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Depressive Disorders Through Pregnancy: A Study of an Antenatal Cohort in a Nigerian Tertiary Hospital

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Abstract: Anxiety and depressive disorders affect up to a fifth of pregnant women, even in countries of the West African sub-region. Few longitudinal studies are reported in this environment. Little is known about the incidence and course of depressive disorders in pregnancy. This study thus aimed to determine the incidence, progression and socio-demographic variables associated with depression in pregnancy. Fifty-six women in their first trimester and 146 women in their second trimester attending the antenatal clinic of the University of Calabar teaching hospital were recruited into a cohort. One hundred and eighty-seven women were followed-up to term of pregnancy. Calculated sample size was 175. This study was prospective. Assessments were 8 weeks apart with clinical interviews carried out on all respondents, assisted by the Mini International Neuropsychiatric Interview (MINI) for making diagnoses and the Hospital Anxiety and Depression Scale (HADS) for a symptom count. Each respondent was assessed at least once in subsequent trimesters after recruitment. From the obtained results, the mean age of respondents was 29.31 years (SD ±4.86). Most of the women were socially advantaged. Using strict MINI criteria for major depressive episode (MDE), the incidence was 0(0%), 3(1.5%) and 4(2.1%) in the first, second and third trimesters, respectively. Using clinical criteria, the incidence of depressive disorders, including minor depressive disorders, was 0(0%) in the first trimester, 9(4.6%) in the second trimester and 5(2.8%) in the third trimester. For MDE using MINI criteria, the cumulative incidence was 7(3.5%) and using clinical criteria, it was 14(6.9%). Mean HADS depression scores consistently and significantly decreased throughout pregnancy. There were no risk factors for severity of depression at term. *Conclusions*: New cases ofdepressive disorders occur in pregnancy. Distressing symptoms may be more in early pregnancy. Early booking for antenatal care (ANC) and screening measures should be instituted to detect those with clinically significant symptoms.

Key words: Depression · Incidence · Pregnancy · Antenatal

INTRODUCTION

Mood disorders, schizophrenia and specific anxiety disorders among women of reproductive age (15-44 years) contributes as much as 7% to the global burden of disease (GBD) of women of all ages and 3.3% of the GBD of both sexes [1]. Depression ranks number five among the contributors to GBD, for both sexes and, fourth for women alone [2]. It is predicted that it will rise to second position by the year 2020.

Unfortunately, the economic costs are also increasing [3] and are likely to continue increasing unless measures are put in place to mitigate this rise. In the United States of America alone, the economic burden of major depressive disorder, bipolar disorder and dysthymia was estimated to be US$ 83.1 as at the year 2000 after putting together the direct medical costs, suicide related mortality costs and indirect workplace costs [4]. In Nigeria, it is estimated that it would cost 4, 680 naira per year to treat depression at the primary care level using an older anti-depressant and if government would scale up treatment coverage at this cost to 40%, 69, 608 disability-adjusted life years (DALYs) will be averted per year [5]. These estimates were at year 2000 exchange rates when US$ 1 was equal to 104 naira [5].

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Depression is frequently seen with anxiety [6]. Low mood predominates in depression with its attendant consequences on functioning of the affected individual. Worrying, on the other hand, predominates the picture in anxiety disorders, with its disabling effects on the individual. Women are generally more vulnerable to these disorders [7, 8]. The peak age of onset of depressive and anxiety disorders also coincides with child-bearing years. There is little or no documented difference between the pattern of symptoms of depression in pregnancy and in non-pregnant women [9]. Anxiety is common during pregnancy and may be more pronounced when it coexists with depression. Additionally, the physical experiences of pregnancy, such as fatigue, sleep disruption, weight change and concentration difficulties, can overlap with the symptoms of depression and thus confuse the diagnostic picture [10].

The increased emotional and physical demands during pregnancy, further increases the susceptibility of women of child-bearing age to developing anxiety and depression. Many women experience physiological, psychological and social changes related to pregnancy and want to adapt to these changes [11]. However, changing circumstances without preparation can cause mental and emotional problems and the influence of hormones associated with pregnancy can aggravate the occurrences of these changes [12]. Studies show that women are more likely to develop symptoms of depression in pregnancy than in the postnatal period [13]. Epidemiological studies have reported the prevalence of depression in high-income countries (HICs) to range from 4% to 20% [14, 15]. Current estimates of the prevalence of depression in pregnancy vary widely ranging from 8.3% to 44% in Africa [16].

It has been reported that prevalence of depression is higher in the 1st and 3 rdtrimester compared to the 2 nd trimester [17], but a cross-sectional study in Ilorin found no difference in psychiatric morbidity for the three trimesters [18]. An international study, however, found highest morbidity in the second trimester and lowest in the first trimester [14]. This will suggest a need for a longitudinal study aimed at understanding in which trimesters of pregnancy women may need more psychosocial support.

This study aimed to determine the incidence, progression and socio-demographic factors associated withdepression in an antenatal cohort. Specifically, we intendto determine the incidence of depressive disorders in each trimester of pregnancy, to investigate the progression of depressive symptom scores through the trimesters of pregnancy and to determine the relationship between the socio-demographic characteristics of pregnant women and the severity of depression at term.

MATERILAS AND METHODS

Study Location: This study was conducted at the Antenatal clinic (ANC) of the University of Calabar Teaching Hospital (UCTH) Calabar, Nigeria. The UCTH is probably the most patronized health facility in the city because of its location within the city, low charges and availability of health practitioners in a variety of specialties. Booking starts by 8am and closes by 4pm.

Selection of Respondents: Subjects were recruited into the study by Systematic random sampling method. Attendees to the ANC who are within their 4th to 20th weeks of gestation constituted the sampling frame derived from the clinic register. A fair die was tossed to determine the first subject using the derived list. Subsequent subjects were determined using a calculated sampling interval. Recruitment continued for up to 10 weeks until sample size was completed.

Study Design: A prospective, cohort design was used in this study to allow for the estimation of incidence and permit a determination of the progression of symptom scores.

Ethical Consideration: Ethical approval was obtained from the Ethical Review Board of the University of Calabar Teaching Hospital where the study was conducted. Permission was also obtained from the Head of Department of Obstetrics and Gynecology. Informed consent was obtained from potential participants and data obtained was treated as confidential. Participation was voluntary and refusal to give consent did not affect the quality of care given to patients.

Sample Size Determination: The sample size for this study was calculated using the relation below:

$n = z^2pq/d^2$ [19-21]

Other researchers studying depression in pregnant women have used similar sample sizes [22, 23].

Inclusion Criteria: Antenatal care attendees between 4 and 20 weeks of gestation, women aged between 18 and 45 years as well as those residing within Calabar to permit easier follow-up.

Exclusion Criteria: Women taking prescribed medication for an anxiety and/or depressive disorder, Womenwhorefuse to give consent to the study and women who are too ill to participate in the study.

Study Duration: The total length of the study (recruitment and follow up) was 7 months.

Instruments: The instruments that were used to collect data from participants in this study are:

Sociodemographic Variables Questionniare: A questionnaire designed by the researcher was used to collect information from participants concerning variables like age, level of education, marital status, medical history and obstetric history. The questionnaire was interviewer administered. The numbering on each questionnaire wasused to track the participants as these numbers corresponded with those on a tracer sheet which was used for follow-up. The tracer sheet contained respondents' phone numbers, 2 additional contact phone numbers per respondent, home addresses in Calabar among other necessary information needed for follow up.

Hospital Anxiety and Depression Scale (HADS): The HADS is a brief (14-item), self-report measure of anxiety and depression developed by Zigmond and Snaith [24]. The authors recommend a score of 0-7 to be normal, 8-10 borderline, 11-21 abnormal scores for the depression subscale. Validity coefficients reported in a Nigerian antenatal population are, sensitivity of 90.1% for the depression subscale and specificity of 91.1% for the depression subscale and a misclassification rate of 9.3% for the depression subscale [25, 26].

Mini-International Neuropsychiatry Interview (MINI): The MINI is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States and Europe, for DSM-IV and ICD-10 Axis 1 psychiatric disorders [27]. The interview is divided into 16 modules (A-P) corresponding to categories of diagnoses. For this study, the module A (Major Depressive Episode) was used to interview participants. Most of the diagnoses that can be made with this instrument are current though a few lifetime diagnoses can also be made. It took approximately 15 minutes to administer the instrument to each respondent.

Procedure for Administration of Instruments: Subjects consisting of ANC attendees within 4 to 20 weeks of gestation were recruited to participate in the study as first or initial engagement E_0. All subjects were assessed for presence and severity ofdepressive disorders using MIN (module A). The socio-demographic variables questionnaire was also administered at E_0 only. Subsequently, subjects without MDE were followed up for repeat assessment after eight (8) weeks. Subjects with MDE were referred to the Psychiatry unit of the University of Calabar Teaching Hospital (UCTH), but were also followed up for repeat assessment for MDE after eight (8) weeks. This constituted the second engagement E_1 for subjects with or without MDE. A repeat (third) engagement E_2 of all subjects with or without MDE was carried out at 8 weeks after second engagement or E_1 with each subject. For some subjects (those recruited at 20 weeks of gestation), their E_2 corresponded with term and did not need further assessments. For others, they were followed up till term when they for assessed for the last time. This constituted the fourth engagement E_T for subjects with or without MDE. During each engagement, the presence and severity of MDEwere determined including adherence to referral and the form of treatment provided at referral center (for those that were referred). These engagement periods coincided with the routine ANC clinic visit appointment dates for easy access to subjects. Loss to follow-up was minimized using GSM text message to remind subjects of their clinic appointment visits. Those that did not come for their appointments were contacted on phone and interviewed at their homes with the help of social workers posted to the ANC.

Statistical Analysis: Data was analyses were performed with Statistical Package for the Social Sciences (SPSS) version 21.0. Frequency counts and chi-squared (x^2) tests were used for categorical variables while continuous variables were analyzed using the t-test and analysis of variance (ANOVA) when comparing more than 2 groups. The level of significance was set at 0.05 for all tests.

RESULTS

Sociodemographic Characteristics of Respondents: A total of 202 women were recruited into the study. Fifty-six women (27.7%) were in their first trimester of pregnancy while 146 (72.3%) where in their early second trimester. For a balanced comparison, these two groups of women were considered separately in some analyses as seen in subsequent tables. On the whole, about 187 women (92.6%) were followed to term while 12 women (5.9%) lost their pregnancies at different times during follow up. Three women (1.5%) could not be reached on any of the 3 phone numbers they volunteered, neither were the addresses they gave valid. Of the 15 women that were lost to follow-up, 7 women were of the group recruited in the first trimester of pregnancy while 8 women were of those recruited in the second trimester.

The mean age of respondents was 29.31 ± 4.86 years, with a range of 18 to 44 years. More than half of the respondents (66.8%) were raised in monogamous family settings as children while the rest were either raised in polygamous family settings or by single parents. Most (92.6%) of the women enjoyed financial assistance in times of need, an aspect of social support. More than two-thirds of these women (70.8%) had attained a tertiary level of education and more than half (65.3%) had a paid employment outside the home. Only 7 women (3.4%) had an average family monthly income of less than 20, 000 naira ($100) per month.

Pregnancy-Related Characteristics and Other Clinical Information of Respondents: Most (80.7%) of the women were eager to get pregnant and were happy when they realized that they were pregnant (Table 1). A hundred and nine women (54.0%) did not have significant problems in their last pregnancy and with regards to the index pregnancy, 177 respondents (87.6%) did not experience frequent or chronic illness in present pregnancy. Less than a third (22.8%) of the women had never been pregnant in the past. Majority of respondents (93.6%) were not presently on any chronic medication outside the routine haematinics. More than half of the women (53.0%) had a mean Packed Cell Volume of 33% or more.

Progression of Depression (HADS SCORES) Through the Trimesters among Respondents Recruited in the First Trimester: Nine women (16.1%) and 18 women (32.1%) out of 56 women recruited in the first trimester of pregnancy scored above cut-off (score of 8) in the anxiety and depression subscales respectively of the Hospital Anxiety and Depression Scale (HADS) in the first trimester. The proportions of those who scored above cut-off in this group decreased to 5 (10.2%) and 7 (14.3%) out of 49 women (7 women in this group had miscarriages between first and second trimester) for the anxiety and depression subscales of the HADS respectively in the second trimester anddecreased further to 3 (6.1%) out of 49 women for both subscales by the third trimester as shown in Table 2.

Table 1: Pregnancy-related characteristics and other clinical information of respondents (N=202)

Variable	Frequency (N=202)	Percentage (%)
News of present pregnancy		
Happy	163	80.7
Not	39	19.3
Problem in last pregnancy		
Yes	47	23.3
No	109	54.0
Never been pregnant	46	22.6
Illness in present pregnancy?		
Yes	25	12.4
No	177	87.6
Number of past pregnancy		
Nil	46	22.8
1	46	22.8
2	55	27.2
3	28	13.9
More than 3	27	13.3
Taking medication other than routine drugs		
Yes	13	6.4
No	189	93.6
Current use of psychoactive substance		
Yes	3	1.5
No	199	98.5
Packed Cell Volume (%)		
Less than 30	13	6.4
30 – 32	81	40.1
33 and above	108	53.0
No information	1	0.5

Progression of Depression (HADS SCORES) Through the Trimesters among Respondents Recruited in the Second Trimester: A similar pattern of decreasing frequencies of those who scored above cut-off in the HADS subscales was also obtained among 146 respondents recruited in the second trimester of pregnancy as shown in Table 5.4. Twenty-eight women (19.2%) of 146 women in the second trimester scored above cut-off in the anxiety subscale, whereas only 10 (7.2%) scored such by the third trimester. The same trend can be seen for scores in the depression subscale of HADS for this group in Table 3.

Table 2: Distribution of HADS scores through pregnancy among respondents recruited in first trimester (N = 56)

HADS subscale	First Trimester (n=56) n(%)	Second Trimester (n=49*) n(%)	Third Trimester (n=49*) n(%)
Depression			
Score <8	38(67.9)	42(85.7)	46(93.9)
Score =8	18(32.1)	7(14.3)	3(6.1)

*Seven women suffered miscarriages sometime before they reached the second trimester of pregnancy and this explains why *n* dropped from 56 to 49.

Table 3: Distribution of Hads Scores Through Pregnancy Among Respondents Recruited I in Second Trimester (N=146)

HADS Subscale	Second Trimester (n=146) n(%)	Third Trimester (n=138*) n(%)
Depression		
Score <8	121(82.9)	127(92.0)
Score =8	25(17.1)	11(8.0)

*Eight women of the 146 respondents recruited in their second trimester of pregnancy suffered a miscarriage at some time before their third trimester of pregnancy or were lost to follow up

Table 4: Incidence of Depression in the Trimesters of Pregnancy Among Respondents

Mini and Clinical Diagnoses	First Trimester n(%)	Second Trimester n(%)	Third Trimester n(%)	Cumulative Incidence ?n(%)
MDE	0(0.0)	3(1.5)*	4(2.1)†	7(3.5)
CLINICAL MDE	0(0.0)	9(4.6)	5(2.8)	14(6.9)

Incidence of Depression in the Trimesters of Pregnancy: During the clinical interviews, mild depressive disorders were found but did not meet strict criteria of the Mini International Neuropsychiatric Interview (MINI) which diagnosed disorders of moderate and above severity as described earlier. The cumulative incidence of MDE meeting MINI criteria was 3.5% over the entire period of pregnancy Table 4.

Diagnostic Status Through the Trimesters of Pregnancy among Respondents Recruited in the First Trimester: A single case of MINI MDE diagnosed in the second trimester had persisted into the third trimester (eventually recovered at 28-week gestational age), but the third and first trimesters had no new cases of MINI MDE among the 56 respondents recruited in their first trimester. Two women met clinical criteria for a minor depressive disorder in the second trimester, with one of them experiencing remission during the same trimester and the other eventually experiencing remission in the third trimester. No new cases of minor depressive disorder were identified in the first and third trimesters.

Diagnostic Status Through the Trimesters of Pregnancyamong Respondents Recruited in the Second Trimester of Pregnancy: Two new cases of MINI MDE were identified in the second trimester and 4 more cases in the third trimester making 6 cases of which 2 recovered in the third trimester. The clinical criteria identified 4 new cases of a minor depressive disorder in the second trimester and 3 in the third trimester. Three women with a minor depressive disorder recovered in the third trimester.

DISCUSSION

Sociodemographic, Pregnancy and Clinical Characteristics of Respondents: Majority (89.1%) of the women in this study were married. This distribution as regards marital status is similar to what was obtained in a study by Thompson and Ajayi in their sample of 314 women in western Nigeria, where they found that 93% of their respondents were married [29]. These figures, however, are higher than what is obtained in the general population e.g. 71.4% in the Nigeria Demographic and Health Survey (NDHS) of 2013, NDHS [30]. They difference may be in the fact that married women are more likely to afford antenatal care and may thus be over-represented in ANC populations.

Most of the women in this study were Christians. This is not surprising as majority in the southern or coastal parts of West Africa practice the Christian religion. The socioeconomic characteristics of respondents in this study suggested that, relatively advantaged women may have been over-represented in the study sample. Over 90% of them had attained to secondary education or higher, while less than 2% had only primary education or no education. Women of higher educational status are more likely to be of higher socioeconomic status and thus afford thehigh ANC bills at our study site.

Less than 20% of the women in this study were unemployed and largely dependent on their husbands for 'up-keep', as well as, spending most of their time at home. This is similar to a 20% rate of unemployment status reported among 165 Greek pregnant women by

Gourounti *et al*. [31]. Thompson and Ajayi 2016 however reported lower unemployment rates of 3.2% among pregnant women in western Nigeria [29]. These differences may be due to the different ways of assessing employment status and the different employment opportunities available to women in various parts of sub-Saharan Africa.

The average family incomes per month of respondents in this study were grouped according to a method used by Oguoma *et al*. [32]. Close to 70% of respondents belonged to the high and upper middle income groups, further showing the predominance of the socially advantaged in our study sample. Most researchers in the West African sub region have reported higher proportions of pregnant women in the low income groups or low socioeconomic status. Adewuya *et al*. [22] for instance, found that 39.4% of their study sample consisted of women of low socioeconomic status. The raise of ANC fees and consequent selection of women who can afford to pay at our study site may contribute to our relatively unusual findings.

In this study, 80.7% of women were happy when they knew they were pregnant and were eager to have the baby. This may be because women that planned to get pregnant are more likely to go for antenatal care and thus over-represented in ANC populations.

Less than a third of respondents (23.3%) in this study reported to having frequent or severe illness in the last pregnancy. A study in the West African sub-region among women attending ANC in semi-urban areas reported 13.3% of participants as having had a pregnancy-related admission during the previous pregnancy [22]. This was another specific though limited way to assess the same parameter. Our study also found that 12.4% of respondents had serious or chronic illness in present pregnancy while the study [22] aforementioned reported a rate of 6.1% having had a pregnancy-related admission in current pregnancy. The higher rates of illness in previous and present pregnancies reported in our study may be due to the fact that not all serious illnesses in pregnancy require admission.

Also, majority (98.5%) of respondents in this study were currently not using any psychoactive substances. This is similar to what is reported by Thompson O and Ajayi I reported in a Nigerian antenatal population where 99.7% did not smoke cigarettes during that pregnancy and 94.2% also did not use alcohol in any form. [29] It is possible that most pregnant women decide to avoid psychoactive substance use in pregnancy to avoid harm to their unborn child.

Most the respondents had social advantages like being raised in a monogamous family setting (66.8%). This was an attempt to explore childhood settings they may have been raised in, as children in monogamous settings are more likely to have experienced fewer childhood adversities than in other settings [33]. Thompson and Ajayi [29] similarly reported that 78.5% of women in their antenatal sample were from monogamous families.

Majority (92.6%) of the respondents enjoyed financial/instrumental support (practical help) from spouse/family in times of need. Less than half (45.6%) of women in a study by Biratu *et al*. [34] had good social support. The possible reason for this difference from our finding is that their study was conducted at a primary care setting were antenatal care is affordable and assessable for the general population, including those with more social disadvantages.

The relationship between age and depression in pregnancy is inconsistent and conflicting in the literature. We found that there was no association between age and anxiety/depressive symptoms at term of pregnancy. Ratcliff et al working with immigrant pregnant women in Geneva also found no association between age and antenatal depression [35]. Bodecs *et al*. [36] also found a lack of association between maternal age anddepression in a Hungarian antenatal population. In this study, we restricted ourselves to working with the adult population including only those between ages 18 and 45 years. Our average age was 29.31 years while that in the study [37] just mentioned was 26.86. This may have contributed to our difference in findings. Their sample had more representation of younger women and this may explain why they may have found a significant relationship between young age and anxiety disorders in pregnancy.

Incidence of Major Depressive Episode in Pregnancy: A cumulative incidence of 3.5% and an incidence of 2.1% in the third trimester for MDE are reported in this study. Banti *et al*. [38] in a prospective study of perinatal depression in Italy reported a cumulative incidence of 2.2% for depressive disorders in pregnancy lower than ours. Martini *et al*. [39] also reported an even lower cumulative incidence of depressive disorders in pregnancy of 0.9% among 109 women in Europe that have never had depressive disorders before in life. The aforementioned studies were all carried out in high-income countries and with diagnostic instruments (SCID and CIDI) different from ours (MINI). These may explain the difference in rates. Local studies using

diagnostic instruments to study depression in pregnancy are few. One of suchreported a rate of 8.3% current DSM-IV depressive disorder among women in the third trimester of pregnancy in south-west Nigeria [22]. This rate may have included depressive disorders present before pregnancy unlike our study where such were excluded. Their rate also included minor depressive disorders which makes their rate comparable to our incidence of 6.9% when minor depressive disorders are added.

Progression of Depression Towards Term among Respondents: Progression of disorders has been variously defined in the literature [40]. This study proposed to study the course of anxiety and depressive disorders in a cohort of pregnant women who did not have those disorders at the time of recruitment into the study. Progression of depression could be considered using two different approaches, the progression of diagnosed disorders andor the progression of symptoms.

First, we could consider the progression of disorders in the few new cases that were picked up at some point during pregnancy but before term. Using this approach, we would be aiming to answer questions such as the following: Of the new cases picked up, how many persisted till term? How many resolved before term? In order to answer this question, the course and progression of disorder in each of the identified cases was examined and presented in a diagram (Figures 5.3 and 5.4). Since the incidence was lowa case by case consideration was possible.

This study revealed that 6(42.3%) of the 14 women with a depressive disorder experienced remission of symptoms during pregnancy, most within 8 weeks. They did not experience another episode during the pregnancy and could thus be said to have recovered. These findings are not surprising considering that mild depressive disorders can be self-limiting and remit spontaneously even without treatment [41]. The Netherlands Mental health survey and incidence study even reported that as much as 50% of those with untreated MDE recovered within 3 months and 63% within 6 months [42].

More than half, though of those with an anxiety disorder (64.3%) and a depressive disorder (57.7%) had the disorder persisting for the rest of the pregnancy. Some of these may persist as post-partum disorders with an addition from recurrences from those who had remission, largely because they did not seek help in the psychiatry clinic they were referred to. Most of them gave as a reason for not attending the psychiatric clinic that they did not think their condition was serious enough to warrant seeking expert help. Stigma to mental illness in our environment may also contribute to their reluctance to seek help despite evidence showing the effectiveness of a variety of mental health interventions [43].

The second approach would be to consider the progression of depressive symptoms in the cohort as a whole. The first approach, i.e. considering only disorders would be limited to the very small number of cases that were picked up during pregnancy. The advantage of the symptom progression approach is thatdepressive symptoms in the entire cohort is considered and its rates taken as a general indicator of mental well-being in the group. Since pregnancy impacts upon every member of the group both physically and psychologically, this approach would be useful in determining the overall effect of pregnancy on the mental health.

A significant and consistent reduction of mean scores was also reported in this study from early pregnancy to late pregnancy. A similar reduction from the 18^{th} to the 32^{nd} week of gestation of mean scores has also been reported in a prospective study of more than 8, 000 pregnant women in England. [13] Teixeira *et al* on the other hand reported a U-shaped pattern of change in mean STAI scores with first and third trimester scores highest and lower scores in second trimester [44]. This further supports the notion that the first trimester is a turbulent period for the mental health of most mothers trying to adjust to the physiological and psychological changes of pregnancy. The second trimester is a period of relative calm and stability as shown by the reduction in scores. Our study showfurther reduction in scores possibly as a result of the joy of anticipating the birth of a new child.

Limitations of Study: The study was conducted in a setting where only those who could afford to pay for services and thus the socially advantaged were over-represented. This limits the generalizability of our findings.

Additionally, our study may not have been adequately powered because of our sample size to detect some anxiety disorders in our population.

Our study is also limited by our inability to recruit all our subjects in the first trimester which would allow for more uniform assessment timing making it easier to compare observations.

Another limitation of our study is the absence of a control group that would have further increased the strength of our findings.

Authors Contributions: This work was carried with the collaboration of all the authors (Emmanuel Omamurhomu Olose, Owoidoho Udofia and Egbeh Samuel Otu). All the authors designed the study. Emmanuel Omamurhomu Olose wrote the protocol for the study. In addition, all the authors did the literature search and data analysis. Emmanuel Omamurhomu Olose and Owoidoho Udofia wrote the initial draft of the article while Egbeh Samuel Otu drew all the tables. All the authors made corrections for the final draft of this manuscript.

Competing Interest: The authors have declared no competing interest

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