ORIGINAL ARTICLE

Potentially harmful medication use and the associated factors among pregnant women visiting antenatal care clinics in Mbarara Regional Referral Hospital, Southwestern Uganda

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ABSTRACT

Background: Pregnancy management using medications has been challenging for both healthcare providers and pregnant women, given the fear of teratogenicity effects and the potential for fetal harm. In the developing world, poor health-seeking behavior of patients, delayed initiation of antenatal care (ANC), and low level of educational status of mothers could contribute to the issue of drug safety in pregnancy.

Aim: The aim of the study was to determine the prevalence and factors associated with potentially harmful medication use in pregnancy.

Methods: A cross-sectional study was conducted from April 1 to June 6, 2021, including 209 pregnant women on ANC follow-up at a referral hospital in Southwestern Uganda. The simple random sampling technique was employed to select study participants. Interviewer-administered questionnaires were used to collect the history of medication use since conception and then the participant's ANC card was reviewed to determine prescribed drug regimens and their indications. Statistical Package for the Social Sciences version 23.0 was used for analysis.

Results: Out of the 1,422 medications used by 209 women, 665 (42.2%) were category C, and 182 (11.5%) were category A. A total of 92 (44.0%) pregnant women used at least one potentially harmful medication during the current pregnancy. Having more than average monthly income (adjusted odds ratio [aOR] = 2.32 [1.04, 5.14 at 95% confidence interval (CI)]), having a chronic disease (aOR = 3.24 [1.17, 8.97 at 95% C.I]), using 7 and more medications (aOR = 9.12 [4.11, 20.24 at 95% CI]), and use of herbal medicines (aOR = 4.50 [2.10, 9.87 at 95% CI]) were shown to be risk factors.

Conclusion: The proportion of pregnant women that used at least one potentially harmful medication is higher than in previous studies. Having comorbidities and taking more medications increase the risk of receiving a potentially harmful medication during pregnancy.

Relevance to Patients: This study identified the gaps in the use of medicines during pregnancy which will enable the development and implementation of protocols for optimizing prescribing practices in pregnant women by focusing on the safety of the fetus.

1. Introduction

Pregnancy care is one of the great challenges in medicine The potential of short- and long-term toxicity following intra-uterine exposure to drugs emphasizes the need of having-up-to date information on the types and frequencies of exposure of pregnant women to pharmacological agents [1].

Although use of drugs during pregnancy remains inevitable and common, information regarding their safety remains scarce and unreliable [2]. Hemodilution and negative iron balance throughout pregnancy may lead to iron deficiency anemia [3]. Alterations to the immune status of the pregnant woman lead to impaired-cell mediated immunity with increased susceptibility to certain infections [4]. Thus, pregnant women may need routine prophylactic medications to prevent such conditions. In addition, drugs are prescribed for pregnant women to treat pre-existing chronic conditions such as diabetes, hypertension, and epilepsy or to treat pregnancy-related disorders such as pregnancy-induced hypertension, and gestational diabetes [5]. Thus, drug therapy in pregnancy presents challenges to both healthcare providers and pregnant women's therapeutic decision-making [6]. To guide safe drug use during pregnancy, the U.S Food and Drug Administration (FDA) classified drugs into the following major categories; A, B, C, D, and X with categories D and X indicating evidence of risk in pregnancy [7].

In the developing world, poor health-seeking behavior of patients, delayed initiation of antenatal care (ANC), low level of educational status of mothers, lack of up-to-date information for health-care providers, poor access to health facilities, and low level of training of health-care providers could contribute to the issue of drug safety in pregnancy. In Ethiopia, 51.4% to 56.3% of pregnant women received United States FDA (US FDA) category C medicinal products [8,9]. However, few studies have described the extent, type, and pregnancy risk category of drugs during pregnancy in Uganda. Therefore, this study was conducted to determine the reasons for use, classes of medications used, potential harm, and the associated factors in pregnant women on ANC follow-up.

2. Methods

2.1. Study setting, study design and study populations

This cross-sectional study was conducted from the ANC clinic of Mbarara Regional Referral Hospital (MRRH), which is located in the southwestern region of Uganda, attending to about 50 mothers daily. The study involved all pregnant women who attended the ANC clinic of MRRH between the April 1 and the May 6, 2022, and who gave their informed consent. We excluded pregnant women with incomplete medication use records.

2.2. Sample size and sampling

The sample size was estimated using the sample size determination formula for a single population proportion. We considered a study conducted in Bair Dar city, Ethiopia [10]; which reported that 16.2% of the participants used potentially harmful medications, with a 95% confidence level and 5% tolerable sampling error.

$$n = \frac{Z^2 pq}{d^2}$$

Where n = The minimum sample size, Z = Reliability coefficient for desired interval (CI) for 95% = 1.96, p = 0.162, q = 0.838, d= desired interval (degree of precision) = 0.05, N= 209

Simple random sampling was used to recruit participants into the study until the target sample size was attained.

2.3. Data collection and study variables

Structured questionnaires were used to collect patient-related information including socio-demographic characteristics and medication history. Before the study began, we had pretested the questionnaire among ten pregnant women in the same facility, and revisions were made focusing on improving its validity. History of medication use (prescription, non-prescription, and herbal medicine) from conception to the current ANC visit was obtained and recorded. Then the participant's ANC card was reviewed to determine prescribed drug regimens and their indications.

The independent variables included socio-demographic characteristics of women, age, marital status, education level, residence, income, gravidity, pregnancy trimester, and chronic medical conditions, number of medications used by the women. The dependent variables were overall medication use and potentially harmful medication use. The Ethical approval was obtained from Mbarara University Research Ethics Committee (REC) Reference Number, Mbarara University of Science and Technology [MUST]-2022-375).

2.4. Data management and analysis

The collected data were cleaned using Epi-Info and entered into International Business Machine Statistical Package for Social sciences version 23.0 for analysis. Based on the US FDA definitions for each pregnancy risk category, we operationalized potentially harmful medication as any drug with pregnancy risk category C, D, or X. Descriptive statistics were used to summarize the independent and dependent variables. Chi-square was used to determine the distribution of different variables among those who were prescribed harmful drugs and those who were not. Bivariate and multivariate logistic regression was used to determine the factors associated with the use of potentially harmful medications. All independent variables with $P \leq 0.25$ were at bivariate logistic regression level and were included for multivariate logistic regression. Variables with values ≤0.05 at multivariate logistic regression were identified as factors associated with the use of potentially harmful medications.

3. Results

3.1. Participants' characteristics

Among the 209 pregnant women studied, over a third (80, 38.3%) were youth 24 years and younger. Most (79.9%) of the participants dwelled in urban/semi-urban areas, over three-quarters (79.4%) had a monthly income of <250,000 UGX, and most (85.6%) of them lived within a 3 km distance from a health facility (Table 1). Almost one-third (31, 14.8%) of the participants had been diagnosed with any chronic condition, over a half (118, 56.5%) had been pregnant <3 times in total, and about a half (112, 53.6%) had attended at least 3 ANC visits on the day of

Table 1. The socio-demographic characteristics of pregnant women attending the ANC clinic at MRRH, April–May 2022

Variable	Frequency	Percentage
Age category		
≤24	80	38.3
>24	129	61.7
Participant marital status		
Single	7	3.3
Married	202	96.7
Participant's place of residence		
Urban	167	79.9
Rural	42	20.1
Participant's religion		
Catholic	63	30.1
Anglican/Protestant	99	47.4
Muslim	29	13.9
Born Again	18	8.6
Participant's level of education		
Primary	61	29.2
Secondary	98	46.9
Tertiary	50	23.9
Participant's occupation		
Unemployed	66	31.6
Employed	52	24.9
Self employed	91	43.5
Monthly income category		
≤250000	166	79.4
>250000	43	20.6
Distance from the nearest health facility		
≤3	179	85.6
>3	30	14.4

ANC: Antenatal care, MRRH: Mbarara Regional Referral Hospital

the interview, and almost two-thirds (125, 59.8%) presented for their first ANC visit at a gestational age of 13 weeks and above. About half (50.7%) of the participants were in the third trimester of pregnancy, with a mean gestational age of 25.7 ± 8.8 weeks (Figure 1).

3.2. Reasons for drug use

Out of 1136 prescription medications, 545 (38.3%) were used for prophylaxis infections including malaria, helminthiasis, and tetanus; followed by 351 (24.7%) medications indicated for the prevention of anemia during pregnancy, management of pain (131, 9.2%), treatment of suspected infections (108, 7.6%), and baby's wellbeing (84, 5.9%) (Table 2).

3.3. Prescription drugs used

A total of 1136 prescription medications were used by 199 pregnant women during their current pregnancy, of which; folic acid, ferrous sulfate, pyrimethamine, sulfadoxine, and tetanus toxoid vaccine constituted the majority (856, 75.4%) of the
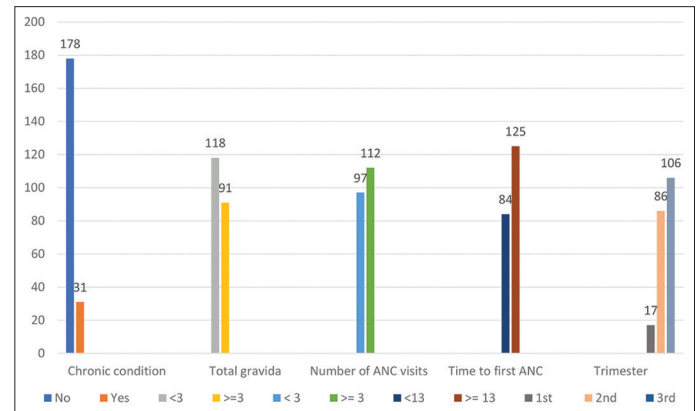

Figure 1. Reproductive, disease, and obstetric characteristics of pregnant women attending antenatal care clinic at Mbarara Regional Referral Hospital, April–May 2022.

medications used, and therefore classified as routine medications according to the national guideline [11]. In general, antimicrobials (excluding antivirals) (621, 54.6%) and anti-anemic preparations (345, 30.3%) were the most frequently used classes of medications (Table 3).

3.4. Non-prescription and herbal medicines use

Out of 86 non-prescription medications used during the current pregnancy, analgesics were the most commonly (51, 59.3%) used followed by respiratory/nasal decongestants (12, 14%) and alimentary tract agents (9, 10.5%). Out of the 23 herbal medicines reported to have been used, only 3 crude extract formulations (V Wash, Elocof, and Cough Linctus) had received partial authorization (notification) for distribution and sale in Uganda by the National Drug Authority. Particularly, three plant extracts: *Ekyoganyanza* (45), *Esununu* (39), and *Esitimwa* (29) were the most commonly used herbs (Table 4).

The majority (125/209, 60.0%) of the pregnant women used at least one herbal medicine during their current pregnancy; 88 (70.4%) used it during second trimester followed by 51 (40.8%) and 40 (32.0%) of the participants who used an herbal during the first and the third trimester, respectively.

3.5. Pregnancy risk categorization of medicines used during pregnancy

Out of the 1422 medications used, 665 (42.2%) were category C, 182 (11.5%) were category A, and 159 (11.2%) were category B. Over one-third (410, 28.8%) of all the medicines used were FDA pregnancy risk category N (Not assigned); 209 (51.0%) of which were prescribed medicines, and 23 were herbal medicines. Excluding the 856 routinely prescribed medications, paracetamol (16.1%), Efavirenz (0.5%), and Warfarin (0.5%) constituted the most commonly used (prescription and non-prescription) category C, D, and X medications, respectively (Figure 2).

Overall, a total of 92/209 (44.0%) pregnant women used at least one potentially harmful medication during the current pregnancy. Out of these, 68 (73.9%) used prescription medications; the

majority (46/68, 67.6%) used them during the second trimester followed by the first trimester (13, 19.1%). Overall, 99 (8.7%) of prescribed medications and 73 (84.9%) of the non-prescription medications were determined to be potentially harmful at the time of use (Figure 3)

3.6. Factors associated with potentially harmful medication use

Out of 13 independent variables included in the univariate logistic regression, five variables including age, level of education, monthly income, having at least one chronic disease, and the total number of drugs used were statistically significant; and nine variables that met the criteria ($P < 0.25$) were included in the multivariable logistic regression. At multivariate analysis, four variables remained statistically significant. Accordingly, pregnant women who had an average monthly income > 250,000 Ugx were about 2.32 times (adjusted odds ratio [aOR] = 2.32 [1.04, 5.14 at 95% CI]; p-value 0.039) more likely to use a potentially harmful medication during pregnancy compared to those with a lower average monthly income. Similarly, women that had been diagnosed a chronic disease were about 3.24 times (aOR = 3.24 [1.17, 8.97 at 95% C.I]; p-value = 0.023) more likely to use potentially harmful medication. Likewise, those who used seven and more medications had about 9.12 odds (aOR = 9.12 [4.11, 20.24 at 95% C.I]; P-value <0.001) of using a potentially harmful medication compared to those that used <7 medications during the current pregnancy. Finally, women that did not report

Table 2. Reasons for drug use among pregnant women attending ANC clinic at MRRH, April – May 2022

Clinical indications	Frequency	Percentage
Prophylaxis of infection	545	38.3
Supplement	351	24.7
Pain	131	9.2
Bacterial infection	108	7.6
Baby's well-being	84	5.9
HIV	60	4.2
Heart burn/gastritis	30	2.1
Flu	25	1.8
Fungal infection	16	1.1
General well-being	15	1.1
Threatened abortion	13	0.9
Nausea and vomiting	7	0.5
Malaria	7	0.5
Fever	7	0.5
Allergy	6	0.4
Appetite	6	0.4
Diabetes mellitus	5	0.4
Others	6	0.4

Preventions for preeclampsia, fibroids, venous thromboembolism, hyperlactation. ANC: Antenatal care, MRRH: Mbarara Regional Referral Hospital
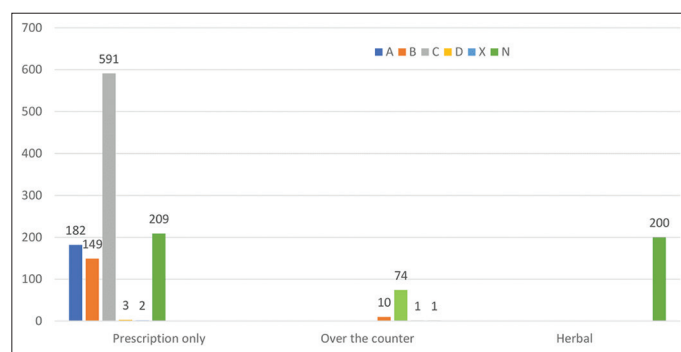

Figure 2. United States Food and Drug Administration pregnancy risk categorization of medicines used among pregnant women attending antenatal care clinic at Mbarara Regional Referral Hospital, April–May 2022.

**Table 3.** The drug prescribing patterns among pregnant women attending ANC clinic at MRRH, April – May 2022

Pharmacologic category	Specific drugs	Frequency (%) N=1136	Proportion of potentially harmful medications 99 (35.4%)
Antimicrobials	Pyrimethamine[C] (165), Sulfadoxine[C] (165), Mebendazole[C] (146), Amoxicillin[B] (27), Clotrimazole[B] (20), rythromycin[B] (11), Cefixime[B] (10), Trimethoprim[C] (9), ulfamethoxazole[C] (9), Azithromycin[B] (9), Ampicillin[B] (6), Miconazole[C] (6), Metronidazole[B] (5), Ceftriaxone[B] (4), Cloxacillin[B] (4), Ketoconazole[C] (4), Nitrofurantoin[B] (3), Nystatin[A] (3), Amoxicillin/clavulanic acid[B] (2), Lumefantrine[C] (2), Artemether[C] (2), Cefuroxime[B] (2), Ciprofloxacin[C] (1), Clindamycin[B] (1), Quinine[C] (1), Tinidazole[C] (1), Metronidazole[B]/povidone[B]	621 (54.6%)	*42 (6.8%)
Anti-anemic preparations	Folic Acid[A] (177), Ferrous Sulfate[N] (167), Ferric ammonium[B] (1)	345 (30.3%)	*1 (0.3%)
Antiretrovirals	Lamivudine[C] (19), Dolutegravir[N] (18), Tenofovir[B] (20), Efavirenz[D] (2)	57 (5.0%)	21 (36.8%)
Hormonal and biologics	Tetanus Toxoid Vaccine[C] (38), COVID 19 vaccine[N] (5), Insulin[B] (4), Dydrogesterone[B] (3), Betamethasone[C] (1), Levonorgestrel[X] (1), Progestin[B] (1), Prednisolone[C] (1).	54 (4.7%)	3 (5.6%)
Alimentary tract agents	Magnesium trisilicate[N] (11), Omeprazole[C] (5), ondansetron[C] (4), Drotaverine[N] (4), Vitamin C[A/C] (4), Multivitamin[C] (1)	29 (2.6%)	9 (31.0%)
Analgesics	Tramadol[C] (8), Paracetamol[C] (8), Ibuprofen[C/D] (3)	19 (1.7%)	19 (100.0%)
Antihistamines	Cetirizine[N] (2), Chlorpheniramine[B] (2), Cyproheptadine[B] (2)	6 (0.7%)	0 (0%)
Antithrombotic agents	Aspirin[C/D] (2), Enoxaparin[B] (1), Warfarin[X] (2)	5 (0.4%)	4 (80.0%)

[A]FDA pregnancy risk category A; [B]FDA pregnancy risk category B; [C]FDA pregnancy risk category C; [D]FDA pregnancy risk category D; [X]FDA pregnancy risk category X; [N]FDA pregnancy risk category N. *Without routine medications. ANC: Antenatal care, MRRH: Mbarara Regional Referral Hospital

Table 4. Over-the-counter and herbal medications use among pregnant women attending ANC clinic at MRRH, April–May 2022

Drug therapy category	Pharmacologic classification	Specific drugs (frequencies)	Total number of medications (N=86)	Potentially harmful medication (N=73)
Over the counter medications	Analgesics	Paracetamol[C] (51)	51 (59.3%)	51 (100%)
	Respiratory/Nasal decongestants	Pseudoephedrine[C] (5), Guaifenesin[C] (2), Bromohexine[C] (1), Menthol[D] (1), Ambroxol[C] (1), Salbutamol[C] (1), Terbutaline[C] (1)	12 (14.0%)	12 (100%)
	Alimentary tract agents	Multivitamin[C] (2), Vitamin B complex[C] (2), Omeprazole[C] (1), Sucralfate[B] (1), Oxetacaine[B] (1), Ferrous Sulfate[N] (1), Vitamin B12[C] (1)	9 (10.5%)	4 (44.4%)
	Antihistamines	Chlorpheniramine[B] (8)	8 (9.3%)	0 (0%)
	Psychostimulants	Caffeine[C] (6)	6 (7.0%)	6 (100%)
Herbal medications		Unknown herb (69), Ekyoganyanza (45), Esunnu (39), Esitimwa (29), Elocof (2), V wash (2), Ekyogelo (2), Eshabuka (2), Banana leaves (1), Mubwa (1), Omujaja (1), Okra (1), Omusheshe (1), Omusurokyi (1), Omuziranfu (1), Cough linctus (1), Ekyizera (1), Ekyirogorogoro (1), Jovita (1), Kirungi (1), Kigyera (1), Omubirizi (1), Omubura (1), Omunyamizi (1)	23	23[N]

[A]FDA pregnancy risk category A; [B]FDA pregnancy risk category B; [C]FDA pregnancy risk category C; [D]FDA pregnancy risk category D; [X]FDA pregnancy risk category X; [N]FDA pregnancy risk category N. ANC: Antenatal care, MRRH: Mbarara Regional Referral Hospital
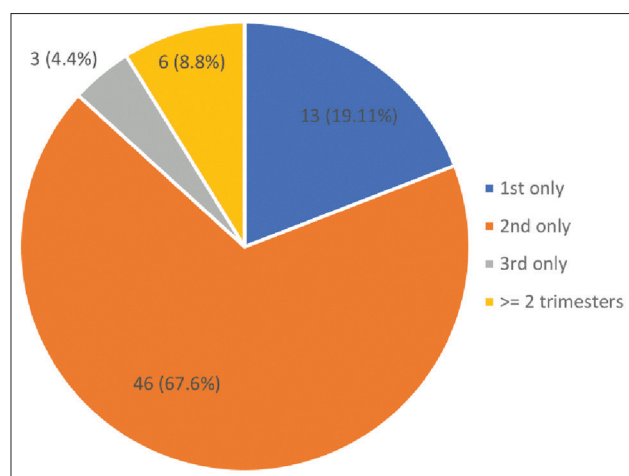
Figure 3. Number of pregnant women on follow up at antenatal care clinic of Mbarara Regional Referral Hospital who used potentially harmful prescription medications, April – May 2022.

any use of herbal medicines during the current pregnancy were about 4.50 times more likely (aOR = 4.50 [2.10, 9.87 at 95% CI]; p-value <0.001) to use of potentially harmful medications than those who did (Table 5).

4. Discussion

Out of 1136 prescription medications, 545 (38.3%) were used for the prophylaxis of infections including malaria, helminthiasis, and tetanus; followed by 351 (24.7%) medications indicated for prevention/treatment of anemia during pregnancy. On the other hand, the majority of non-routine medications were used to manage pain (131, 9.2%), to treat suspected infections (108, 7.6%), and for fetal wellbeing (84, 5.9%). This is in line with a study from Ethiopia that reported minor illnesses and prophylaxis for anemia were the most frequent reasons for drug use during pregnancy [10,12]. Hemodilution and negative iron balance

throughout pregnancy, particularly in the latter half, may lead to iron deficiency anemia [13]. Alterations to the immune status of the pregnant woman lead to impaired cell-mediated immunity with increased susceptibility to certain infections [14]. National guidelines recommend the routine use of different prophylactic antimicrobials and nutritional supplements. In our study, the average number of drugs used during pregnancy was 5.8 ± 3.1 drugs. Contrary to our findings, the average number of drugs used during pregnancy was 2.3 drugs in Oman [15], and between 1.1 and 1.8 in Ethiopia [8,16]. This is lower than our findings probably because they considered only prescription medications whereas our study included all prescription, non-prescription, and herbal drugs. To this effect in this study, 125/209 (59.8%) of the women used at least one herb/herbal product.

A total of 1136 prescription medications were used by 199 (95.2%) pregnant women during their current pregnancy. The majority (856, 75.4%) of the prescribed medications were classified as routine according to the national guideline. Antimicrobials (621, 54.6%) and anti-anemic preparations (345, 30.3%) were the most frequently used classes of medications. This is consistent with findings from a study in India that reported antimicrobial medications to be the most prescribed among pregnant women [17]. Folic acid (15.6%), ferrous sulfate (14.7%), and pyrimethamine/sulfadoxine (14.5%) were the most commonly used specific drugs during pregnancy; particularly during the second and third trimesters. This is in agreement with a previous study in Ethiopia that showed folic acid and ferrous sulfate to be the most commonly (37.6%) used specific drugs. Finally, in line with our findings, a study done in Tanzania [18] and Ethiopia [19] showed that analgesics were the most commonly used medications among pregnant women.

Analgesics were the most commonly used (51, 59.3%) non-prescription drugs, followed by respiratory/nasal decongestants (12, 14%), and alimentary tract agents (9, 10.5%). This is in line with the previous studies that showed analgesics, particularly paracetamol to be the most frequently used non-prescription

Table 5. Factors associated with use of potentially harmful medications among pregnant women attending ANC clinic at MRRH, April–May 2022

Variable	Category	Potentially harmful medication used (%)		COR (95% CI)	P-value (< 0.25)	aOR (95% CI)	P-value (<0.05)
		No	Yes				
Age (years)*	≤24	52 (65)	28 (35)	0.55 (0.31 – 0.97)	0.040	0.61 (0.31 – 1.23)	0.165
	>24	65 (50.4)	64 (49.6)	1			
Occupation*	Unemployed	37 (56.1)	29 (43.9)	1.20 (0.63 – 2.28)	0.583	1.10 (0.47 – 2.56)	0.827
	Employed	25 (48.1)	27 951.9)	1.65 (0.83 – 3.28)	0.153	1.42 (0.58 – 3.46)	0.445
	Self Employed	55 (60.4)	36 (39.6)	1			
Level of education*	Primary	40 (65.6)	21 (34.4)	0.45 (0.21 – 0.96)	0.040	0.77 (0.29 – 2.05)	0.602
	Secondary	54 (55.1)	44 (44.9)	0.69 (0.35 – 1.38)	0.295	1.08 (0.46 – 2.54)	0.860
	Tertiary	23 (46.0)	27 (54.0)	1			
Religion*	Catholic	37 (58.7)	26 (41.3)	0.58 (0.24 – 1.39)	0.216	0.51 (0.18 – 1.46)	0.212
	Protestant	67 (57.3)	50 (42.7)	0.61 (0.27 – 1.37)	0.231	0.55 (0.20 – 1.45)	0.225
	Muslim	13 (44.8)	16 (55.2)	1			
Distance from the nearest health facility (km)	≤3	100 (55.9)	79 (44.1)	1.0 (0.47 – 2.25)	0.935		
	>3	17 (56.7)	13 (43.3)	1			
Place of residence	Urban	96 (57.5)	71 (42.5)	0.74 (0.38 – 1.46)	0.383		
	Rural	21 (50)	21 (50)	1			
Monthly income (Ugandan Shillings)*	≤ 250,000	100 (60.2)	66 (39.8)	1		1	
	>250,000	17 (39.5)	26 (60.5)	2.32 (1.17 – 4.60)	0.016	2.32 (1.04 – 5.14)	0.039
Total gravida	<3	67 (56.8)	51 (43.2)	0.93 (0.54 – 1.61)	0.791		
	≥3	50 (54.9)	41 (45.1)	1			
Number of ANC visits	<3	58 (59.8)	39 (40.2)	0.75 (0.43 – 1.30)	0.302		
	≥3	59 (52.7)	53 (47.30	1			
Time to 1st ANC visit (weeks)*	<13	42 (50.0)	42 (50.0)	0.67 (0.38 – 1.16)	0.154	0.57 (0.29 – 1.11)	0.097
	≥13	75 (60.0)	50 (40.0)	1			
Chronic conditions*	No	108 (60.7)	70 (39.3)	1		1	
	Yes	7 (24.1)	22 (75.9)	4.85 (1.97 – 11.95)	0.001	3.24 (1.17 – 8.97)	0.023
Total number of drugs*	<7	73 (76.0)	23 (24.0)	1		1	
	≥7	44 (38.9)	69 (61.1)	4.98 (2.73 – 9.09)	< 0.001	9.12 (4.11 – 20.24)	< 0.001
Herbal medicine use*	No	40 (47.6)	44 952.4)	1.74 (1.0 – 3.1)	0.052	4.50 (2.10 – 9.87)	< 0.001
	Yes	76 (61.3)	48 (38.7)	1			

*P < 0.25, aOR: adjusted odds ratio, ANC: Antenatal care, MRRH: Mbarara Regional Referral Hospital

drug [20,21]. Similarly, the previous reports indicate that respiratory and alimentary tract agents equally constitute the most common non-prescription drugs used during pregnancy [22]. The profound gastrointestinal and respiratory complaints have been associated with increased serum progesterone in the second trimester of pregnancy [23]. Almost two-thirds (59.8%) of the study participants used at least one herb/herbal product during their current pregnancy, with an average of 1.00 ± 1.0 herbs/herbal products. Our finding is higher 33.1% (51/154) compared to the prevalence of herb/herbal product use in Mwanza, Tanzania [18]. However, our finding is comparable to reports of 50.4% [24] and 51.2% [25] herb/herbal product use among women attending the ANC clinic in two health facilities in Ethiopia. Particularly, three plant extracts, namely; Erlangea tomentosa *"Ekyoganyanja"* (45), Crassocephalum vitellinum "*Esununu*" (39), and Hoslundia opposita Vahl *"Esitimwa"* (29) together constituted up to 113/200 (56.5%) frequency of herbal medicines use among all study participants. The pregnancy risks of all the 23 herbs/herbal products reported to have been used were unknown; and only three crude extract formulations (V Wash, Elocof, and Cough Linctus) were currently authorized under conditions for distribution and sale in Uganda by the National Drug Authority. In southwestern Uganda, in addition to their consumption in the diet, the majority of pregnant women boil the leaves of these three herbs and drink them to prevent or manage pregnancy-related health problems, for example, infections, constipation, and loss of appetite. Saponins, tannins, steroids, phenols, flavonoids, and alkaloids identified in the three plants tend to increase tissue growth and boost immunity; thus prevent or treat sexually transmitted infections, urinary tract infections, and threatened abortions as commonly experienced in pregnancy [26,27]. Majority of women used herbal medicines during the second trimester (88, 70.4%) followed by the first (51, 40.8%) and third (40, 32.0%) trimesters of pregnancy. This is in contrast with the findings of the study in Nekemte, Ethiopia [24]

where majority (69.8%) of women used herbs/herbal products in the first trimester of pregnancy.

Based on the US FDA risk classification system, majority of the drugs used by pregnant women in our setting belonged to category C (665, 42.2%). This finding is comparable to proportions of 51.4% and 56.3% in two studies conducted in Ethiopia [8,9]. On the other hand, the proportion of category C medications in our study is remarkably higher compared to only 12.8% in Bahir Hospital, Ethiopia [10]; and 2.9% in a medical Centre in India [28]. This discrepancy can be explained by the recommendation of mebendazole and Pyrimethamine/Sulfadoxine, both of which are FDA pregnancy risk category C, as routine medications during pregnancy by Ugandan Clinical guidelines. However, excluding the routine prescribed medications, paracetamol (16.1%), Efavirenz (0.5%), and Warfarin (0.5%) constituted the most commonly used (prescription and non-prescription) category C, D, and X medications, respectively. This finding is consistent with findings by Mohammed [9].

Almost a half (44.0%) of the pregnant women used at least one potentially harmful medication to the fetus in utero. This proportion is higher than 18.6% in a study in Ethiopia [22] probably because the later considered prescribed medication belonging to US FDA risk categories C, D, and X only. However, in this study, we incorporated any drug of US FDA pregnancy risk categories A and B that were used at certain time of pregnancy when they should be avoided; in addition to medications belonging to US FDA pregnancy risk categories C, D, and X. Out of the 172 potentially harmful medications used by the study participants (excluding routine medications), 8.7% were prescription medications, and 84.9% of the non-prescription drugs. This highlight a significant potential risk pregnant women are exposed to while using non-prescription drugs. Eight (4.7%) of the potentially harmful medications were FDA pregnancy risk category A or B. Although their use can be warranted upon proper benefit/risk assessment, category C drugs like paracetamol have the potential to cause both structural and nonstructural fetal/neonatal toxicities. Even though gestational periods of fertilization/implantation (days 0 – 17) and organogenesis (days 18 – 55) are critical as far as respective drug-related embryonic death and adverse fetal malformations are concerned [29]; physiologic/neuropsychiatric fetotoxic drug effects, for example, neurocognitive disorders, are equally important. In our study, paracetamol constituted 84.3% of all analgesics used, of which indiscriminate prenatal use has been linked with adverse neurodevelopmental outcomes; especially hyperactivity, attention-disorders [30], and wheezing among young children [31]. Although warfarin (category X) use should be limited to pregnant women with prosthetic heart valve [32], in our study two women without the specified indication were prescribed warfarin. Prescribers should always consider safer alternatives even when a clear reason for drug use is identified. Warfarin use is strongly associated with dose-dependent fetotoxicity throughout pregnancy [33]. Nitrofurantoin is safe in absence of glucose-6-phosphate dehydrogenase deficiency and is commonly used to treat urinary tract infections in pregnancy

(Category B); however, its use is should be avoided at term (week 38 – 42 of pregnancy), and during labor or delivery due to risks of fetal hemolytic anemia [34]. In the current study, two women used nitrofurantoin at term. Ascorbic acid was another category A drug that was determined to be potentially harmful medication when used at high dose (>200 mg/day) as it has been associated with fetal microsomia [35]. Nevertheless, several pregnant women in this study received high dose ascorbic acid (500 mg/day and above) for COVID-19 management. The majority (67.6%) of the women used potentially harmful prescription drugs during the second trimester followed by the first trimester (19.1%). This finding is in agreement with findings by Geresu *et al*. [8], where 70.6% of all potentially harmful drugs were used in the second trimester. In our study, most of the women presented to the ANC clinic during the second trimester with a mean time to first ANC visit of 14.5 ± 5.4 weeks. The national guideline also recommends week-13 of pregnancy for the first ANC visit. Our findings demonstrate a critical need for targeted measure, including comprehensive medication management and counseling, as well as prescriber training and patient education on the need to exercise cautious drug use throughout pregnancy. About one-third (28.8%) of all the medications used (including prescription, non-prescription, and herbs/herbal products) had not been assigned a US FDA pregnancy risk category (N); 209 (51.0%) of which were prescribed medicines mostly ferrous sulfate, and 200 (48.8%) were herbal medicines. These group of drugs, whether newer agents (COVID-19 vaccines, Dolutegravir [DTG]) or those with an experience of long-term use (Cetirizine and drotaverine), may present an equally concerning teratogenic risk as those already classified, as there can be drastic maternal-fetal drug exposure profiles, based on the trimester of pregnancy [36], physiologic/pharmacokinetic changes, and substitution of individual drug product formulation, when used during pregnancy [29,37,38]. For example, regardless of the seemingly trivial prevalence (0.12%) and conflicting findings on the risk of neonatal neural tube defects in DTG – exposed mothers in Africa [39-41]; the decision on whether to halt or continuing the use of DTG peri-conception remains a big question to clinicians and pregnant women [42]. This, therefore, becomes concerning in situations where there is no complete data, however, national guidelines necessitate all eligible pregnant women to use the drug. Previous phytochemical screening of the 3 commonly used herbs (Erlangea tomentosa *"Ekyoganyanja,"* Crassocephalum vitellinum *"Esununu,"* and Hoslundia opposita Vahl *"Esitimwa"*) revealed presence of tannins, phenols, and alkaloids, however, limited preclinical toxicological evidence indicate direct fetal risks of miscarriage, and shortened fetal development [27]. Therefore, singular or combined use of herbal remedies should be deemed potentially harmful in pregnancy as the pregnancy risk is mainly unknown. Given the preclinical evidence of harm to the fetus and the overall uncertainty of their safety during pregnancy, herbs/herbal products should be better avoided when safer alternatives including non-pharmacologic or conventional remedies are available for the management of the specific condition. Understanding potential herb-

drug interactions resulting into indirect fetotoxic effects, and dose-dependent fetotoxic concerns is an area open for further scientific research for the commonly used herbal medicines.

Pregnant women who had an average monthly income >250,000 Ugx were about 2.32 times more likely to use a potentially harmful medication during pregnancy compared to those with a lower average monthly income. This association was also reported from a study in US [43]. Similarly, a study in India showed that higher socio-economic status was significantly associated with self-medication during pregnancy [28]. Pregnant women with the lowest income tend to self-medicate with herbal products probably because they are usually cheaper [44]. In the current study, the potential harm of herbs and herbal products used during pregnancy was not accounted for because almost all of them were not well studied and pregnancy risk is unknown.

Women that had been diagnosed with a chronic disease were about 3.24 times more likely to use potentially harmful medications. This finding is in line with those from the previous studies: in British Columbia [45], in a European study [46], in a multinational study [47], and in Hawaii [48] that showed that being diagnosed with a chronic comorbidity significantly increased the odds of prescription drug use during pregnancy. Likewise, those who used 7 and more medications had about 9.12 odds of using a potentially harmful medication compared to those that used <7 medications during the current pregnancy. In general, patients with more number of comorbid conditions use higher number of drugs and are at a higher risk of developing adverse drug reactions [49]. In the current study, women that did not report any use of herbal medicines during the current pregnancy were about 4.50 times more likely to use a potentially harmful medication than those who did. This might reflect that the pregnant women used herbal medicines as alternatives of conventional medications for self-medication. This finding was in contrast with a study in Congo that showed herbal drug use to be a risk factor for self-medication with conventional medications that are potentially harmful [50]. This discrepancy may be explained by the differences in the socio-economic and cultural differences in the two study populations. Congolese pregnant women tended to self-medicate with both conventional and herbal products whereas in the current study, pregnant women more often self-medicated solely with herbal remedies as alternatives for conventional products.

5. Conclusion

The current study revealed unrestricted access and high level of use of prescription, over the counter and herbal medicines by pregnant women in all trimesters. The high level of the use of medications potentially harmful to the fetus and herbal products with unknown pregnancy safety profile highlights the need of interventions aimed at counseling pregnant women about potential mother and fetal adverse drug outcomes, particularly, in women with chronic comorbid conditions. The national treatment guidelines should also be revised by removing potentially harmful medications from list of routine medications in pregnancy whenever safer alternatives are available.

Conflicts of Interest

The authors declare no competing interest on this study or its publication.

Ethical Approval and Consent to Participate

This study was approved by the REC of Faculty of Medicine, MUST (MUST-REC). Administrative clearance was obtained from the Head of the Gynecology and Obstetrics, Mbarara Regional Referral Hospital. A written informed consent was obtained from each of the study participant prior to interview. Participant confidentiality was maintained during and after data collection.

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