Preterm Births Factors at Kampala International University Teaching Hospital, Ishaka-Bushenyi District

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ABSTRACT

The study aimed to identify factors influencing preterm deliveries at Kampala International University Teaching Hospital, Ishaka - Bushenyi District, and develop measures to reduce them. The research used cross-sectional and descriptive data collection methods, with respondents selected using purposive sampling. The majority of respondents were prime gravidas (35.6%), followed by multigravida (more than 4) (26.7%). The study found numerous factors with high associations to preterm birth among these women. It recommended increasing health education on family planning, attending ANC clinics early, and intensifying monitoring of high-risk mothers, particularly those with multiple pregnancies, multi gravida, shorter interpregnancy intervals, and a history of preterm birth. The study concluded that numerous factors were associated with preterm birth among these women.

Keywords: factors, preterm births, pregnancy, antenatal care

INTRODUCTION

World Health Organization [1], defines preterm deliveries as babies born alive before 37 weeks of pregnancy are completed. The cause for preterm deliveries is in manysituations elusive and unknown; many factors appear to be associated with the development of preterm deliveries, making the reduction of preterm deliverieschallenging proposition [2, 3, 4]. Premature infants are at greater risk for short- and long-term complications, including disabilities and impediments in growth andmental development [5, 6].The [7], estimates that in 2016, approximately 10.6% of all live births globallywere preterm. It is estimated that globally, more than 3 million babies are born prematurely and prematurity accounts for 10% of neonatal mortality, or around 500,000 deaths per year [8]. In Africa, preterm deliveries are also on the rise in some countries with Nigeria having an estimated 236,148 preterm deliveries, while South Africa has 71,901 and in Kenya 57,498 deliveries per year, while Uganda has an estimated 42,690 preterm deliveries each year [9]. The predisposing factors of preterm deliveries are many and these include previouspreterm deliveries, chronic conditions such as high blood pressure, uterine or cervical problems such as uterine infections, being underweight or overweight, poor nutrition during pregnancy as well as malaria among many others [10]. Preterm delivery is the major cause of neonatal mortality [10]. The shorter the term of pregnancy, the greater the risks of mortality and morbidity for the baby primarily due to the related prematurity [11]. Premature babies have an increased risk of death in the first year of life (infant mortality), with most of thatoccurring in the first month of life (neonatal mortality) [12]. Globally, in the U.S. where 550,000 prematures are born each year, prematurity is the leading cause of neonatal mortality at 25% [13]. Premature babies are also at greater risk for having subsequent serious chronic health problems [14], The factors responsible for preterm deliveries include trauma and domestic violence during pregnancy, lack of prenatal care, having had multiple miscarriages or abortions among others [15].

METHODOLOGY
Study Design and Rationale

The study design was cross-sectional and descriptive, employing both quantitative and qualitative data [16] collection methods.

Study Setting and Rationale

The study was carried out at the Neonatal ward of Kampala International University Teaching Hospital, Ishaka –Bushenyi District, of Western Uganda. KIU-TH is located in the town of Ishaka, in Bushenyi District, western Uganda, approximately 330 kilometers (210 mi), by road, southwest of Kampala, Uganda`s capital city. It runs under a private/public partnership, but is government aided because it is a training facility. It has about 700 beds it offers many health care services including immunization, obstetrics andemergency care, HIV/AIDS management services, surgical, medical and pediatrics laboratory services, nutrition services, family planning services, antenatal and post-natal services among many others. It also offers specialized services eg ENT, Orthopedics, Oncology etc. The study setting was selected because there are many registered cases of preterm deliveries at the hospital every month and it is well known and easily accessible to by the researcher since she is a service provider there.

Study Population
The study included mothers who have a preterm delivery in the Neonatal ward ofKampala International University Teaching Hospital, Ishaka -Bushenyi District.

Sample size determination
The sample size was determined using the Slovin's formula [17].

$$n = \frac{N}{(1 + Ne^2)}$$

Where,
n = estimated sample size
N= The population size that was derived from a daily average admission of preterm babies of 10 babies and an estimated data collection time of 10 days which approximates the population to 100
e = margin of error (5%) with the level of precision of 0.05

$$n = \frac{100}{(1 + 100 \times 0.05^2)} = 80$$

Therefore 80 mothers of preterm babies were expected to be at the facility during thetime of data collection.

The desired sample size was determined by scaling down the estimated sample size

$$S = \frac{n}{1 + \frac{n}{N}}$$

Where,

S was the desired sample size

N was the expected sample population (100)n was
the estimated sample size (80)

$$S = \frac{80}{1 + \frac{80}{100}} = 45$$

Therefore 45 mothers of preterm babies were recruited for this study.

Sampling Procedure

The respondents for the study were selected using purposive sampling to get the available respondents who met the study criteria and include them in the study. In this procedure, the researcher simply selected mothers in the neonatal unit who met the study criteria andinclude them in the study. This continued until the total of 163 respondents are achieved.

Inclusion Criteria

The study included only mothers who have a preterm delivery at Kampala International University Teaching Hospital and had voluntarily consented to participate in the study.

Exclusion Criteria

The study excluded mothers who do not have preterm deliveries, those who are in poor condition and cannot talk, eg, those who are depressed as a result of the outcome of pregnancy, as well as those who refuse to voluntarily consent to participate in the study.

Research Instruments

Data was collected using an approved semi-structured questionnaire, designed in English which consisted of both open and closed ended questions. This tool was chosen becauseit allowed for the efficient and confidential collection of data in the shortest time possible.

Data Collection Procedure

The researcher collected data from one respondent at a time. The researcher sampled respondents from the Neonatal ward without research assistants. This improved efficiency and confidentiality during the data collection. Data was collected for 41 days. Depending on the availability of respondents, the researcher plans to interview 4 mothers per day.

Data Analysis

The collected data was first analyzed manually by tallying, after which the researcher presented them in tables, graphs and pie charts generated by Microsoft Excel Version, 2013.

Ethical Considerations

A letter of introduction was obtained from Kampala International University Faculty of Clinical Medicine and Dentistry introducing the researcher and seeking permission to carry out the study from the administration of Kampala International University TeachingHospital and seeking permission to conduct the study. After permission is granted, the researcher was introduced to the in-charge of the Neonatal ward who thereafter introduced the researcher to the respondents. Participants were assured of maximum confidentiality and numbers instead of names were used to identify respondents. The study was only commenced after the objectives of the study have been well explained to participants and making sure they have understood and consented to participate in the study. The interview process took place in the duty room because of the sensitive nature of some questions and one mother at a time were interviewed [18].

RESULTS
Table 1: shows the bio data of the respondents

Variable		Frequency(n)	Percent (%)
Age	< 19 years	8	17.8
	20 – 28 years	20	44.4
	29 – 34 years	7	15.6
	>34 years	10	22.2
Marital status	Single	7	15.6
	Married	38	84.4
	Divorced	0	0
Weight	< 30kg	0	0
	30 - 45 kg	0	0
	46 - 55kg	13	28.9
	56 - 65kg	20	44.4
	66 - 75kg	9	20.0
	>75kg	3	6.7
Height	<140 cm	2	4.4
	141-150 cm	3	6.7
	151-165cm	32	71.1
	166-175 cm	8	17.8
	>176 cm	0	0
Level of education	Tertiary / university	8	17.8
	Secondary	15	33.3
	Primary or None	22	48.9
Weeks of amenorrhea	< 28 weeks	4	8.9
	28 - <32 weeks	12	26.7
	32- <34 weeks	8	17.8
	34 - <37 weeks	21	46.7
Mode of delivery	SVD	36	80.0
	Caesarian section	9	20.0

Table 1 shows that the majority 20 (44.4%) were of ages 20 to 28 and 15.6% were between 29 to 34 years. This finding indicates that preterm birth was more common among married women 38 (84.4%) with 7(15.6%) singles none had divorced. On Maternal weight, 44.4% of the respondents were between 56-65 kg body weights at their first ANC and 3 (6.7%) were the least with > 75 kg.As related to level of education of respondents, it shows that 22 (48.9%) had only attended primary education or none whereas 8 (17.8%) attended tertiary and university. Respondents who delivered between 34 and <37 weeks were 21 (46.7%) ofall the respondents and 4(8.9%) delivered at less than 28 weeks of gestation. 38 (80%)of the respondents delivered by spontaneous vaginal delivery (SVD) and 20% delivered by emergency caesarian section.

Table 2: shows residence of the respondents

Response	Frequency (n)	Percent (%)
Village	16	35.6
Trading center	12	26.7
Municipality	4	8.9
City	13	28.9
Total	45	100.0

The table 2 above shows the respondents residence ranging from village, town council municipality to city with percentage residence of 37.8%, 24.4%, 8.9% and 28.9% respectively.
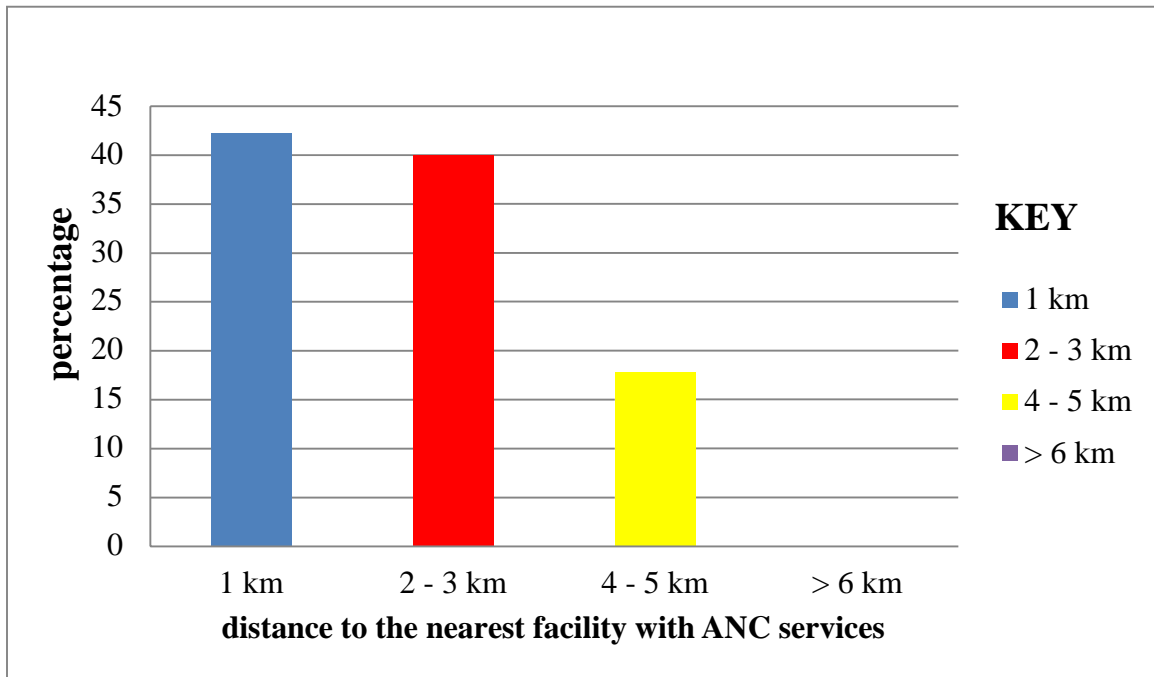
Figure 1: shows the distance to the nearest health facility with ANC services

The figure 2 above shows that 19(42.25) of the respondents were only living 1kmaway from the health facility with ANC services, 18(40%) and 8(17.8%) were 2-3km and 4-5km away. None of the respondents was travelling for more than 6km to access the ANC clinic.

Table 3: shows the responses on smoking and alcohol consumption

Variable	Response	Frequency	Percentage
Smoking (n=45)	Yes	11	24.4
	No	34	75.6
Duration of exposure to smoke (n=11)	1 − 2 hours	3	27.3
	3 − 5 hours	5	45.4
	Active smokers		18.2
	Once in a week		9.1
Alcohol consumption (n=45)	Yes	11	24.4
	No	34	75.6
How often they drink (n=11)	Daily		27.3
	Sometimes		54.5
	Once in a while		18.2
When they started drinking (n=11)	Before index pregnancy	9	81.8
	1st trimester	1	9.1
	2nd trimester	1	9.1
	3rd trimester	0	0

Table 3 above indicates the respondents who were smoking actively or passivelyduring or even before the index pregnancy.24.4% (11) of the respondents were actively or passively smoking and the majority of the respondents 75.6% (34) were neither smoking actively nor passively.

Results indicated that the duration of exposure to the smoke was 45.4% (5) exposed at least 3 to 5 hours daily, 27.3% (3) were between 1 to 2 hours of daily exposure and those who were actively smoking and those who were not often exposed or exposed once a week were 18.2% and 9.1% respectively.On alcohol consumption, 24.4% were using alcohol while the majority of the respondents were not drinking before and even after conception of the index pregnancy. Among the respondents who were drinking alcohol, 27.3% were drinking daily, 54.5% (6) used to drink sometimes and 2 were drinking once in a while. 81.8 % (9) started drinking before the index pregnancy, those who started during the first and second trimesters were both at 9.1% and none of the respondents had started drinking in the third trimester.

Table 4: showing occupation of mothers

Response	Frequency (n)	Percentage (%)
Formal	11	24.4
Informal	34	75.6
Total	45	100

Table 6 compared the respondents with their occupation and the majority75.6% (34) was doing casual work including house wives, peasants and street vendors. Only 11(24.4%) had formal jobs that included nursery teachers, secondary teachers and a lawyer.
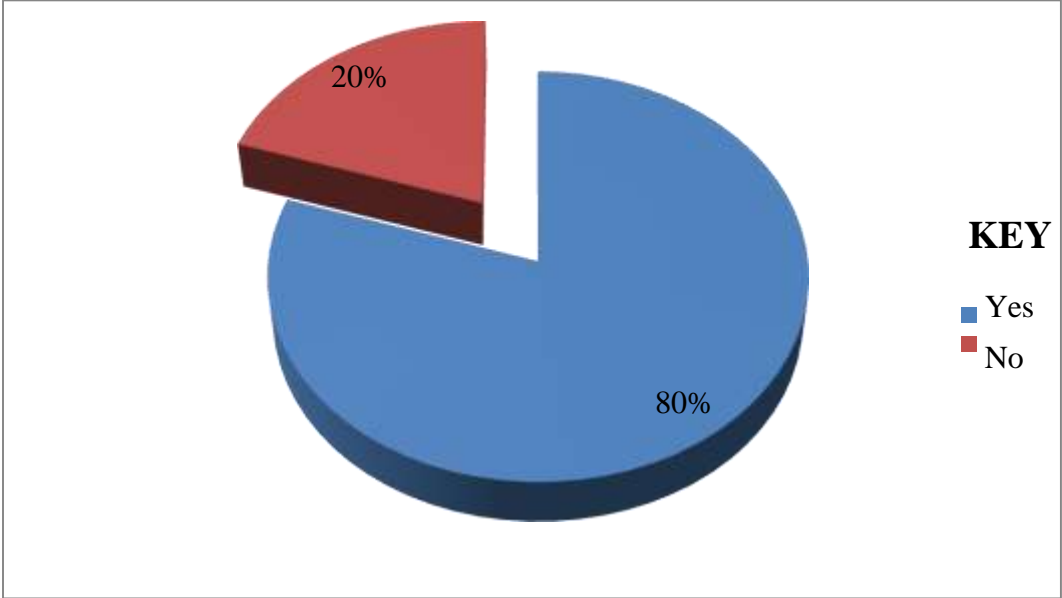
Figure 2: pie chart showing work that involved lifting, sitting and standing for a longtime

Figure 2 shows that 80% of the respondents were involved in the work that involved siting, standing and lifting and only 20% of them were not involved in any work that required them to sit stand for long or lift.
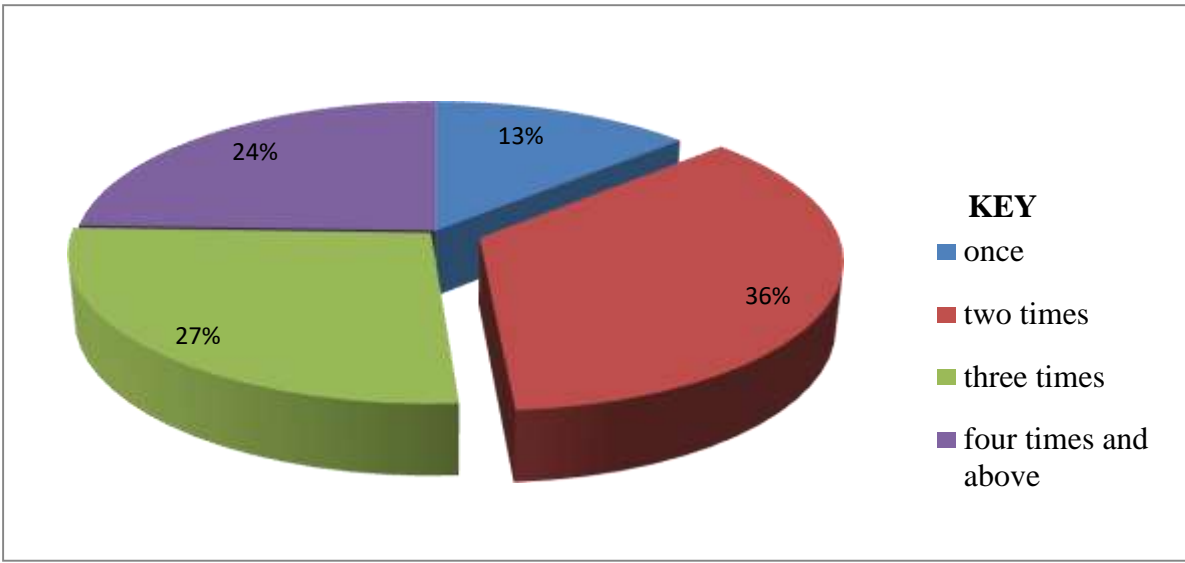

Figure 3: shows number of ANC visits attended

Figure 3 shows the number of times attended by respondents at different stages during their index pregnancies.13.3%, 35.6%, 26.7% and 24.4% attended once, twice, three times and four times and more respectively.

Table 5: Gestational age at booking and reason for booking in the 2ⁿᵈ and 3ʳᵈtrimester

Response		Frequency(n)	Percent %
Gestationalat age booking	1ˢᵗ trimester	23	51.1
	2ⁿᵈ trimester	20	44.4
	3ʳᵈ trimester	2	4.4
Reason for booking In the 2ⁿᵈ and 3ʳᵈ trimester	Busy at work	10	46.7
	Un aware of pregnancy	6	28.3
	Long distance and transport issues	4	19.1
	Ignorant about the importance of early booking	2	9.5

Table 5 above indicates that 51.1% (23) booked during their first trimester, 42.2 % (19) in the second trimester and 6.7% (3) in their third trimester. Concerning reasons why mothers booked during their second and third trimesters.47.6% of the respondentsreported that they were busy at work, 23.8% were unaware that they were pregnant, 19.1% (4) reported that long distance and transport issues to the facility affected their booking. 9.5 % (2) did not know the importance of booking in first trimester. This section involved maternal characteristics majority the number of times she has ever conceived. The table below shows that 35.6% of the respondents were prime gravid, 13.3% were gravid two ,15.6%, 8.9% and 26.7% were gravid three, four and more than four respectively.
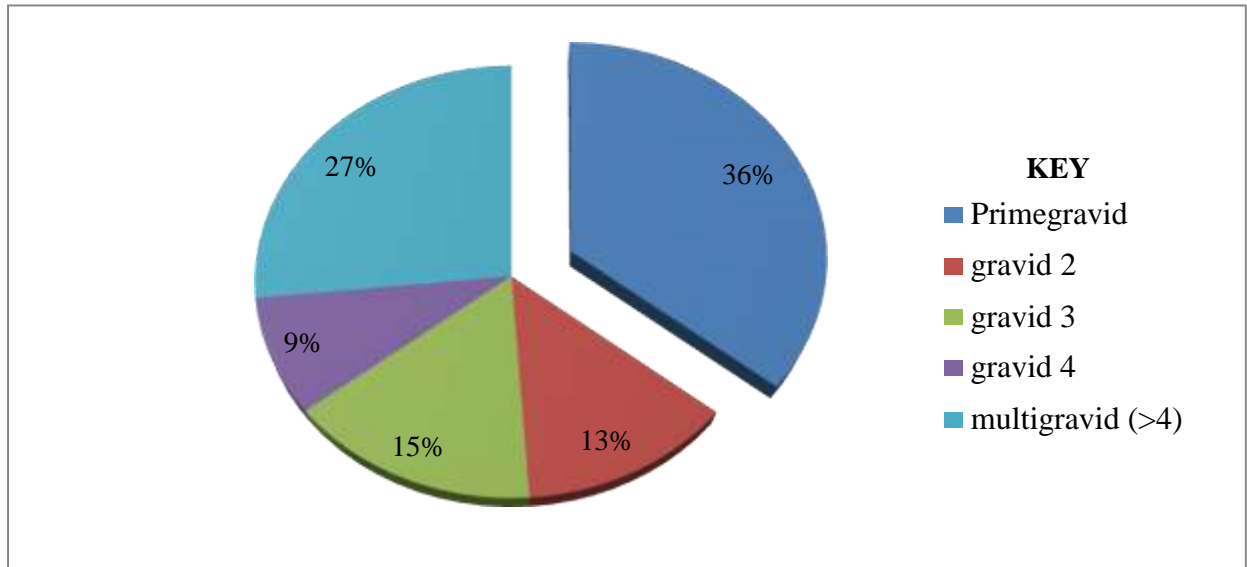

Figure 4: shows Parity of the respondents

Participants who had a history of preterm delivery were 57.8% as compared to the 42.2% that had never had any preterm delivery that also included the prim parity.
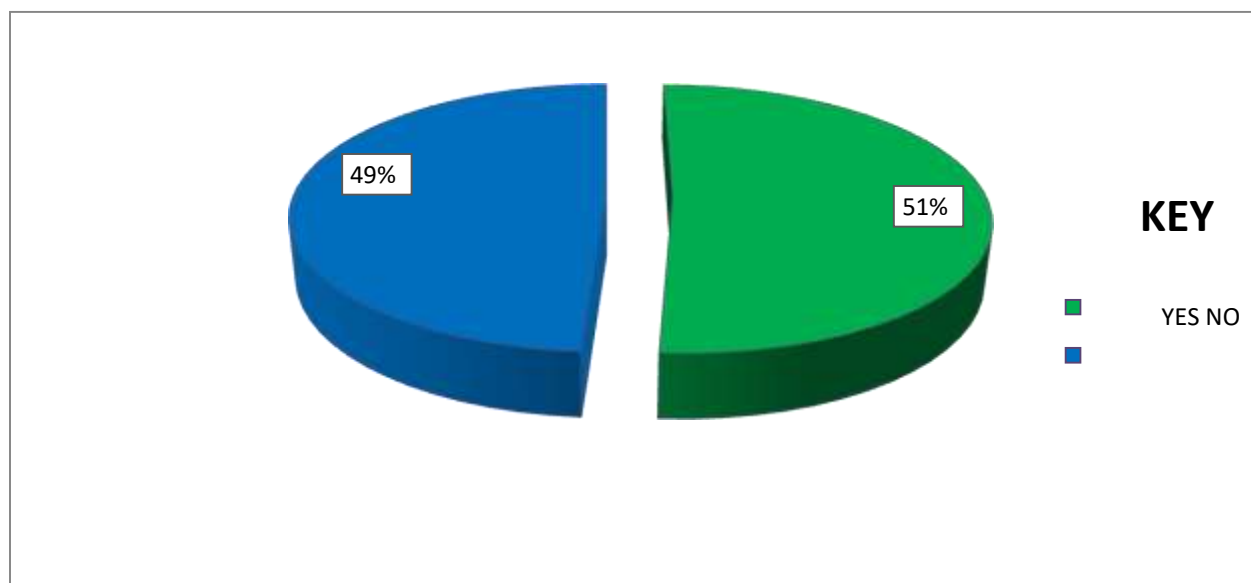
49% 51% **KEY**

YES NO

Figure 5: shows pregnancies with more than one baby

Figure 5 above assessed respondents on pregnancy with more than one baby. 51.1% ofthe respondents have had a multiple pregnancy and 48.9% have never had one in their life time.

Table 6: Number of babies in a single pregnancy

Response	Frequency (n)	Percentage %
Twins	23	100
Triplets	00	0
Four babies	00	0
Total	23	100

Table 6 above shows that among all the respondents that have had pregnancies with more than one babies have had twins. None of the respondents have ever had triplets or four babies in a single pregnancy. The response from participants who had a pregnancy with more than one baby, only 4(17.4%) were delivered above 37 weeks of gestation and the majority 19 (82.6%) were delivered premature (below 37 weeks of gestation). Result about inter-pregnancy interval indicated that 34.5% of the respondents conceived wen their babies were just 6 months old, 41.4% ,17.2% and 6.9% had an inter-pregnancy interval of one, two and three years and above respectively.

DISCUSSION

The mean age of the participants was 25 years (range 20-28) years. 85.3% of the respondents were married while 14.7% were single this may be due to the fact that the majority of the respondents were in the reproductive age bracket appropriate for marriage.   These findings are almost similar to those of a study done in Kenya where the age range of the women was between 26 ± 5 years with majority (89%) being aged 20 years and above. Regarding the level of education, 48.9% of the mothers had attained primary education. This could be due to the low social economic status of the majority population in the area. These findings are in line with the result from a study carried out in Spain, where educational level of ≤ secondary studies had an increased risk of preterm birth [19]. The study showed that 37.8% of the mothers who participated in the study resided in villages. This was related to the fact that the majority of the respondents were referrals in from remote facilities. These

findings correspond with the findings of a study done in Ethiopia where mothers that resided in rural areas and in big cities were significantly predisposed to preterm birth with 34.7% and 65.3% respectively [20]. This is due to the type of work they do and the location of the facilities with ANC services. About occupation, the findings showed that 64.4% of the mothers were casual workers with the majority being house wives whereas 35.6% of the mothers were formally employed. This related to the work that casual workers do which involves lifting, standing or sitting for a long period of time. These findings differ from those inSomalia where 82% of the mothers were housewives, 12.7% had private businesses and 4.7% of the mothers were employed by the government [21]. On Lifestyle of the participants, it indicated that respondents who were smoking actively or passively during or even before the index pregnancy were 24.4% (11) and themajority of the respondents 75.6% (34) were neither smoking actively nor passively. Those that were exposed to tobacco smoke their duration of exposure was 45.4% (5) exposed at least 3 to 5 hours daily, 27.3% (3) were between 1 to 2 hours of daily exposure and those who were actively smoking and those who were not often exposed or exposed once a week were 18.2% and 9.1% respectively. This was attributed to their places of residence where by the biggest number of exposed participants resided in city suburbs. These findings were not in line with those of [22] in a study done in Kawempe and Nagulu hospitals Kampala Uganda where mothers who were smoking at home were 4.44 times greater than that among mothers who never had preterm babies. Concerning alcohol consumption findings show that the majority of the respondents 75.6% were not drinking before and even after conception of the index pregnancy, among the 24.4% that were using alcohol, 54.5 % (6) used to drink sometimes and 27.3% drinking daily. This was not in line with the findings of the study in Western Australia where preterm birth was associated with moderate and higher levels of prenatal alcohol consumption for the group of women who ceased drinking before the second trimester. Heavy alcohol consumption during the second and third trimesterswas associated with increased risk of preterm delivery among pregnant women in a Prospective cohort study done in Japan [23]. Mothers who were $151 - 165$ cm were the majority of the participants 71.1%. This was not in line with the findings in a study done among Indian women where decreased maternal height of less than 1.5m was mentioned among the factors that contributed greatly to preterm births [24]. Concerning marital status, the majority of the respondents (85.3%) were married. This was related to type of work the participants used to do during the pregnancy period that involved more of physical stress with or without help of their husbands. This finding indicated that preterm birth was more common among married women than the singles and the divorced. This was contrary to the findings in a cross-sectional study done in Spain where single mothers were reported to have an increased risk of delivering preterm babies and LBW [11].

CONCLUSION

Uganda has a high preterm birth rate, accounting for 35% of all neonatal deaths worldwide. In November 2021, the MRRH NICU admitted 967 neonates, with 53.8% being preterm babies. 37.6% of these babies died due to preterm birth conditions, accounting for 69% of the 284 neonatal deaths. Factors associated with preterm birth include socio-demographic and maternal factors such as multiple pregnancy, maternal height, interpregnancy interval, maternal age, and occupation.

REFERENCES

1. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/250796).
2. Barros, F.C., Rabello, Neto, D.L., Villar, J., Kennedy, S.H., Silveira, M.F., Diaz- Rossello,
3. J.L., Victora, C.G. (2018). Caesarean sections and the prevalence of preterm and early-term births in Brazil: Secondary analyses of national birth registration. *BMJ Open*, 8,e021538.
4. Egesa, W. I., Odoch, S., Odong, R. J., Nakalema, G., Asiimwe, D., Ekuk, E., ... & Kumbakulu, P. K. (2021). Germinal Matrix-Intraventricular Hemorrhage: A Tale of Preterm Infants. *International journal of pediatrics*, *2021*, 6622598.
5. Egesa, W. I., Odong, R. J., Kalubi, P., Yamile, E. A. O., Atwine, D., Turyasiima, M., ... & Ssebuufu, R. (2020). Preterm Neonatal Mortality and Its Determinants at a Tertiary Hospital in Western Uganda: A Prospective Cohort Study. *Pediatric health, medicine and therapeutics*, *11*, 409-420.

6. Kumar, S., Stecher, G., Li, M., Knyaz, C. and Tamura, K. (2018) MEGA X: Molecular Evolutionary Genetics Analysis across Computing Platforms. Molecular Biology and Evolution, *35*, 1547-1549. https://doi.org/10.1093/molbev/msy096
7. Misrach Z. L., Vempati P., Vulli V. R., Suberu S. A. (2018). The Effect of Fenugreek Seed powder in Augmenting Expressed Breast Milk Volume from Mothers of Preterm Infants at Tikur Anbessa Neonatal Intensive Care Unit. Global Journal for Research Analysis 7 (3)

8. World Health Organization (2018) World Health Statistics 2018: Monitoring Health for the SDGs, Sustainable Development Goals. Geneva.

9. Iltaf, G., Shahid, B., Khan, M.I. (2017). Incidence and associated risk factors of low birthweight babies born in Shaikh Khalifa Bin Zayad Al-Nayan Hospital Muzaffarabad, Azad Jammu and Kashmir. *Pak. J. Med. Sci.* 33, 626–630.
10. Wagura, P.,Wasunna, A., Laving, A.,Wamalwa, D.,Ng'ang'a, P. (2018). Prevalence and factors associated with preterm deliveriesat Kenyatta national hospital. *BMC Pregnancy Childbirth*, 18, 107.
11. Mohammad L Rahman, Deepika Shrestha, Tsegaselassie Workalemahu, Jing Wu, Chunming Zhu, Cuilin Zhang, Fasil Tekola-Ayele, Maternal and Offspring Genetic Risk of Type 2 Diabetes and Offspring Birthweight Among African Ancestry Populations, *The Journal of Clinical Endocrinology & Metabolism*, Volume 104, Issue 11, November 2019, Pages 5032–5042, https://doi.org/10.1210/jc.2018-02756
12. Hidalgo-Lopezosa, P., Jimenez-Ruz, A., Carmona-Torres, J.M., Hidalgo-Maestre, M., Rodriguez-Borrego, M.A., Lopez-Soto, P.J. (2019). Socio-demographic factors associated with preterm deliveriesand low birth weight: A cross-sectional study. *Women Birth*, 32, e538–e543.
13. Tshotetsi, L.,Dzikiti, L.,Hajison, P.,Feresu, S. (2019). Maternal factors contributing to low birth weight deliveries in Tshwane District, South Africa. *PLoS ONE*, 14, e0213058
14. Zini, M.E.,Omo-Aghoja, L.O. (2019). Clinical and socio-demographic correlates of preterm deliveries in two tertiary hospitals in southern Nigeria. *Ghana Med. J.* 53, 20–28.
15. Talie, A.,Taddele, M.,Alemayehu, M. (2019). Magnitude of Low Birth Weight and Associated Factors among Newborns Delivered in Dangla Primary Hospital, Amhara Regional State, Northwest Ethiopia, 2017. J. *Pregnancy*, 3587239 Tamura, N., Hanaoka, T., Ito, K., Araki, A., Miyashita, C., Ito, S.,Minakami, H.,Cho, K., Endo, T., Sengoku, K. (2018). Different Risk Factors for Very Low Birth Weight, Term-Small-for-Gestational-Age, or preterm deliveriesin Japan. Int. J. Environ. Res. *Public Health*, 15, 369.
16. Cantarutti, A., Merlino, L., Monzani, E., Giaquinto, C., Corrao, G. (2016). Is the Risk of Preterm Birth and Low Birth Weight Affected by the Use of Antidepressant Agents duringPregnancy? A Population-Based Investigation. *PLoS ONE*, 11, e0168115.
17. Ugwu, Chinyere. N. and Eze Val, H. U. (2023).Qualitative Research. IDOSR JOURNAL OF COMPUTER AND APPLIED SCIENCES 8(1) 20-35. https://www.idosr.org/wp-content/uploads/2023/01/IDOSR-JCAS-8120-35-2023.docx.pdf
18. Slovin, E. (1960) Slovin's Formula for Sampling Technique. https://prudencexd.weebly.com/
19. Ugwu Chinyere Nneoma, Eze Val Hyginus Udoka, Ugwu Jovita Nnenna, Ogenyi Fabian Chukwudi and Ugwu Okechukwu Paul-Chima (2023). Ethical Publication Issues in the Collection and Analysis of Research Data. NEWPORT INTERNATIONAL JOURNAL OF SCIENTIFIC AND EXPERIMENTAL SCIENCES (NIJSES) *3*(2): 132-140. https://nijournals.org/wp-content/uploads/2023/07/NIJSES-32-132-140-2023.pdf

20. Hidalgo-Lopezosa P, Jiménez-Ruz A, Carmona-Torres JM, Hidalgo-Maestre M, Rodríguez-

Borrego MA, López-Soto PJ. Sociodemographic factors associated with preterm birth and low birth weight: A cross-sectional study. Women Birth. 2019 Dec;32(6):e538-e543. doi: 10.1016/j.wombi.2019.03.014. Epub 2019 Apr 9. PMID: 30979615.

21. Aregawi, G., Assefa, N., Mesfin, F. *et al.* Preterm births and associated factors among mothers who gave birth in Axum and Adwa Town public hospitals, Northern Ethiopia, 2018. *BMC Res Notes* **12**, 640 (2019). https://doi.org/10.1186/s13104-019-4650-0

22. Killeen, G.F., Govella, N.J., Lwetoijera, D.W. *et al.* Most outdoor malaria transmission by behaviourally-resistant *Anopheles arabiensis* is mediated by mosquitoes that have previously been inside houses. *Malar J* **15**, 225 (2016). https://doi.org/10.1186/s12936-016-1280-z

23. Clift AK et al. Smoking and COVID-19 outcomes: an observational and Mendelian

24. randomisation study using the UK Biobank cohort. Thorax. 2021 Sep 12.

25. Ikehara S, Kimura T, Kakigano A, Sato T, Iso H; Japan Environment Children's Study Group. Association between maternal alcohol consumption during pregnancy and risk of preterm delivery: the Japan Environment and Children's Study. BJOG. 2019 Nov;126(12):1448-1454. doi: 10.1111/1471-0528.15899. Epub 2019 Aug 25. PMID: 31386246; PMCID: PMC7003893.

26. Tellapragada C, Eshwara VK, Bhat P, Acharya S, Kamath A, Bhat S, Rao C, Nayak S, Mukhopadhyay C. Risk Factors for Preterm Birth and Low Birth Weight Among Pregnant Indian Women: A Hospital-based Prospective Study. J Prev Med Public Health. 2016 May;49(3):165-75. doi: 10.3961/jpmph.16.022. Epub 2016 May 31. PMID: 27255075; PMCID: PMC4898897.