnant women who did not deliver in UCH, Ibadan were excluded.

Survey instrument: Relevant data was extracted from the health records and were entered into a pre-designed proforma which was developed using information in the literature. The proforma contained sections related to the sociodemographic and obstetrics characteristics, clinical presentation, complications, and pregnancy outcomes.

Outcome variables: The maternal and fetal outcome were termed good whenever there was no complication and no deaths in the mothers and babies, respectively. Women or babies with any complication and/or maternal and fetal deaths, respectively, were termed poor outcomes.

Data management and analysis: The data was entered and analysed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp, Armonk, NY, USA). Normally distributed numeric variables were summarized using their means and standard deviations (mean$\pm$SD). Categorical variables were summarized and presented using frequency tables with proportions and charts as appropriate. The Chi-square (χ^2) and Fisher's exact tests were used to test significance for categorical variables and the level of significance was set at $p < 0.05$.

Ethical consideration: The ethical principles of confidentiality, autonomy, beneficence and non-maleficence were maintained. Ethical approval was obtained from the University of Ibadan, and the University College Hospital, Ibadan, Institutional Review Board (UI/EC/22/2204).

RESULTS

During the 5-year period, 9759 pregnancies were managed at UCH, Ibadan, Nigeria, out of which 74 women had SCD, giving a prevalence of 0.65%. The medical case record retrieval rate was 85.0% as only 63 health records were found and eligible for review. The mean age was 28.8+/- 4.1years with majority (54.0%) within the age range of 25 -29 years. About 61.7% of the women had tertiary level of education, while 4.8% had no formal education. Women with HbSS accounted for 63.5% while the remaining were HBSC (36.5%). This is shown in Table I.

Most (60.3%) booked for ANC, with over three-quarters (76.7%) booking in the second trimester. The median gestational age at booking was 18.5 (14.8-21.3) weeks. Forty- six (74.6%) women were admitted during the antenatal period, with most of them admitted only once during pregnancy. A little over half (50.8%) of the women had vaginal delivery. The majority (92.1%) had live births. This is shown in Table II.

Anaemia was the most common antepartum complication occurring in fifty women (79.4%) and with 50% of them requiring transfusion of least one unit of blood. The most common intrapartum complication was fetal distress (15.9%) while LBW infants (17.5%) and NICU admission (15.9%) were the two highest fetal complications. This is shown in Table III.

Forty-five women (71.4%) had good maternal outcome while four women (6.3%) died, all deaths occurred among the un-booked pregnant women. The fetal outcome was good in thirty-nine patients (61.9%). This is shown in Figure 1.

There was an association between good maternal outcome and booking for antenatal care (p=0.01), while having tertiary level of education(p=0.04) and being a multigravida (p=0.03) were statistically significant associations for good fetal outcome. This is shown in Table IV.

DISCUSSION

This study found the prevalence of SCD in pregnant women to be 0.65% which was similar to 6.9 per 10,000 deliveries reported in Abakaliki, Nigeria[10]. Previous studies had revealed lower prevalence rates ranging from 0.14- 0.34%[7,11,12] Although, these studies were also conducted in tertiary centres, the low prevalence could be due to relative subfertility among SCD women, and many more of the affected children died earlier in childhood. Thus, they did not survive to the reproductive age group. Also, it may be due to the availability of more and better equipped secondary health facilities around the study sites, where pregnant women with SCD were managed, hence leading to less referrals to tertiary centers. However, other researchers have reported higher prevalence rates ranging from 1.0-1.16%[5,9,13], which may be due to the improved health care service delivery and referral system in the study environment. In addition, the costs and affordability of fees for health care services may affect the prevalence rates, since payments are mostly from out-of-pocket[9,14,15].

In our study, HbSS accounted for about two-thirds (63.5%) with the remaining pregnant women being HbSC (36.5%). This was similar to findings of previous studies in Nigeria and Europe, however a study in Jos, Nigeria, reported a much higher proportion of SCD pregnant women with HbSS (97.4%)[9-11,16]. The reason for this higher rate of HbSS is unknown but it may be due to the criteria for laboratory diagnosis and a much lower sample size compared to this study[11,13].

The mean maternal age for this study was 28.8+/- 4.1years, with a modal age bracket of 25-29 years. This was similar to a previous study conducted in the United Kingdom which reported that 81% of the women were within the age range of 25-39years[16]. With improved quality of health care, SCD women are healthier and surviving to the reproductive age group, even in developing countries, unlike in the past years.

Majority (61.1%) of the women had tertiary education. This was similar to the study by Nwabuko et al. which reported that 56% had tertiary education[7]. On the contrary, Kahansim et al. in their study reported that the majority had secondary education[11]. This variation could be due to poor access to quality education in the geo-political zone where the study was carried out. The impact of education on health seeking behavior of SCD pregnant women cannot be over emphasized, as this study revealed that majority (86.7%) of booked SCD pregnant women had at least the tertiary level education compared with only 24% of un-booked that had similar level of education. Improving literacy rates must be a top priority for families and policy makers.

Two-thirds of SCD pregnant women booked for ANC with three-quarters of these women making the first visit in the second trimester. This observation is worrisome as these group of patients ought to have benefitted from preconception care or at least early booking in the first trimester which would have offered them the opportunity to be properly educated on the implications of their SCD on pregnancy, institute appropriate preventive measures, early diagnosis of complication and treatment, birth preparedness and development of a plan for delivery. Since most women with SCD are more likely to consults other physicians before obstetricians, there is a need to emphasize health education on pregnancy-related events. In addition, the media may be used to disseminate information on the need for SCD women to access healthcare regularly especially in the pre-pregnancy or early pregnancy. These may help to reduce late presentation,

complications, morbidities and mortalities associated with SCD in pregnancy. The importance of early booking is that it will afford the women the opportunity to have more contacts with antenatal healthcare provider, thereby optimizing the benefits of ANC.

Majority of the women (58.7%) had at least one previous parous experience and most pregnant women book late most especially multiparous women as against the World Health Organization (WHO) recommended pre-conception care and early booking before 12 weeks of gestation[17-19]. Multiparous women may have a wrong belief that they have more knowledge and experience about pregnancy, while pregnancy risk has been shown to increase with increasing parity[16,20]. However, Nwabuko et al. showed that the majority booked after first trimester (83.1%)[7].

More than half of the women had one or two children. SCD in pregnancy is high-risk, in which preconception care is paramount for adequate preparedness for pregnancy and early booking for good and effective management to improve pregnancy outcome[7]. In addition, limiting family size will reduce the frequency of exposure to sickle cell crisis and improve overall survival rate for the SCD woman. Thus, ensuring that SCD women have access to contraceptives is imperative including addressing the barriers to contraception access.

Anaemia in pregnancy was the most common complication reported in this study. This is corroborated by previous studies especially in the developing countries[16,20,21]. About 3 in 4 pregnant women with SCD had anaemia with packed cell volume (PCV) of less than 30.0%; however, only 39.7% required antepartum blood transfusion and mostly un-booked. The low level of transfusion compared with the level of anaemia is not surprising as SCD is a chronic condition with majority of SCD pregnant women having steady state packed cell volume and are not usually symptomatic. Other studies have reported a much higher rate of antepartum blood transfusion to about a rate of 70.0%[13,22]. This may be due to many reasons, but blood transfusion has its risks and should be given to women only when necessary. SCD women had malaria infection, this might have contributed to the prevalence of anemia among them.

Women with HbSS experienced more severe complications than HbSC; 85.0% of HbSS and 70.0 % of HbSC had anaemia. Similar studies done by Olugbenga et al. and Elenga et al. reported that pregnant women with HbSS experienced more maternal and perinatal complications than HbCC and HbSC[9,23]. The most common crisis reported in this study was vaso-occlusive crisis, which occurred in about half of the women. Similar findings were noted in Ghana where vaso-occlusive crisis occurred in 57.0% of women, however a few other studies have reported hyper-hemolytic crisis as the most common crisis that occurred in 70.6% of cases[21,24]. SCD women must be empowered with information about preventive measures for these crises. The multidisciplinary team of specialists too must be regularly trained and equipped to manage such crisis whenever it occurs.

A high incidence of caesarean section (CS) of 46.1% was observed in this study, which is similar to few other studies, however some studies have reported higher CS rates of approximately 65%[23-25]. These CSs were necessitated due to the high incidence of maternal and fetal complications among pregnant SCD women. This will also depend on the nature of presentation and whether the women are booked or un-booked for ANC[23]. Notwithstanding, the goal of management should be to achieve vaginal delivery as much as possible, except if CS is indicated to prevent maternal and fetal morbidity and mortality. In well managed SCD women, a vaginal delivery rate of 75.0% have been reported[26].

This study reported live delivery in 92.1% of the women; however, other births were complicated by intrauterine growth restriction (IUGR), Neonatal Intensive Care Unit (NICU) admissions for various indications such as prematurity, birth asphyxia, low birth weight, and

perinatal deaths. Other studies have reported that most perinatal deaths are due to prematurity;[23,27] however, most of the perinatal deaths in this study were due to asphyxia. This is because most of the pregnant SCD women in this study delivered after 37 weeks of gestation.

Our study reported that most of the women (71.4%) had good maternal outcomes, however some women experienced undesirable outcomes such as NICU admission, postpartum hemorrhage, and perinatal deaths amongst others. These constitute a burden to the patients, their families and health systems. Other studies have reported similar incidences of poor maternal outcomes, and this shows that SCD in pregnancy is a high-risk pregnancy that requires multi-disciplinary care to improve maternal and perinatal outcomes[13,20].

In this study, women who had tertiary level of education or higher (p=0.01) was significantly associated with good maternal outcome. This suggests that higher level of education among women with SCD will improve understanding and health seeking behavior, thus improving the health outcomes. A similar association between the level of education(p=0.04) and good fetal outcome was also observed in this study, so its importance cannot be underemphasized. Women who are multigravida (p=0.03) also had statistically significant associations with good fetal outcome. Previous studies among pregnant women have showed similar finding[28,29].

Ensuring that pregnant women with SCD book at a health facility with obstetrician or skilled antenatal care provider is expected to improve the maternal outcome. However, booking status was not associated with good maternal and fetal outcomes in this study, although other studies done in developing countries had revealed poor fetal and maternal complications[26,27,30]. Nevertheless, early booking, with multidisciplinary care is paramount to improving the fetal-maternal outcome in SCD pregnant women.

In this study, parity had an influence on fetal outcome as multigravidas had better fetal outcomes. Though, there is paucity of literature on the role of parity, this may be explained by the fact that women in their first pregnancy may have poor preparation for pregnancy, difficult labour and delivery, poor knowledge of newborn care, poor decisions making and health seeking behavior. More studies will be needed to evaluate this observation, however, what has been advocated in the literature is that women with SCD should be encouraged to have family planning and pre-conception care to ensure good maternal and fetal outcomes irrespective of the parity[15,31,32].

CONCLUSION:

This study observed that there was a high prevalence of SCD among pregnant women in this environment, with anaemia being the most common maternal complication. Majority of pregnant SCD women had good maternal and fetal outcomes with women having ANC and tertiary level of education being strong determinants. Therefore, there is need to improve the educational level of women, continued knowledge of the disease, in relation to physiologic changes in pregnancy and pregnancy-SCD interaction among women living with SCD planning to conceive using pre-conceptional assessment and counselling, emphasizing on importance of early booking and multi-disciplinary care to improve maternal and perinatal outcome. Genetic counselling is paramount for HBSS women during the preconception period and early antenatal period. This will afford them the opportunity of partner screening and prenatal diagnosis in order to reduce prevalence of HBSS.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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Table 1: Sociodemographic characteristics of the women.

Variable	Frequency (n = 63)	Percentage (%)
Age in years		
20 – 24	8	12.7
25 – 29	34	54.0
30 – 34	13	20.6
≥ 35	8	12.7
Level of education		
Non-formal	3	4.8
Primary	4	6.3
Secondary	17	27.0
Tertiary	39	61.9
Occupation		
Un-skilled	32	50.8
Skilled	31	49.2
Parity		
Primigravida	26	41.3
Multigravida	37	58.7
Genotype		
SS	40	63.5
SC	23	36.5

Table 2: Obstetrics characteristics of the women.

Variable	Frequency (n = 63)	Percentage (%)
Booking status		
Booked	38	60.3
Un-booked	25	39.7
Trimester at booking (n=38)		
First	6	15.8
Second	29	76.3
Third	3	7.9
Hospital admission during pregnancy		
Yes	**47**	**74.6**
No	16	25.4
Number of times admitted during pregnancy(n=47)		
1	32	68.1
2	12	25.5
3	2	4.3
Missing	1	2.1
GA at Delivery in weeks		
< 34	5	7.9
34 – 36	13	20.6
≥ 37	45	71.5
Mode of Delivery		
Vaginal delivery	32	50.8
Urgent/Emergency CS	18	28.5
Planned/Scheduled CS	11	17.5
Neonatal Outcome		
Live birth	58	92.1
Still birth	3	7.9
Duration of post-partum hospital stay (in days)		
1-5	53	86.9
> 5	8	13.1

Table 3: Maternal and fetal complications among the women.

Variable		Frequency (n = 63)	Percentage (%)
Maternal	**Antepartum**		
	Miscarriage	2	3.2
	Anaemia	50	79.4
	Urinary tract infection	15	23.8
	Sequestration crisis	4	6.3
	Hyper-haemolytic crisis	11	17.5
	Vaso-occlusive crisis	35	55.6
	Preeclampsia	7	11.1
	Pseudo-toxaemia of pregnancy	1	1.6
	Malaria	35	55.6
	Intrapartum		
	Fetal distress	10	15.9
	Shoulder dystocia	1	1.6
	Obstructed labour	2	3.2
	Postpartum		
	Postpartum haemorrhage	4	6.3
	Sepsis	4	6.3
	Intensive care unit (ICU) admission	7	11.1
Fetal	Prematurity	3	4.8
	IUGR	7	14.3
	Birth asphyxia	7	14.3
	LBW	11	17.5
	Early neonatal death (ENND)	1	1.6
	Intrauterine fetal death (IUFD)	2	3.2
	NICU admission	10	15.9

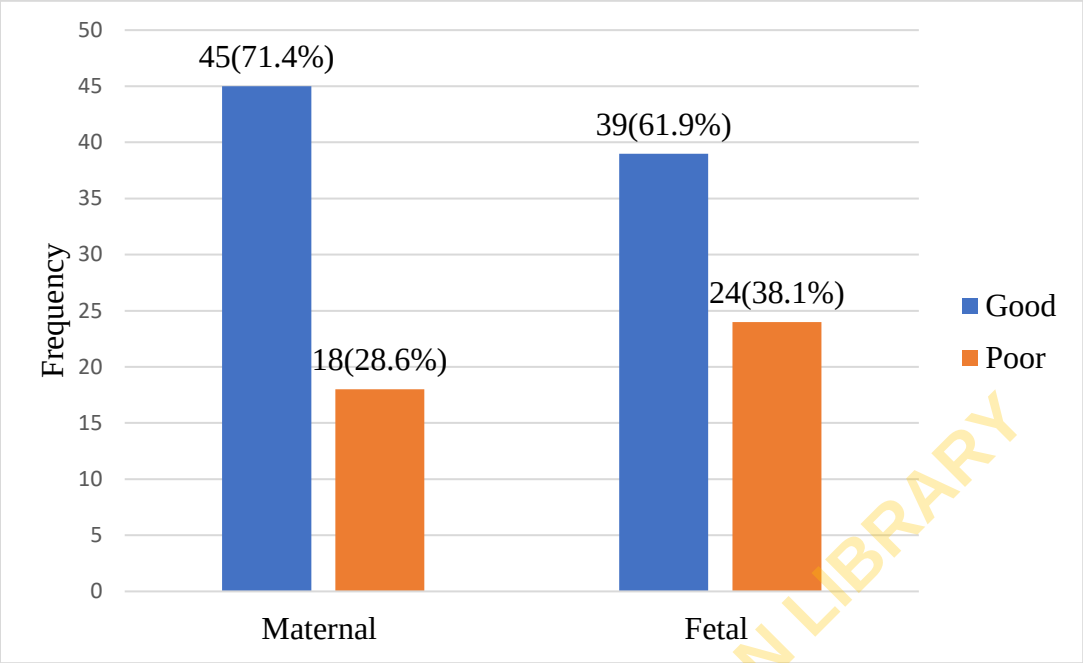

Figure 1: Maternal and fetal outcomes among the women.

Table 4: Associations with maternal and fetal outcomes among the women

Variable		Maternal outcome		Total	χ^2	p- value
		Good	Poor			
Age in years	20 – 24	5(62.5)	3(37.5)	8(100.0)		
	25 – 29	24(70.1)	10(29.1)	34(100.0)	1.74	0.63
	30 – 34	11(84.6)	2(13.4)	13(100.0)		
	≥ 35	5(62.5)	3(37.5)	8(100.0)		
Level of education	Non-tertiary	14(58.3)	10(41.7)	24(100.0)	3.26	0.71
	Tertiary	31(79.5)	8(20.5)	39(100.0)		
Occupation	Un-skilled	23(71.9)	9(28.1)	32(100.0)	0.01	0.94
	Skilled	22(71.0)	9(29.0)	31(100.0)		
Parity	Primigravida	18(69.2)	8(30.8)	26(100.0)	0.11	0.75
	Multigravida	27(73.0)	10(27.0)	37(100.0)		
Booking status	Booked	32(84.3)	6(15.7)	38(100.0)	7.66	0.01
	Un-booked	13(52.0)	12(48.0)	25(100.0)		
		Fetal outcome				
		Good	**Poor**			
Age in years	20 – 24	4(50.0)	4(50.0)	8(100.0)	1.48	0.70
	25 – 29	23(67.7)	11(32.3)	34(100.0)		
	30 – 34	8(61.5)	5(38.5)	13(100.0)		
	≥ 35	4(50.0)	4(50.0)	8(100.0)		
Level of education	Non-tertiary	11(45.8)	13(54.2)	24(100.0)	4.25	0.04
	Tertiary	28(71.8)	11(28.2)	39(100.0)		
Occupation	Un-skilled	19(59.4)	13(40.6)	23(100.0)	0.18	0.67
	Skilled	20(64.5)	11(35.5)	31(100.0)		
Parity	Primigravida	12(46.2)	14(52.8)	26(100.0)	4.66	0.03
	Multigravida	27(73.0)	10(27.0)	37(100.0)		
Booking status	Booked	27(71.1)	11(28.9)	38(100.0)	3.40	0.06
	Un-booked	12(48.0)	13(52.0)	25(100.0)		