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Association Between Preeclampsia and Hormonal Contraceptive Use among Pregnant Women in Northwest Ethiopia: A Case-Control Study

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ABSTRACT

Objective: This study was aimed to determine the association between preeclampsia and hormonal contraceptive use among pregnant women admitted in public hospitals in Gojjam zones, northwest Ethiopia.

Methods: An institution-based unmatched case-control study was conducted in public hospitals in Gojjam zones, northwest Ethiopia. Women with preeclampsia were cases and without preeclampsia were controls. One hundred ten cases and 220 controls were selected using consecutive sampling method. The data were collected through measurements, and conducting face-to-face interviews. Then it was entered using EPI Info and exported to STATA 14 for analysis. Bivariate and multivariate logistic regressions were done to determine the association between hormonal contraceptive use and preeclampsia. Variables with p-values < 0.05 in the multivariate logistic analysis were considered as statistically significant association with preeclampsia. The results were presented using text, tables and figures.

Results: A total of 330 women were involved in this study. The mean age of cases and controls was 28 ± 6 years standard deviations and 27 ± 5 years standard deviations respectively. About 65 (59.1%) of cases and 105 (47.7%) of controls had no formal education. Preeclampsia was associated with multiple gestational pregnancies (AOR = 2.75; 95% CI: 1.20-6.28); and women who used implants (AOR = 0.39; 95% CI: 0.13-0.96). There was no significant association between preeclampsia and other hormonal contraceptives.

Conclusion: There was an association between hormonal contraceptive use and preeclampsia. Women who used implants prior to their pregnancy were less likely to be exposed to preeclampsia as compared with controls. Further studies should be conducted on the association of hormonal contraceptive use and preeclampsia to get more consistent findings. Women who have preferred using contraceptive are better to be encouraged to take estrogen free hormonal contraceptives.

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Abbreviations

ANC: Antenatal Care
AOR: Adjusted Odds Ratio
COR: Crude Odds Ratio
HTN: Hypertension
IUCD: Intrauterine Device
OC: Oral Contraceptive
PIH: Pregnancy Induced Hypertension
SD: Standard Deviation

Introduction

Preeclampsia is one of the pregnancy complications that can develop after 20 weeks of gestation, during delivery, or even after delivery [1]. According to the latest International Society for the Study of Hypertension in Pregnancy (ISSHP) updated guidelines, preeclampsia is gestational hypertension accompanied by one or more of the following new-onset conditions at ≥20 weeks' gestation: Proteinuria, other maternal end-organ dysfunction, including: neurological complications, pulmonary edema, hematological complications, acute kidney infection, with or without right upper quadrant or epigastric abdominal pain, liver involvement, and uteroplacental dysfunction [2]. Although new-onset proteinuria is frequently present, some women may also

have hypertension and other preeclampsia signs or symptoms in the absence of proteinuria [1-3]. The pregnancy complication has a great impact in developing nations where medical interventions are potentially ineffective due to the late presentation of cases [4]. Prenatal contraception, history of hypertension, primigravida, and maternal history of preeclampsia, history of diabetes, multiple gestation pregnancies, nulliparity, and family history of hypertension are some of the risk factors for the development of preeclampsia [5-7]. The most popular birth control method worldwide is hormonal contraception [8]. Ethiopian women as a whole had a prevalence of contraception of 29.0%. Injectable hormonal contraceptives were most commonly used in Ethiopia. About 49.1% of women in the Amhara region used any method, while 48% of women used any modern method. Nearly half (47.8%) of women used hormonal contraceptives, which include 1.3% pills, 0.2% an IUCD, 38.6% injectable, and 7.7% implants [9].

The use of contraception has not been associated with preeclampsia [10]. However, there is no association between the use of IUCDs and preeclampsia in parous women [11]. There was no association between long-term hormonal contraceptive use and high blood pressure [12]. Recent use of oral contraceptives was associated to a lower risk of preeclampsia. According to a British study, the use of intrauterine devices lowers the incidence of preeclampsia, especially if they are removed within a year after conception. In contrast, another study carried out in England found that mean diastolic and systolic blood pressure measures were considerably higher in oral contraceptive users than in non-users [13,14]. Contrarily, recent use of hormonal contraceptives was associated with an increased risk of preeclampsia. But, this only in women who had been using these contraceptives for more than 8 years [15,16]. Similarly, women who used oral contraceptives before conception had a greater chance of developing preeclampsia than other hormonal contraceptives [17]. An increase in BP was shown to be positively associated with longer use of oral contraceptives (OC) [18].

Preeclampsia requires special attention because it is a multisystem disorder that can advance quickly. This includes observation in a tertiary care facility, and induction of labor to terminate pregnancy is the only definitive treatment for this condition [19]. In Ethiopia, maternal mortalities due to preeclampsia have dramatically increased. However, majority of deaths caused by preeclampsia and eclampsia can be prevented. Studies on the use of contraceptives have mostly focused on determinants, and prevalence of pregnancy-induced hypertension (PIH), with little focus preeclampsia [20]. The impact of frequently used hormonal contraceptives on blood pressure during pregnancy is unclear. To the best of our knowledge, there has been no research on the association between hormonal contraceptive use and preeclampsia in Ethiopia, especially in the study area. Therefore, the aim of this study was to determine the association between preeclampsia and the use of hormonal contraceptives.

Materials and Methods

Study Design and Setting

An institution-based unmatched case-control study was conducted among pregnant women who attended antenatal care and were admitted for delivery in Hospitals found in Gojjam zones from February 01 to April 30, 2017. There are about 16 public hospitals in the two zones during the survey. These public hospitals serve in the outpatient, emergency, gynecology and obstetrics, medical, and pediatric wards and have large patient volumes. The study was carried out in four selected public hospitals. These hospitals were Finote Selam General Hospital (FSGH), Asrade Primary Hospital (APH), Debre Markos Comprehensive and Specialized Hospital (DMCSH), and Shegaw Motta Primary Hospitals (SMPH).

Definition of Cases and Controls

Cases: According to the latest International Society for the Study of Hypertension in Pregnancy (ISSHP) updated guidelines, preeclampsia is gestational hypertension accompanied by one or more of the following new-onset conditions at ≥20 weeks' gestation: Proteinuria, other maternal end-organ dysfunction, including: neurological complications, pulmonary edema, hematological complications, acute kidney infection, with or without right upper quadrant or epigastric abdominal pain, liver involvement, and uteroplacental dysfunction [2].

Controls are pregnant women whose systolic blood pressure < 140 or diastolic blood pressure < 90 mmHg and proteinuria and absence of the above conditions after 20 weeks of gestation.

Population and Exclusion Criteria

The source populations included all pregnant women who attended antenatal care (ANC) or delivery services in public hospitals in the Gojjam zones of Amhara region, northwest Ethiopia. The study populations were pregnant women who came to the selected hospitals for ANC or delivery services during the study period. Cases were diagnosed and confirmed by obstetrics and gynecology physicians. Pregnant women with eclampsia, pre-existing renal disease, or seriously ill were excluded.

Sample Size Determination

The sample size was calculated using Open Epi version 2.3 statistical software and the formula for single population difference by assuming the case-to-control ratio of 1: 2 with a significant level of 95%, power of 80%, and a 2.00. Due to the absence of a previous study conducted in Ethiopia on the association between hormonal contraceptive use and preeclampsia, the proportion of contraceptive use among controls was taken from the general population in the 2014 Ethiopian Demography and Health Survey (EDHS) in the Amhara region [9]. After adding a 10% non-response rate, 330 study participants were involved in the study.

Sampling Procedures

The four hospitals were selected purposefully due to their high patient flow rates among other hospitals. Cases were confirmed by physicians during the study period. The diagnosis included history taking, clinical manifestations, a physical examination, and laboratory tests. Due to the rare nature of the cases, they were selected consecutively after they were diagnosed and confirmed to have preeclampsia. The next two corresponding controls were selected in the same manner as the cases (Figure 1).

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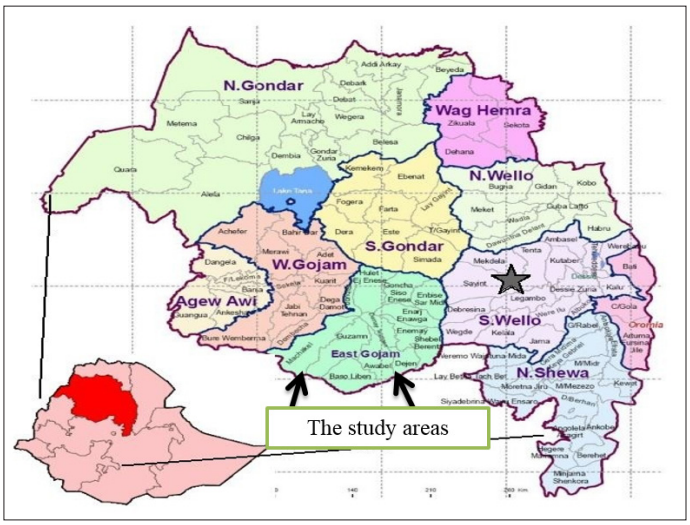

Figure 1: Administrative maps of Amhara region

Data Collection Procedures

A questionnaire was prepared by reviewing previous studies (5,9-15). The questionnaire was designed in the English language. Then it was converted into the Amharic language and translated back into the English language to check its consistency. The tool was pretested and validated before being used as an original data collection tool.

The data were collected using an interviewer's administrative questionnaire and measurements. They were interviewed about their socio-demographic characteristics, medical history, obstetrical factors, hormonal contraceptive use histories and behavioral factors by trained and experienced health professionals. The measurements included the blood pressure, weight, height, and urine of the women. Blood pressure was measured while the women were seated in an upright position using a mercury sphygmomanometer apparatus. Proteinuria and other clinical data were obtained from measurements.

Data quality control

Eight midwifery professionals who have experience in data collection were recruited as data collectors. The training was given for data collectors and supervisors about two days before the data collection period. A clear explanation of the purpose of the study was provided to the respondents at the beginning of the interview. Close supervision was done by the principal investigator and supervisors. The data from each respondent was checked for its completeness, consistency, and accuracy.

Data Processing and Analysis

After data collection, the data was checked, coded, and entered into the EPI-info version 7 software. Then the data was transformed to STATA version 14 for statistical analysis. Descriptive analyses like mean and standard deviation were performed. Bivariate and multivariable logistic regressions were done to identify the eligible variables for multivariate logistic analysis. Those variables with a p-value less than 0.05 in the multivariable logistic regression analysis were considered statically significant association. Texts, tables and figures 2 were used to present the data.

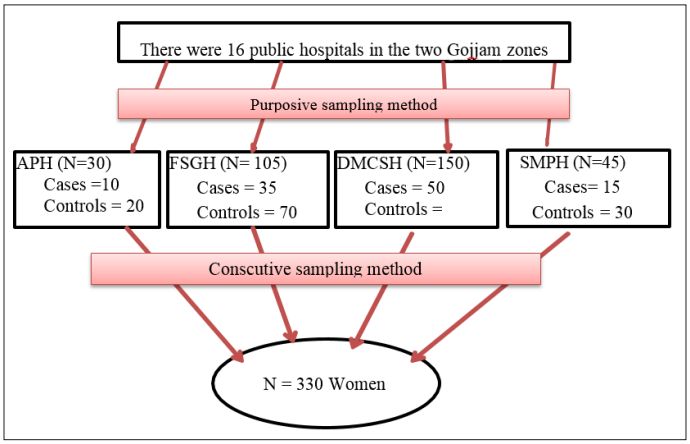

Figure 2: Sampling procedures to select the study participants

Results

Socio-Demographic Characteristics

A total of 330 women were involved in this study. The mean age of cases and controls was 28 ± 6 SD and 27±5 years, respectively. About 65 (59.1%) of cases and 105 (47.7%) of controls had no formal education. Nearly half (51.8%) of cases and (55.0%) of the controls were in the age range between 20-29 years old. Similarly, 107 (97.3%) of the cases and 218 (99.1) of the controls were married. Forty-four (40.0%) of the cases and 105 (47.7%) of the controls were housewives. Half (50.0%) of the cases and 100 (45.0%) of the controls lived in the rural area (Table 1).

Table 1: Socio-demographic characteristics of women attended ANC or delivery, Northwest Ethiopia

Socio-demographic characteristics	Categories	Case (110) n(%)	Control (220) n(%)
Mother's age (years)	< 20 years	30(27.3)	70(31.8)
	20-29 years	57(51.8)	121(55.0)
	30-39 years	21(19.1)	27(12.3)
	40- 49 years	2(1.8)	2(0.9)
Mother's education	Cannot read and write	51(46.4)	81(36.8)
	Can read and write only	14(12.7)	24(10.9)
	Primary school	10(9.1)	31(14.1)
	Secondary school and above	8(7.3)	37(16.8)
Marital Status	Currently Married	107(97.3)	218(99.1)
	Currently unmarried	3(2.7)	2(0.9)
Occupation	Housewife	44(40.0)	105(47.7)
	Merchant	12(10.9)	30(13.6)

	Government employee	23(20.9)	36(16.5)
	Farmer	28(25.5)	41(18.6)
	*Others	3(2.7)	8(3.6)
Current residence	Urban	55(50.0)	120(55.6)
	Rural	55(50.0)	100(45.4)

Note: * Other: Student laborer, hotel, café, and restaurant worker

Obstetric Factors

Among women who attended ANC or delivered in hospitals, 48 (43.6%) of cases and 71 (32.3%) of controls were gravida one. About 16 (14.5%) of the cases and 14 (6.4%) of the controls had multiple gestational pregnancies (Table 2).

Table 2: Obstetric factors in women who had ANC or gave birth in Northwest Ethiopia

Obstetric factors	Categories	Case n(%)	Control n(%)
Gravidity	Gravida1	48(43.6)	71(32.3)
	Gravida 2-4	45(40.9)	112(50.9)
	Gravida ≥5	17(15.5)	37(16.8)
Parity	Nulliparous	53(48.2)	90(40.9)
	Parous	57(51.8)	130(59.1)
The multiplicity of current pregnancy	Single	94(85.5)	206(93.6)
	Multiple	16(14.5)	14(6.4)
Ever attended Antenatal care	Yes	98(89.1)	207(94.1)
	No	12(10.9)	13(5.9)

Contraceptive Use Related Results

About 95 (86.4%) of cases and 176 (80.0%) of controls were using contraceptives before their current pregnancy. One (0.91%) case and 1 (0.45%) control used IUCD before their current pregnancy. About 11 (11.7%) of the cases and 17 (9.7%) of the controls used oral contraceptives before their current pregnancy. About 79 (84.0%) of cases and 141(80/6%) of the controls used injectable contraceptives before their current pregnancy. About 62(78.5%) of the cases and 108 (76.6%) of the controls used injectable contraceptives more than two years. About 12 (12.8%) of the cases and 41 (23.4%) of the controls used implants before this pregnancy. Of which, 4 (33.3%) of cases and 16 (24.2%) of controls used more than five years.

Associated Factors of Preeclampsia

After controlling for confounding factors, a multivariable logistic regression analysis was used to determine the relationship between hormonal contraceptive use and preeclampsia. Thus, the final variables included in the model were the number of current pregnancies, prior use of oral pills, duration of OC use, and injectable and implant contraceptives. Multiple pregnancies increase the risk of developing preeclampsia. This implies that pregnant women who had multiple pregnancies were 2.75 (95% CI: 1.20–6.28) times more likely to develop preeclampsia as compared with women without preeclampsia. In contrast, this study showed that pregnant women who used implants were 0.39 (95% CI: 0.13-0.96) times less likely to develop preeclampsia compared with controls. There was no significant association between preeclampsia and other hormonal contraceptives (Table 3).

Table 3: Association of hormonal contraceptives and preeclampsia

Characteristics		COR (95% CI)	AOR (95% CI)
Implants used before current pregnancy (n=269)	Yes	0.48(0.24, 0.96)	0.39 (0.13, 0.96) *
	No	1	1
Oral contraceptives used before current pregnancy(n=169)	Yes	1.23(0.55, 2.75)	1.06(0.40, 2.57)
	No	1	1
Injectable used before current pregnancy (n= 269)	Yes	1.27(0.65, 2.47)	0.63(0.24, 1.70)
	No	1	1
The multiplicity of pregnancy (n =330)	Single	1	1
	Multiple	2.50(1.17, 5.34]	2.75(1.20, 6.28) *

*statistically significant at $p < 0.05$

Discussion

Preeclampsia is one of the pregnancy-induced disorders that have greatly increased in our country without clear etiological factors. It is currently one of the major causes of maternal and infant mortality. Therefore, this study aimed to determine the association between preeclampsia and hormonal contraceptives among pregnant women in public hospitals.

Women who had implants before getting pregnant had a 61% lower likelihood of developing preeclampsia as compared with controls. This result was consistent with a Thai study [21]. This may be because a newer progestin, drospirenone, has antimineralocorticoid diuretic properties but does not contain an estrogen hormone element. In postmenopausal women, intradermal estrogen insertion appears to have a small blood pressure-lowering impact and may be a safer alternative for hypertensive women because it bypasses the first-pass hepatic degradation of estradiol [22]. Implants also contain smaller dosages of progesterone-only hormone [23].

An investigation done in China, however, found no correlation [10]. The study strategy used in China was a cross-sectional study, which may not have shown potential cause-and-effect correlations, which could explain the variation in the results. In China, the outcome variable was also non-specific, which implies that it included the three types of PIH, which were gestational hypertension, preeclampsia, and eclampsia. This could change how each form of pregnancy-induced hypertension is associated with the implant. This may also be a result of the socioeconomic and lifestyle distinctions between the two nations.

Contrarily, there was no association between preeclampsia and oral or injectable contraceptives in this study. This result was in line with research done in New York. However, an Indonesian investigation found that oral contraceptives were a risk factor for preeclampsia [16]. Emerging data from recent clinical trials shows that oral estrogen therapy causes postmenopausal women's systolic blood pressure to slightly rise without having any discernible effects on diastolic blood pressure. The mechanisms causing this specific increase in systolic blood pressure are still unknown; however, it may be brought on by the liver's supraphysiologic estrogen levels. Similar to the previous impact, utilizing large doses of estrogen causes a mean increase in blood pressure while using hormonal contraceptives [24]. Additionally, it depends on the duration of contraceptive use, the amount of estrogen (ethinyl estradiol) content, and the content of progesterone hormone taken [24,25]. As an oral contraceptive, a more recent progestin elevates blood pressure because of the greater impact of estrogen [22]. This could possibly be a result of the small sample size and the confounding effects of nearby passive smoking in that study.

In this study, there was no association between preeclampsia and duration of contraceptive use. This may be because women may not remember exactly how long they took these contraceptives for. This indicates that recall bias, particularly among controls, may be not well remembered. However, when saw the crude odds ratio, we found that the odds of preeclamptic women using oral contraceptives for at least 24 months prior to their current pregnancy were 2.88 times higher than the odds of those women who had not yet developed preeclampsia. Similarly, the odds of having preeclampsia were 1.20 times higher in women who had been using injectable contraception for less than 24 months. The result was consistent with a study conducted in Australia, but both of the findings were insignificant in multivariate analysis [12].

Conclusions

This study revealed the presence of an association between preeclampsia and the use of hormonal contraceptives among pregnant women. Women who used implants prior to becoming pregnant had a lower risk of preeclampsia than those who did not. It would be preferable if healthcare professionals paid closer attention when distributing contraceptives. It should conduct further research about this association and other determinants of preeclampsia by incorporating more clinically measurable biomarker factors.

Authors' Contributions

AWA, AWT: Participated in the conception, design, data collection, data analysis, discussion, manuscript drafting, and writing. AWA, ST, AA, GAA: Participated in manuscript writing, critically reviewing and approving the manuscript. All authors read and approved the final version of this manuscript.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Disclosure Statement

The authors declare that they have no competing interests.

Ethics Approval and Informed Consent

Ethical approval was obtained from Addis Ababa University, School of Public Health Institutional Review Board with the ethical approval number SPH 001/2017. A written letter was given to each hospital from the School of Public Health. Written informed consent was obtained from the respondents. The confidentiality and privacy of the respondents' responses were maintained.

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