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Does Pregnancy Potentiate the Occurrence of Adverse Drug Reactions to Antiretroviral Drugs among Nigerian Women?

Article by Samson C Emelike
Senior Technical Officer, Abuja
E-mail: scemelike@gmail.com

Abstract

HIV transmission can occur from mother to child during pregnancy, delivery and breastfeeding. The use of Anti-Retroviral Drugs (ARD or ARVs) in Prevention of Mother to Child Transmission can significantly reduce this mode of transmission. The use of ARVs has been associated with occurrence of noxious effects known as Adverse Drug Reactions (ADRs). It is well known that women react more to drugs than men and some reasons proffered by some literature include hormonal differences in both sexes; but it is not known whether pregnancy can increase the chances of women reacting adversely to ARVs.

Objective: The objective of the research is to investigate whether pregnancy can potentiate the occurrence of ADRs to ARVs.

Methodology: The research employed a cross sectional Study Design on 150 HIV positive pregnant women, who were receiving ARVs at the time of study but who started ARVs before the current pregnancy. A simple Random Sampling Technique was employed in selecting the subjects. A well-structured questionnaire was applied on the selected women to collect data.

Data Analysis: The result was analyzed in a Mcnemar's test using Statistical Package for Social Sciences to determine the strength of association between the variables pregnancy and occurrence of ADRs for both the pregnant and the non-pregnant statuses of the same subjects.

Result: The result showed that pregnancy does not contribute to the occurrence of Adverse Drug Reactions to Antiretroviral drugs among HIV pregnant women.

Keywords: *Pregnancy, adverse, drug, reaction, ARVs, potentiate.*

Introduction

HIV infection can be transmitted from mothers to their unborn children during pregnancy, delivery and breastfeeding. It has been estimated that pregnancy, childbirth and breastfeeding account for 15-45% chances of transmission if no intervention is provided.

The use of Antiretroviral drugs (ARDs or ARVs) during pregnancy and breastfeeding significantly reduces the chances of transmission to less than 1%.

The use of ARVs is associated with occurrence of Adverse Drug Reactions (ADRs). These are unwanted and noxious effects associated with the use of drugs, in this case ARVs. These effects are most times responsible for poor adherence to medication which ultimately results to poor treatment outcomes.

ADRs occur more in women than in men. This gender tilted phenomenon has been explained to be due to several reasons including the biology of the female gender, the physiology, hormonal contents and some social traits of the female entity. For instance, females react to Nevirapine more adversely than the male counterpart at the same CD4 count of say 400cells/ml^3 due to reasons adduced above.

Recently, the world has become ambitious to end the HIV/AIDS epidemic by the year 2030. To achieve this, it has given itself a target of ensuring that 90% of the world population living with the virus would know their status by the year 2020. It intends to place 90% of the population diagnosed with the virus on Highly Active Anti-Retroviral Therapy (HAART), and hopes to achieve maximal viral suppression in 90% of those placed on HAART. This is the 90-90-90 paradigm of HIV interventions.

This ambition is laudable; however, the second and last 90s of the target depend largely on good medication adherence to succeed. In the presence of unintended and noxious effects from ARVs,

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patients who are placed on HAART would not continue medication, and the target of maximal viral suppression could be a mirage.

This project, having taken into perspective the peculiarity of the female gender being unfavorably disposed to exhibiting ADRs, therefore seeks to investigate whether pregnancy will increase the occurrence of these unintended noxious effects or not. If it does, then pregnancy would be considered as a barrier to achieving this ambitious target of ending the HIV/AIDS epidemic in 2030.

Pregnancy is defined as absence of menses with the evidence of conception in a woman. It is a time when a woman carries an offspring in her womb. Pregnancy is associated with hormonal changes which may interfere with the way women react to ARVs.

Problem statement

Mother to child transmission (MTCT) of HIV is the highest source of new HIV infection in children below the age of 15years (WH), 2015). Nigeria is said to contribute the highest burden of mother to child transmission of HIV (Nkwo 2012). As at 2010, the estimated number of pregnant women, above 15years living with HIV in Nigeria was put at 210,000 (UNICEF, 2010).

In July 2014 in Melbourne, Australia a power consensus was reached in which United Nations and key stakeholders agreed that it was possible to end the global AIDS epidemic in 2030 (UNAIDS 2015). To achieve this, an ambitious treatment target known as 90-90-90 was set for 2020. By this year, 90% of people living with HIV would know their serological status; and then 90% of all diagnosed cases would be receiving sustained antiretroviral treatment (ART) and 90% of all those receiving ART would have sustained viral suppression (UNAIDS 2015). These are all achievable targets. Since MTCT is the highest source of HIV infection in children, an effective Prevention of Mother to Child Transmission (PMTCT) would be required to achieve the second and third 90% targets. Good adherence to medication is required for effective PMTCT. The occurrence of ADR is a major contributory factor to poor medication adherence. This means that ADR can produce poor PMTCT intervention outcomes. Invariably, ADR can hinder the achievement of the 90-90-90 target.

Women react more adversely to drugs than men (Miller 2001). This gender bias in toxicity has been explained based on the female physiology, hormonal differences etc. (Miller 2001). In pregnancy, there are physiological and hormonal changes which can further predispose the pregnant woman to ADR occurrence. Finding out if pregnancy can predispose or potentiate the occurrence on adverse drug reactions to antiretroviral drugs will arm the world to poise better in their quest to end the epidemic within timelines.

Study justification

The outcome of this study would have global impact, considering the contribution MTCT of HIV makes in the global HIV picture. If the result proves that pregnancy increases the chances of ADR occurring, it then means the global treatment ambition of ending the global epidemic of AIDS in 2030 would be a mirage unless some critical measures are put in place to provide alternate regimens with better tolerability profiles. This study therefore becomes handy to forewarn United Nations and key stakeholders on the likely outcomes of PMTCT intervention. This would go a long way in saving resources in terms of finance, human and time.

Objectives

The objective of this study was to investigate whether pregnancy can increase the occurrence of Adverse Drug Reactions to Antiretroviral drugs or not.

Hypotheses

H_o: Pregnancy does not contribute to the occurrence of adverse drug reactions to antiretroviral drugs in HIV pregnant women

H_a: pregnancy contributes to the occurrence of adverse drug reactions to antiretroviral drugs in HIV pregnant women.

Methodology

Study area and period

Two study areas were selected. These were Federal medical center Umuahia and Abia State University Teaching Hospital, Aba both in Abia State of Nigeria. Umuahia and Aba are two major cities in the state. Umuahia is the state capital while Aba is the commercial nerve center, not just for the state alone, but also for the entire South East Nigeria. The choice of these two cities is strategic due to large number of patients that access these facilities.

Study population

The target of this research was HIV positive pregnant women who were currently receiving ARVs and must had started ART prior to the current pregnancy. The sample size was chosen arbitrarily as 150.

Study duration

The study lasted six months between November 2016 and April 2017

Sampling method

The research employed a cross sectional Study Design on 150 HIV positive pregnant women, who were receiving ARVs at the time of study but who started ARVs before the current pregnancy. A simple Random Sampling Technique was employed in selecting the subjects. Subjects who met the inclusion criteria were randomly picked and assigned a serial identification number before administering the questionnaire. This process continued until 150 subjects were selected.

Sample size

Sample size determination was chosen arbitrarily as 150
Inclusion Criteria: Criteria used to include subjects include the following

- Subject must be a female gender
- She must be HIV positive
- Subject must be currently pregnant and taking ARVs during the study.
- Subject must have been on ART prior to current pregnancy

Study tools

Study tools employed in the study are one-on-one interviews, well-structured questionnaire

Data collection

The individual completed questionnaires were collated on Microsoft Excel and consolidated to present the responses of all 150 subjects. Four hospital pharmacists at the selected facilities were engaged to administer the questionnaires and their responses recorded.

Data Analysis

The data obtained is a categorical paired sample data, and it requires McNemar's test to analyze. Using SPSS, the McNemar's test was run to obtain results.

Results

The ADR responses from the 150 subjects is presented in **Table 1** under figures and Tables.

The data in Table 1 was analyzed with McNemar's test in SPSS; the outputs obtained is presented in Table 2a-2c

The result showed that out of the 150 subjects interviewed, 7 subjects experienced ADR (and 147 with no ADR) before pregnancy, and 13 experienced ADR (and 137 with no ADR) during pregnancy. Further disaggregation showed that ADR occurred in 5 paired subjects both before and during pregnancy; 8 experienced ADR only during pregnancy; while 2 experienced ADR only before pregnancy.

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From the Chi-square tests above, the P-value is not statistically significant, and so we accept the null hypothesis that Pregnancy does not contribute to the occurrence of adverse drug reactions to antiretroviral drugs in HIV pregnant women.

The observations and findings of this research will be discussed under two subheadings: - *findings in the absence of pregnancy* and *findings in pregnancy*.

The age distribution of the respondents showed that 70% of the subjects were within the age range 20-29 years, while 30% fell into the 30-39 years' age bracket. About 37% of respondents attained a tertiary education level and 63% with secondary education level. All subjects were pregnant during the study as designed. The ages of pregnancy were distributed as 35% in 1st trimester; 41% in 2nd trimester while approximately 24% were in 3rd trimester. About 47% of the subjects did not have previous pregnancy; 51% had 3 previous pregnancies while 2% had 4 previous pregnancies. Out of the 150 subjects interviewed, 17% did not have knowledge about ARVs for PMTCT during their previous pregnancies, whereas 38% had such knowledge during their previous pregnancies. The result also shows that about 45% of subjects did not have previous pregnancies as reflected in their responses "Not applicable"

Of the 57 subjects that had knowledge about ARVs in PMTCT during their previous pregnancies, all of them knew where to access the drugs. There were 79 subjects representing about 53% of the study population that had previous pregnancies before the current pregnancies and they all accessed ARVs for PMTCT from study center.

Discussion

In absence of pregnancy

All subjects had been on ARVs before current pregnancies with 47% being less than 2 years old on treatment and 53% equal or older than 2 years on treatment. Regarding patient education on medication, 71% of subjects knew the name of the drugs while 29% did not know the names of the drugs they take.

All subjects responded they knew the drugs could cause adverse drug reactions. This looks a bit out of context. If about 17% did not know about the use of ARVs in PMTCT, how then would they have knowledge that they could cause ADRs? All subjects reported to be taking the right number of tablets at the right frequency. Majority reported to be taking the drug at night time, probably coinciding with their bedtimes. 60% reported there were no concomitant medicines while 40% reported to be taking other drugs when taking the drug. These drugs included ACT antimalarial medicines, analgesics, vitamins and antibiotics. Concomitant medicines could trigger drug-drug interactions which may confound possible ADR due to the drug alone, and so this needed to be taken care of. About 97% reported they were on diet not rich in fatty contents. Fatty foods enhance the absorption of Efavirenz thereby increasing the likelihood of causing unwanted effects. Another factor capable confounding the response was alcohol. Alcohol potentiates the CNS effect of EFV. Incidentally, all 150 subjects reported no alcohol consumption during previous pregnancies. Before getting pregnant, about 95% of subjects reported they did not experience ADR while taking the drug; and 5% did. The duration of ADR can give a clue to its severity grading. Grade 1 usually does not last beyond 48hours. About 43% of those reporting to have experienced ADR reported the ADR lasted less than 48 hours, 14% reported the ADR lasted between 3 to 5 days while the rest 43% reported the ADR lasted beyond 5 days. The ability of the ADR to resolve on its own also shows it is less serious in severity. About 86% that experienced ADR reported the ADRs resolved on their own without interventions, and in the remaining 14%, intervention was required to resolve the ADR. None of the subjects was hospitalized due to ADR.

Ability of the affected individual to perform usual activity without assistance gives a clue to the severity grading. From severity grade 2 to grade 4, some form of assistance may usually be required to perform normal duty. Based on the responses provided by the subjects reporting ADR, 86% had WHO severity Grade 1 while 14% had ADR of WHO severity Grade 2.

In pregnancy

We wanted to know the onset of ADR if any, after administration of the drug. About 83% of subjects reported to be between 1 and 3 months old on treatment since the current pregnancy, while 16% was between 4 to 6 months old; and about 1% was between 7 to 9 months old on treatment.

The proportion of subjects who knew the name of the drug during current pregnancy is 85%. There seems to be an improvement over the time. Whereas, during previous pregnancy, only 71% knew the name of the drug.

All subjects reported to be aware the drug could cause ADR. This is the same result prior to pregnancy. All subjects took 1 tablet in a day. This is same result prior to pregnancy. Once a day taken at night.

All subjects reported to be taking other medicines along with the drug. In consideration of possible drug-food interactions, 30% reported to be on diet containing fatty nutrients during current pregnancy.

All subjects reported total abstinence from alcohol. In pregnancy, about 9% of subjects reported to experience ADR as against 5% that reported ADR in the absence of pregnancy. Among all subjects that experienced ADR, the ADR lasted less than 48 hours in 3% of them, lasted for more than 5 days in 2% while in 3%, the ADR lasted between 3 to 5 days. All the subjects that experienced ADR reported that the ADR resolved on their own without interventions. None of the subjects was admitted in hospital due to ADR. Out of 13 subjects that experienced ADR, only 1 (less than 1%) needed assistance to perform usual routine functions.

In grading the ADRs according to WHO severity grading, 69% of those who reported ADR experienced WHO severity Grade 1, 23% experience Grade 2 while about 8% experienced Grade 3 severity ADR.

From the result of the research, the causality between pregnancy and occurrence of ADR is not very significant. However, this does not empirically conclude that pregnancy is not a risk factor to development of ADRs to ARVs. Obviously, there were few limitations namely the size of the population was small in comparison to the population of Abia State; so, it would not be safe to draw an unequivocal conclusion on the result of the research. Another limitation was that the questions required retrospective responses, in which subjects may have trouble recalling past events. From the responses, patient education on the drugs they take was not adequate. Patients should be empowered with adequate knowledge about the medicines they take

Conclusions

From the study, it was established that the ARVs for prevention of Mother to child transmission of HIV were available within the study area; subjects knew about it and they were accessible.

From the Chi-square tests above, the P-value is greater than 0.05 indicating statistically insignificant value, and so the null hypothesis cannot be rejected. We therefore maintain that Pregnancy does not contribute to the occurrence of adverse drug reactions to antiretroviral drugs in HIV pregnant women

This topic should be further researched into, designed as a prospective study that would follow subjects over a period in the absence of pregnancy, and then followed up when pregnant to determine outcome. This will mitigate the impacts of the limitations experienced in this study.

Healthcare workers, especially Pharmacists should be encouraged to provide adequate education to patients on medicines.

Figures and tables

Table 1. Occurrence of Adverse Drug Reactions among HIV positive women receiving Antiretroviral drugs before and during pregnancy

	Occurrence of ADR			**Occurrence of ADR**			**Occurrence of ADR**	
ID	***Before Pregnancy***	***During Pregnancy***	**ID**	***Before Pregnancy***	***During Pregnancy***	**ID**	***Before Pregnancy***	***During Pregnancy***
1	No	No	51	No	Yes	101	No	No
2	No	No	52	No	Yes	102	No	No
3	No	No	53	No	Yes	103	No	No
4	No	No	54	No	No	104	No	No
5	No	No	55	No	No	105	No	No
6	No	No	56	No	No	106	No	No
7	No	No	57	No	No	107	No	No
8	No	No	58	No	No	108	No	No
9	No	No	59	No	No	109	No	No

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10	No	No	60	No	No	110	No	No
11	Yes	Yes	61	No	No	111	No	No
12	Yes	Yes	62	No	No	112	No	No
13	Yes	Yes	63	No	No	113	No	No
14	Yes	No	64	No	No	114	No	No
15	Yes	Yes	65	No	No	115	No	No
16	Yes	Yes	66	No	No	116	No	No
17	No	No	67	No	No	117	No	No
18	No	No	68	No	No	118	No	No
19	No	No	69	No	No	119	No	No
20	No	Yes	70	No	No	120	No	No
21	No	No	71	No	No	121	No	No
22	No	No	72	No	No	122	No	No
23	No	Yes	73	No	No	123	No	No
24	No	No	74	No	No	124	No	No
25	No	No	75	No	No	125	No	No
26	No	No	76	No	No	126	No	No
27	No	No	77	No	No	127	No	No
28	No	No	78	No	No	128	No	No
29	No	No	79	No	No	129	No	No
30	No	Yes	80	No	No	130	No	No
31	No	Yes	81	No	No	131	No	No
32	No	No	82	No	No	132	No	No
33	No	No	83	No	No	133	No	No
34	No	No	84	No	No	134	No	No
35	No	No	85	No	No	135	No	No
36	No	No	86	No	No	136	No	No
37	No	No	87	No	No	137	No	No
38	No	Yes	88	No	No	138	No	No
39	No	No	89	No	No	139	No	No
40	No	No	90	No	No	140	No	No
41	No	No	91	No	No	141	No	No
42	No	No	92	No	No	142	No	No
43	No	No	93	No	No	143	No	No
44	Yes	No	94	No	No	144	No	No
45	No	No	95	No	No	145	No	No
46	No	No	96	No	No	146	No	No
47	No	No	97	No	No	147	No	No
48	No	No	98	No	No	148	No	No
49	No	No	99	No	No	149	No	No
50	No	No	100	No	No	150	No	No

Table 2a. Before Pregnancy * In Pregnancy Cross tabulation

			In Pregnancy		Total
			No	Yes	
Before Pregnancy	No	Count	135	8	143
		% within Before Pregnancy	94.4%	5.6%	100.0%
		% within In Pregnancy	98.5%	61.5%	95.3%
	Yes	Count	2	5	7
		% within Before Pregnancy	28.6%	71.4%	100.0%
		% within In Pregnancy	1.5%	38.5%	4.7%
Total		Count	137	13	150
		% within Before Pregnancy	91.3%	8.7%	100.0%
		% within In Pregnancy	100.0%	100.0%	100.0%

Table 2b. Chi-Square Tests

	Value	Exact Sig. (2-sided)
McNemar Test		.109[a]
N of Valid Cases	150	

a. Binomial distribution used.

Table 2c. Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Before Pregnancy (No / Yes)	42.188	7.056	252.226
For cohort In Pregnancy = No	3.304	1.023	10.667
For cohort In Pregnancy = Yes	.078	.034	.178
N of Valid Cases	150		

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