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ORIGINAL RESEARCH

Prevalence and Factors Associated with the Use of Self-Prescribed Orthodox and Herbal Medications Among Pregnant Women in Remo Zone of Ogun State, Nigeria Akadri Adebayo A*1, Odelola Oluwaseyi I², Adepoju Akinmade A³, Akiseku Adeniyi K⁴, Grillo Elizabeth O¹, Akadri Omobolanle M⁵

¹Department of Obstetrics and Gynaecology, Babcock University, Ilishan-Remo, Ogun State, Nigeria

*Correspondence: Dr AA Akadri, Department of Obstetrics and Gynaecology, Babcock University, Ilishan-Remo, Ogun State, Nigeria. E-mail: bayoakadri@yahoo.com; ORCID - https://orcid.org/0000-0001-8238-2652.

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Abstract

Background: The indiscriminate use of medicines in pregnancy is a public health concern because of the possibility of adverse consequences for both the mother and the developing foetus.

Objective: To determine the prevalence and factors associated with the use of self-prescribed orthodox and herbal medicines among pregnant women.

Methods: A cross-sectional study was conducted in three public health facilities (secondary and tertiary) in Remo Zone, Ogun State, Nigeria, from 1 April 2023 to 30 June 2023. A multistage sampling technique was used to select 262 antenatal clinic attendees. Interviewer-assisted questionnaires were used for data collection.

Results: Overall, 75 pregnant women (28.6%) used self-prescribed medicines. Thirty-nine pregnant women (14.9%) used self-prescribed orthodox medication, 43 (16.4%) used herbal medicines, and seven women (2.7%) used both. Analgesics (17; 43.6%) were the most commonly used orthodox drugs. Pregnant women who engaged in prepregnancy alcohol use were 4.7 times more likely to take self-prescribed orthodox medicines (AOR = 4.7, C.I = 1.5-14.5; p = 0.008). Pregnant women with high-status occupations were 80% less likely to take herbal medication (AOR = 0.2, C.I.= 0.1-0.6; p = 0.003). Similarly, pregnant women with tertiary education were 70% less likely to take herbal medicines (AOR = 0.3, C.I.= 0.1-0.6; p = 0.001).

Conclusion: The use of self-prescribed medicines is prevalent among women attending antenatal clinics in public health facilities in Remo zone Ogun State, Nigeria, with more women engaging in the use of herbal than orthodox medicines.

Keywords: Antenatal care, Alcohol, Herbal medicine, Orthodox care, Pregnancy, Self-prescription.

²Department of Obstetrics and Gynaecology, State Hospital, Ijebu-Ode, Ogun State, Nigeria

³Department of Community Medicine, Babcock University, Ilishan-Remo, Ogun State, Nigeria

⁴Department of Obstetrics and Gynaecology, Olabisi Onabanjo University, Ago-Iwoye, Ogun State, Nigeria

⁵Department of Physiotherapy, General Hospital Iperu, Ogun State, Nigeria

Introduction

Pregnant women often experience a diverse array of symptoms, many of which occur as a consequence of the anatomical and physiological changes associated with pregnancy.[1] These symptoms are often regarded by pregnant women as minor, leading them to engage in selfmedication with orthodox and/or herbal medicines. [2-4] The practice of herbal medication use is widespread in Africa, South America and some parts of Asia. [5,6] The prevalence of selfprescribed drug use in pregnancy was reported to be 36% in Brazil [7] and 72% in France.[8] In Africa, 40.8% and 69% prevalence rates were reported in Ethiopia [9] and Ghana. [6] Researchers in Nigeria have also reported prevalence rates ranging from 31.9% to 51%. [4,10,11]

Several factors make pregnant women take medications without a prescription. Some of these are poverty, ignorance, low education status, and a weak health system. [6,10,12,13] Others include poor legislation regarding the sales of drugs and the widespread availability of both orthodox and herbal medicines in the open markets. [10,13] Regarding herbal medication, some women perceive them to be more effective for some conditions, with fewer side effects compared to orthodox medication. [14] Herbal medicines are also believed in some cultures to improve the well-being of both mother and baby, act as immune boosters, and help to prepare for or ease labour pain. [15,16]

The National Agency for Food and Drug Administration and Control (NAFDAC) is the regulatory authority in Nigeria, which is mandated to regulate and control the advertisement, distribution, sale, and use of orthodox and herbal remedies. [17] However, regulating the pharmaceutical sector often clashes with powerful business interests, making the process contentious. This is especially true in developing countries with weak regulatory

institutions, where most pharmaceutical products are imported.[17] The safety of many orthodox drugs has not been well established in pregnant women, more so for the majority of herbal remedies. [9,18] Pregnant women who take herbal drugs may thus be exposed to inherently toxic medicinal plants or herbal medications that are contaminated during production. Sadly, many pregnancies are not planned in Nigeria, pre-conceptional care is rare, and many women would have taken some drugs before knowing that they are pregnant. [19] Inappropriate use of self-prescribed orthodox medicines such as nonsteroidal anti-inflammatory antidepressants and nasal decongestants has been associated with adverse pregnancy outcomes such as preterm birth, low birth weight, congenital malformations and attention deficit disorder. [4,20] The World Health Organization (WHO) regional office for Africa has been spearheading a regional strategy to promote the incorporation of complementary therapies into the health systems in the African region.[21] Although numerous studies have investigated either orthodox or herbal selfmedication separately, there is limited research on their combined use among pregnant women in Nigeria. This gap in knowledge hinders a comprehensive understanding of potential drug interactions and compounded health risks. This study was thus designed to ascertain the prevalence and factors associated with using selfprescribed orthodox and herbal medicines among pregnant women in the Remo zone, Ogun State, Nigeria.

Methods

Setting

This was a cross-sectional study conducted in the Remo zone in Ogun State. Remo is one of the four zones in Ogun State, southwest Nigeria, and falls within the country's rainforest climatic zone. Its geographical size is 964.3 km², with a projected

population of 797,000.^[22] The people of the Remo zone are predominantly farmers. From the extrapolation of available data, women in the reproductive group (15-49 years) constitute 22.5% of the zone's population. ^[23]

Ethical consideration

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Health Research Ethics Committee of the Olabisi Onabanjo University Teaching Hospital, Ogun state (OOUTH/HREC/665/2023AP).

Study population

The study population was all pregnant women who were attending antenatal clinic at the study sites, i.e. General Hospital Ikenne, General Hospital Isara, and Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu, from 1 April 2023 to 30 June 2023.

Inclusion and exclusion criteria

Pregnant women attending antenatal clinics at the study sites who were at least 18 years of age and whose pregnancies had been confirmed by ultrasound were included in the study. At the same time, women who were too ill and those who had obstetric emergencies at the time of recruitment were excluded from the study.

Sample size determination

The minimum sample size required for the study was estimated using the formula for determining the prevalence of a factor in a descriptive study (n = Z^2 pq/d²). [24] Inputting Z as 1.96, p as 19.2% from a previous study [25] and d as 0.05, the desired sample size was 236. Adjustment for a 10% non-response rate gave a final sample size of 262 women.

Sampling technique

Multistage sampling was used for this study. In stage one, Remo Zone was divided into its three constituent LGAs: Ikenne, Remo North, and

Sagamu. In stage two, the public hospitals that served as secondary or tertiary health facilities in the three LGAs in Remo Zone, Ogun State, were selected because they had good enrolment and attendance data at their antenatal clinics and provided standard antenatal care services. There are two secondary health facilities / General Hospitals (GH) in Ikenne LGA and one in Remo North LGA. One of the two GHs in Ikenne LGA (GH Ikenne) was selected randomly by a coin toss. GH Isara, the only GH in Remo North LGA, was selected, while OOUTH, a public tertiary health facility providing secondary care for Sagamu LGA, was also selected. The three study sites are appropriately spread out across the Remo zone, for which results from the study could be generalised. In stage three, a proportionate allocation method was used to determine the number of women to be interviewed from each health facility after considering the average antenatal clinic attendance in each health facility. The average weekly antenatal clinic attendance was 30, 60 and 90 clients for GH Ikenne, GH Isara, and OOUTH; hence, 44, 88 and 130 pregnant women were recruited from these study sites, respectively. A sampling frame of antenatal attendees was drawn from the antenatal clinic enrolment register, and each attendee was allocated a number. The first respondent in each health facility was selected by simple random sampling through a ballot. Subsequently, every third respondent was chosen until the desired sample size was attained. If a selected pregnant woman declined or was ineligible, the respondent with the following number replaced her. All women who agreed to participate in the study were asked to sign an informed consent form.

Study instrument

The study instrument was a semi-structured, interviewer-administered questionnaire. This instrument was adapted from a previous study in Ibadan, Nigeria. [4] The validity of the questionnaire was established by the subject

experts comprising a pharmacist with prior research experience, an obstetrician, and an experienced midwife. These experts were not part of the study. The questionnaire was pretested on twenty-six pregnant women (i.e., 10% of the calculated sample size) attending an antenatal clinic at GH Iperu, and all necessary adjustments were made.

Data collection and data management

Written informed consent was obtained before data collection. Data collection was done by the researchers and two trained research assistants using interviewer-administered questionnaires. Filled questionnaires were checked for completeness, consistency and accuracy. The data were extracted from the questionnaires and entered into a Microsoft Excel spreadsheet. All data were de-identified and stored in a personal computer, which was password-protected to ensure data integrity and security.

Statistical analysis

Statistical analysis was performed using IBM-SPSS Statistics for Windows version 23.0 (IBM Corp., Armonk, NY, USA). The normality of the distribution of continuous variables was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Maternal age was summarised using mean (S.D), while gestational age, parity, and number of antenatal clinic visits were summarised using median (Q1-Q3). Categorical variables were summarised using frequencies and percentages. The association of each independent variable with self-prescribed drug use was determined using univariate logistic regression analysis. Binary logistic regression analysis performed to determine the factors that were independent predictors of the use of selfprescribed orthodox and herbal medication. The significance level was set at 5% (p < 0.05).

Results

Out of 262 study participants, 75 pregnant women (28.6%) used self-prescribed medicines. Thirty-nine pregnant women (14.9%) used orthodox medicines, while 43 pregnant women (16.4%) used herbal medicines. Seven women (2.7%) used both orthodox and herbal medicines during pregnancy.

Table I depicts the study participants' sociodemographic characteristics, parity, gestational age. One hundred and thirty women (49.6%) were over 30 years of age, while (126; 48.1%) had a parity of 1 or 2. Most participants (197; 75.2%) attained tertiary education. The median gestational age (IQR) of the study participants was 32 (26-36) weeks, and the majority (195; 74.4%) were in the third trimester. The median gestational age (IQR) of women who took herbal medicines was 34 (27-37) weeks, while that of women who took self-prescribed orthodox medicines was 32 (27-37) weeks. The overall mean age (S.D) of study participants was 30.8 (5.1) years. The mean ages (S.D) of women who took orthodox medicines and herbal medicines were 31.2 (4.8) years and 30.2 (6.7) years, respectively. The median parity (IQR) was 1(0-2) in the two groups. The median number of antenatal visits (IQR) was 5(3-6) visits and 5(3-7) visits in women who took orthodox medicines and herbal medicines, respectively, while the median number of ANC visits for all study participants was 4 (2-6) visits. Analgesics (24; 61.5%) were the most commonly used orthodox medicines by pregnant women. This was followed by antimalarial drugs (15; 38.4%), antibiotics (11; 28.2%) and sedatives (6; 15.4%). Antihypertensive drugs and cough syrups were used by two pregnant women each. Regarding the use of herbal medications, all the women reported taking herbal concoctions prepared by boiling leaves, tree barks and some unknown components in water and allowing them to ferment.

Table I: Socio-demographic and obstetric characteristics of study participants

Characteristics		Use of self-prescribed med	icines
	Total (n = 262)	Yes (n = 75)	No (n = 187)
	Frequency (%)	Frequency (%)	Frequency (%)
Age (Years)			
≤30	132 (50.4)	41 (54.7)	91 (48.7)
>30	130 (49.6)	34 (45.3)	96 (51.3)
Parity			
0	101 (38.5)	24 (32.0)	77 (41.2)
1-2	126 (48.1)	40 (53.3)	86 (46.0)
3-4	33 (12.6)	11 (14.7)	22 (11.8)
≥5	2 (0.8)	0 (0.0)	2 (1.0)
Occupation			
Housewife	21 (8.0)	2 (2.7)	19 (10.2)
Trader	101 (38.5)	34 (45.3)	67 (35.8)
Artisan	37 (14.1)	13 (17.3)	24 (12.8)
Civil Servant	38 (14.5)	7 (9.3)	31 (16.6)
Professionals	65 (24.8)	19 (25.3)	46 (24.6)
Marital Status			
Single	6 (2.3)	2 (2.7)	4 (2.1)
Married	256 (97.7)	73 (97.3)	183 (97.9)
Religion			
Christianity	201 (76.7)	56 (74.7)	145 (77.6)
Islam	60 (22.9)	19 (25.3)	41 (21.9)
Traditional	1 (0.4)	0 (0.0)	1 (0.5)
Educational level			
No formal	5 (1.9)	3 (4.0)	2 (1.1)
education Primary	9 (3.4)	0 (0.0)	9 (4.8)
Secondary	51 (19.5)	25 (33.3)	26 (13.9)
Tertiary	197 (75.2)	47 (62.7)	150 (80.2)
Gestational age			
1st Trimester	7 (2.7)	2 (2.7)	5 (2.7)
2 nd Trimester	60 (22.9)	13 (17.6)	47 (25.1)
3 rd Trimester	195 (74.4)	60 (79.7)	135 (72.2)

Private pharmacies were the most common source of information on orthodox medicines (22; 56.4%), followed by the patent medicine stores (8; 20.5%). Four women (10.3%) got information regarding orthodox medicines use from hospital pharmacies, and another four women from leftovers of previous prescriptions. Only one respondent reported getting information from a drug vendor. Twenty-nine women (67.4%) who took herbal medicines reported getting information from "family and friends", six

women (13.9%) reported having personal knowledge of the herbal medications used, and three women (7.0%) got information from health workers and mass media. In contrast, two respondents (4.7%) got information about the use of herbal medicines from Traditional Birth Attendants or Herbalists. The occurrence of "minor symptoms" was the commonest motivation factor for the use of both orthodox (20; 51.3%) and herbal medicines (14; 32.5%) (Table II).

Table II: Motivational factors for use of self-prescribed orthodox and herbal medications

Motivational factors	Self-prescribed orthodox medicines (n=39)		Herbal medicines (n = 43)		
	Frequency	Percentage	Frequency	Percentage	
Minor symptoms	20	51.3	14	32.5	
Need for emergency treatment	2	5.1	3	7	
Long waiting time in hospitals	1	2.6	0	0	
Convenience	8	20.5	3	7	
Lack of access to health facilities	3	7.7	4	9.3	
Had done it before without any harm	5	12.8	8	18.6	
Forced by relatives	0	0	11	25.6	

The commonest symptoms associated with the use of self-prescribed orthodox medicines were headaches/body pains (16; 41.0%). However, the majority of the study participants who took herbal medications during pregnancy reported no symptoms before the use of these medications (25; 58.1%) Table III.

The analysis of socio-demographic and obstetrics factors associated with the use of self-prescribed orthodox and herbal medicines are depicted in Tables IV and V. Univariate analysis revealed that respondents' occupation, pre-pregnancy alcohol use, and contraceptive use were significantly associated with the use of self-

prescribed orthodox medicines (p = 0.044, p = 0.001 and p = 0.036 respectively). In contrast, respondents' occupations and educational levels were significantly associated with using herbal medications (p<0.001).

Logistic regression analysis was performed to ascertain the independent effects of age, occupation, educational level, pre-pregnancy alcohol use, and pre-pregnancy contraceptive use on the likelihood that participants used self-prescribed orthodox and herbal medicines during pregnancy.

Table III: Symptoms associated with use of self-prescribed orthodox and herbal medicines

Symptoms	Self-prescribed orthodox medicines (n = 39)		Herbal medicines (n = 43)	
	Frequency	Percentage	Frequency	Percentage
No symptoms	8	20.5	25	58.1
Headache/ Body Pains	16	41	7	16.3
Malaria symptoms	15	38.5	15	34.9
Weakness/tiredness	4	10.3	0	0
Gastrointestinal symptoms	5	12.8	3	7
Urinary symptoms	4	10.3	0	0
Insomnia	6	15.4	0	0
Respiratory symptoms	2	5.1	0	0

Multiple entries allowed

Women who engaged in pre-pregnancy alcohol use were 4.7 times more likely to take self-prescribed orthodox medicines in pregnancy when compared with those who did not take alcohol (AOR = 4.7, C.I.= 1.5-14.5; p = 0.008). Women with high-status occupations (Civil servants and professionals) were 80% less likely to take herbal medicines during pregnancy when compared to those with low-status occupations (housewives, traders, artisans) [AOR = 0.2, C.I.= 0.1-0.6; p = 0.003]. Similarly, women with tertiary level education were 70% less likely to take herbal medicines in pregnancy when compared to those without tertiary level education (AOR = 0.3. C.I. = 0.1-0.6; p = 0.001).

Discussion

Our findings suggest that approximately one out of every four pregnant women used selfprescribed medicines, with more women engaging in the use of herbal medicines than orthodox medicines. The study also revealed that pregnant women who engaged in pre-pregnancy alcohol use were more likely to take selfprescribed orthodox medication than women who did not take alcohol. Also, highly educated women and those with high-status occupations were less likely to take herbal medicines during pregnancy.

The prevalence of the use of self-prescribed orthodox medications in this study was 14.9%. This is lower than findings from other studies done in southwestern Nigeria. Bello et al. reported a prevalence of 19.2% in Ibadan. [25] A more recent study also done in Ibadan by Adeoye et al. [4] reported a prevalence of 31.9%. In comparison, studies done in Ogbomoso [10] and Osogbo, Osun State [26] reported a prevalence of 51% and 30%, respectively. Regarding the use of herbal medicines in pregnancy, the prevalence in this study was 16.4%. This is higher than reports from Ogbomoso, Oyo State (11.3%) [10] but lower than in Osogbo, Osun State (24.2%) [26] and Ibadan, Oyo state. (21.7%). [4] Possible reasons for the wide disparities in prevalence include cultural differences, ease of access to drugs and varying drug regulatory mechanisms in different regions and countries. [4,7,16]

Table IV: Factors associated with use of self-prescribed orthodox medicines

Predictor	COR	p-value	prescribed orthodox r	p-value
Age (Years)		,		,
≤30	Reference		Reference	
>30	1.2 (0.6-2.4)	0.567	1.6 (0.7-3.3)	0.233
Parity				
Nulliparous	Reference			
Multiparous	0.9 (0.4-1.8)	0.731		
Occupation				
Low status jobs	Reference		Reference	
High status jobs	2.0 (1.0-4.0)	0.044	1.3 (0.6-3.0)	0.471
Educational level				
No tertiary education	Reference		Reference	
Tertiary	1.6 (0.7-3.8)	0.282	1.4 (0.5-3.7)	0.509
Gestational age				
(week) ≤ 20	Reference	0.908		
> 20	0.9 (0.3-3.3)			
Number of ANC visits	((
< 4	Reference	0.198		
≥ 4	1.6 (0.7-3.4)			
Pre-pregnancy alcohol use				
No	Reference		Reference	
Yes	5.2 (1.8-14.9)	0.001	4.7 (1.5-14.5)	0.008
Pre-pregnancy contraceptive use				
No	Reference		Reference	
Yes	2.2 (1.0-4.5)	0.036	1.7 (0.8-3.9)	0.19
Chronic medical condition				
No	Reference	0.315		
Yes	0.6 (0.2-1.7)			

The higher prevalence of the use of herbal medicines compared to orthodox medication is another area of grave concern. The use of herbal medications, in many instances, has sociocultural, religious and spiritual values

among the people. ^[16] Many women in sub-Saharan Africa believe in the efficacy and safety of herbal medicines. ^[6,16] It is also important to note that seven pregnant women used both herbal and orthodox medicines.

Table V: Factors associated with use of herbal medicines

Predictor	COR	p-value	AOR	p-value
Age (Years)				
≤30	Reference		Reference	
>30	0.6 (0.3-1.2)	0.148	0.6 (0.3-1.3)	0.231
Parity				
Nulliparous	Reference	0.22		
Multiparous	1.5 (0.8-3.1)			
Occupation				
Low status jobs	Reference		Reference	
High status jobs	0.2 (0.1-0.4)	<0.001*	0.2 (0.1-0.6)	0.003*
Educational level				
No tertiary education	Reference		Reference	
Tertiary	0.2 (0.1-0.4)	<0.001*	0.3 (0.1-0.6)	0.001*
Gestational age (week)				
≤ 20	Reference	0.939		
> 20	1.1 (0.3-3.8)			
Number of ANC visits				
< 4	Reference	0.473		
≥4	1.3 (0.6-2.6)			
Pre-pregnancy alcohol use				
No	Reference		Reference	
Yes	1.8 (0.5-5.8)	0.339	2.4 (0.6-9.5)	0.227
Pre-pregnancy contraceptive use				
No	Reference		Reference	
Yes	1.2 (0.6-2.5)	0.148	1.9 (0.8-4.7)	0.141
Chronic medical condition				
No	Reference	0.738		
Yes	0.9 (0.3-2.2)			

This may also be challenging because of the potential risk of interactions between the active substances and the possibility of teratogenicity. ^[27] The National Agency for Food and Drug Administration and Control (NAFDAC) has been making efforts to regulate herbal medicines in Nigeria. ^[28] However, the traditional medicine practitioners who are major stakeholders are still averse to subjecting their herbal remedies to modern healthcare safety standards. ^[28] There is

an urgent need for more advocacy to address this.

The commonest self-prescribed orthodox drugs used by pregnant women in this study were analgesics. This is also related to the fact that the commonest symptoms associated with drug use were headaches and body pains. Similar findings were reported in previous studies. [4,7,10,13] While paracetamol, which is the first-line analgesic and antipyretic among pregnant women, is

considered safe during pregnancy, [4] other commonly used analgesics like non-steroidal anti-inflammatory drugs have been associated with miscarriages and premature closure of ductus arteriosus. [29]

The majority of the study respondents decided to use either orthodox or herbal medicines without prescription because they felt that they had minor symptoms. Pereira et al. also reported similar findings from a study in Brazil. [7] The general ease of access to medications without prescription in Nigeria may also be a contributory factor. More than half of pregnant women who took self-prescribed orthodox medicines got their information from private pharmacies, similar to findings from an Ethiopian study. [13] Interestingly, about a quarter of pregnant women who took herbal medicines reported that they were forced to do so by their relatives. Again, this indicates the widespread belief in the efficacy of herbal medicines in traditional African families. [16] It also shows the far-reaching influence relatives, especially inlaws, usually have on women. This underscores the importance of engaging community gatekeepers to drive any intervention to solve this problem.

Logistic regression analysis showed that only pre-pregnancy alcohol use was a significant predictor of the use of self-prescribed orthodox medicines during pregnancy. It can be hypothesised that women who took alcohol may more likely have poor lifestyle choices and thus engage in other harmful practices, including indiscriminate use of self-prescribed orthodox drugs. The factors associated with the use of herbal medicines in pregnancy were occupation and educational level. After adjusting for confounding variables, pregnant women with high-status occupations (Civil servants and professionals) and those with tertiary-level education were less likely to take herbal medicines. These findings are similar to reports from Ibadan (Nigeria) and Cameroun. [4,28] Highly educated women and women with highstatus occupations are likely more conscious of the potential harmful effects of herbal drugs on the foetus and thus avoid them during pregnancy. This study also shows that the number of antenatal visits did not affect the likelihood of taking self-prescribed orthodox drugs. Antenatal care (ANC) is one of the critical interventions for improving maternal health. It is expected to provide an effective platform for health-promoting services through education, nutritional support and drug and substance abuse cessation. [4,30] This study brings to the fore the need for health workers to use the platform of ANC to provide evidence-based information to pregnant women on medication use during pregnancy.

Strengths and Limitations

The multistage sampling technique allowed for selection of a representative study population, thus enhancing the generalizability of the study. Using logistics regression analysis to control for multiple confounders also improved the validity of the study findings. It is, however, important to also appreciate the limitations of the cross-sectional study design used in this study, which meant that one could not ascertain the temporal sequence of exposures and outcomes. This study depended on selfreported assessment of drug use by pregnant women with a potential for underreporting, recall bias or social desirability bias. Moreover, our findings should be applied with caution in other cultural settings, as drug use practices among pregnant women may be grossly affected by government policies and cultural practices.

Conclusion

The use of self-prescribed medicines is prevalent among women attending antenatal clinics in public health facilities in Remo zone Ogun State, Nigeria, with more women engaging in the use of herbal medicines than orthodox medicines. Pregnant women who engaged in pre-pregnancy alcohol use were more likely to take self-prescribed orthodox medication. Also, highly educated women and those with high-status occupations were less likely to take herbal medicines during pregnancy. The findings from this study highlight the popularity of herbal medicine among the study population. While this may justify the recent drive led by the WHO to integrate complementary therapies into the existing healthcare system, it also underscores the importance of paying particular attention to medication safety in pregnancy.

Authors' contributions: AAA1 conceptualised and designed the study. OOI, AAK, GEO and AOM did the literature review. AAA1, OOI, AAK and AOM collected the data, while AAA1 analysed and interpreted the data. AAA1 and AAA2 drafted the manuscript while OOI, AAK, GEO and AOM revised the manuscript for sound intellectual content. All the authors read and approved the final version of the manuscript.

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