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Hormonal Contraceptives Use and Serum Alpha-Fetoprotein Level among Women Accessing Family Planning Clinics in Ogbomoso South Local Government Area, Nigeria

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ABSTRACT: Hormonal contraceptives are widely used, but their effects on liver health and cardiovascular risk factors are not fully understood. This study examined hormonal contraceptive (HC) effects on liver health (serum alpha-fetoprotein, AFP), anthropometrics, and blood pressure in 72 women (40 HC users, 32 non-users). A descriptive cross–sectional study design was conducted over seven months on 72 women attending family planning clinics in Ogbomoso South Local Government Area, Oyo State, Nigeria. A cross-sectional analysis revealed no significant difference in AFP levels between HC users (2.73 ng/ml) and non-users (3.51 ng/ml) ($p>0.05$). However, significant increases in body weight and BMI were observed in HC users ($p<0.05$). Blood pressure showed no significant difference between the groups ($p>0.05$). The majority of HC users relied on progestin-only injectable, with 37.5% using them for 12-24 months. Average ages were 28.88±1.02 for HC users and 27.31±1.13 for non-users. In conclusion, parenteral HCs do not significantly alter AFP levels, but may contribute to weight gain and associated health risks in reproductive-age women.

Keywords: Hormonal contraceptives, Alpha-fetoproteins, Liver neoplasms, Cardiovascular diseases, Reproductive health services

Introduction

Hormonal contraceptives (HCs) are widely used by women of reproductive age globally, despite ongoing investigations into their potential impact on liver health. Contraception remains a crucial aspect of reproductive

health, empowering women to control their fertility and enhance their overall well-being (United Nations Department of Economic and Social Affairs, 2020). According to the World Health Organization, approximately 1.9 billion women of reproductive age (15-49 years) require family planning services, with a significant proportion utilizing modern contraceptive methods (United Nations Department of Economic and Social Affairs, 2022).

In Nigeria, unintended pregnancies remain a public health concern, often leading to unsafe abortions with severe consequences, including maternal mortality. While earlier studies highlighted this issue (Abiodun and Balogun, 2009). Recent data continues to emphasize the need for effective contraception to mitigate these risks.

Synthetic sex steroid hormones in contemporary contraceptives modulate the hypothalamic-pituitary-ovarian axis, preventing ovulation and/or fertilization (Trussell, 2004). These hormones, including progesterone and progestins, are used alone or in combination with estrogens for various medical purposes, including contraception, endometriosis treatment, and management of postmenopausal symptoms (Gouliarmou *et al*., 2018).

Concerns exist regarding the potential for high progesterone dosages to induce liver damage and abnormal liver function tests (Hay, 2008; Tait *et al*., 2008). Liver toxicity can manifest as hepatocellular damage, cholestasis, or a mixed pattern (Ramaiah, 2007).

The association between oral contraceptive use and benign hepatic adenomas (HA) has been explored (van Rosmalen *et al*., 2016). However, the link to hepatocellular carcinoma remains under investigation (Ponnatapura *et al*., 2019; Wang *et al*., 2022). Further research is needed to clarify the long-term effects of HCs on liver health, particularly regarding neoplastic transformations.

Therefore, this study aims to evaluate serum alpha-fetoprotein levels as a biomarker for potential neoplastic transformation of liver cells in women using hormonal contraception for child spacing and/or fertility limitation, attending family planning clinics at selected Primary Health Care Centers in Ogbomoso South Local Government Area, Oyo State, Nigeria.

Materials and methods

Research instrument: Women of child bearing age were selected from three (3) Primary Health Care Centers targeted for family planning services in Ogbomoso South Local Government (LGA). Ethical approval was obtained from 'Research and Ethical Committee' of the Faculty of Basic Medical Sciences, University of Ilorin, Nigeria with the following number: UERC/ASN/2019/1806.

A descriptive cross–sectional study was conducted on 72 volunteer women of reproductive age (19 to 49 years) attending family planning clinics in selected Primary Health Care centers. A suitable sampling technique was used to select the respondents on clinic days. A structured self- administered questionnaire was used for data collection. The questionnaire was adapted from a DHS-IV model (ORC Macro model, 2001) and filtered to suit the purpose of the study. The research instrument was validated using the face and content validity method. The questionnaire was validated by 4 experts who scrutinized and made corrections. A pre-test of carried out on 10% of respondents at the family planning clinics in Okelerin, Ibrahim Taiwo and Ayetoro, Primary Health Care centres, Ogbomoso South Local government Area, Oyo State Nigeria.

Demographic and clinical data were obtained by self-administered questionnaire (SAQ) after written informed consent. Questionnaires included information on socio-demographic and anthropometrics, fertility, knowledge of source of contraception, knowledge and types of contraceptive use, duration of use for each prescription and experienced side effects, Stratified random sampling technique was used to classify respondent into hormonal contraceptive user (HCU) and non-hormonal contraceptive user (NHCU). As at the time of data collection, the participants were currently on progestin-only injectable (POI; depo-medroxyprogesterone acetate (DMPA), combined estrogen-progesterone injectable (COPI; depo-medroxyprogesterone acetate with estradiol), levonorgestrel-implantable (LNG-implantable: IUCD and Norplant).

Measurement of blood pressure: Blood pressure reading was based on JNCVII classification and guidelines (Moawad and Hassan 2005). The brachial arterial blood pressure in volunteers was measured using digital Blood pressure monitoring Omron model: HEM-432C (Omron Healthcare International Company, Vernon Hills, Illinous, China) in sitting position after 30 minutes rest, with arm at heart level. The cuff was wrapped around the left arm just about 3 cm above the cubital fossa of the elbow. Hypertension was defined as systolic and diastolic blood pressure >140/90 mmHg or documented use of antihypertensive medications in a previously diagnosed person with hypertension (Chobanian *et al*., 2003).

Measurement of weight and height: The body weight of each respondent was taken and recorded in kilograms with a mechanical bedroom weighing scale (Yongkang Zhezhong Weighing Apparatus Factory, China) and it was standardized and adjusted to zero error as described by (Yorkin *et al*.,2013).

Height in meters was measured with a Seca model stadiometer, with the subject standing feet together without shoes, back and heel against a vertical ruled bar to which a movable horizontal bar was attached. During measurement, the horizontal bar was brought to vertex of the head of the subject and the reading at this level was read to the nearest millimeter.

Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of the height in meters [weight (Kg)/height (m^2)] and obesity defined as BMI $\geq$ 30 kg/m^2 as recorded in the Standard Treatment Guideline of Nigeria (Nuttall, 2015). Similarly, BMI of <18.0 kg/ m^2, 18.5-24.9 kg/ m^2, 25-29 kg/ m^2 and > 30 kg/m^2 were characterized as underweight, normal, overweight and obese respectively.

Blood sample collection: Left ante-cubital vein was accessed for blood collection. A 5 ml sterile hypodermal needle and syringe was used for the collection. The sample was then transferred into appropriately labeled plain bottle, allowed to clot and centrifuged at 3000 rpm for 15 min. The serum was stored in a freezer at -20 ºC and then analyzed as required.

Determination of serum AFP: Quantitative measurement of AFP in human serum was performed using AFP ELISA kit (Randox, Crumlin, United Kingdom) and procedure was followed as described by manufacturer (abcam). The principle is a solid phase sandwich assay method which is based on a streptavidin- biotin principle. The standard samples and the biotinylated anti-AFP antibody reagent were added into designated wells, coated with Streptavidin. Endogenous AFP in the patient's serum binds to the antigenic site of the biotinylated Anti-AFP antibody. Simultaneously, the biotinylated antibody was immobilized onto the wells through the affinity Streptavidin-Biotin interaction. Unbound protein and excess biotin conjugated antibody were washed off by wash buffer. Upon the addition of the horseradish peroxidase (HRP) conjugated Anti-AFP antibody reagent, a sandwich complex is formed, the analyte of interest being in between the two highly specific antibodies, labeled with Biotin and HRP. Unbound protein excess enzyme conjugated antibody reagent was washed off by wash buffer. Upon addition of the substrate, there was color formation whose intensity is directly proportional to the concentration of AFP in the samples. A standard curve was prepared relating color intensity to the concentration of the AFP according to the company's description.

Data analyses: Independent t-tests with Bonferroni correction for continuous variables and Chi-square test for categorical variables were used appropriately. Continuous variables were expressed as means ± standard deviation. Statistical significance level of 0.05 was considered at 95% confidence interval. All statistical analyses were carried out using Statistical Package for Social Sciences (SPSS) version 20 (IBM Corporation, Armonk, NY).

Results

Socio-demographic characteristics of the respondents: A total of 72 volunteers participated in this study; the result showed the HCU 40 (56%) and NHCU 32 (44%) have average age of 28.88±1.02 years and 27.31±1.13 years respectively. Meanwhile, the ages (in years) at menarche HCU vs NHCU were 32 (44.5 %) vs 28 (40.9 %) at 12-14 years; 8 (11.1 %) vs 3(4.2 %) at 15-17 years and 0 vs 1(1.4 %) at >17 years of age.

Furthermore, 3 (4.2%) vs 13 (18.1%) and 37 (51.4%) vs 19 (26.4%) were single and married respondents for HCU vs NHCU respectively. All with significant differences of p=0.001; p=0.047; and p=0.001 for number of respondents, ages at menarche and marital status when compared to control. Among the participants, 15 (20.8%) vs 20 (27.8%) and 25 (34.7%) vs 12 (16.7%) practices Islam and Christianity while the educational status with level of literacy of 25 (34.7%) vs 13 (18.1%) for tertiary, 8 (11.1%) vs 2 (2.8%) for secondary, 1(1.4%) each for basic and 6 (8.3%) vs 16 (22.2%) for no formal education respondents (Table 1).

Table 1: Socio-demographic characteristics of the respondents

Parameter	Users	Nonusers	Total	Chi-squares	P
No of Women	40(56)	32(44)	72(100)	11.29	0.001[a]
Age (year)	28.88 ±1.02	27.31±1.13		1.026	0.308
Age-at Menarche					
12-14 yrs	32(44.5%)	28(40.9%)	60(85.4%)	12.753	0.047[a]
15-17 yrs	8(11.1%)	3(4.2%)	11(15.3%)		
>17 yrs	0	1(1.4%)	1(1.4%)		
Marital status					
Single	3(4.2%)	13(18.1%)	16(22.2 %)	11.286	0.001[a]
Married	37(51.4%)	19(26.4%)	56(77.8 %)		
Religion					
Islam	15(20.8%)	20(27.8%)	40(55.6%)	4.445	0.035[a]
Christian	25(34.7%)	12(16.7%)	32(44.4%)		

Parameter	Users	Nonusers	Total	Chi-squares	P
Educational status					
Illiterate	6(8.3%)	16(22.2%)	22(30.6%)	11.18	0.011[a]
Primary	1(1.4%)	1(1.4%)	2(2.8%)		
Secondary	8(11.1%)	2(2.8%)	10(13.9%)		
Tertiary	25(34.7%)	13(18.1%)	38(52.8%)		

[a] Significant difference were considered at p< 0.05, with 95% CI.

Descriptive and clinical characteristics of the respondents: In Table 2, the blood pressure of HCU and NHCU were observed with no significant difference at p=0.95 with systolic blood pressure of 120.28 ± 2.46 *vs* 120.06 ± 2.20 respectively, whereas that of diastolic blood pressure was 78.10 ±2.19 *vs* 78.25±1.77 at p= 0.96. However, there were significant differences in weight 62.50 ±1.79 *vs* 54.69 ±2.10 at p=0.01; height 1.61 ±0.01 *vs* 1.57±0.02 at p=0.04 and BMI 23.88±0.59 *vs* 21.68±0.62 at p=0.01 respectively. The serum AFP of HCU and NHCU were not significantly different 2.73±3.70 *vs* 3.51±6.90 at p=0.54.

Table 2: Descriptive and clinical characteristics between hormonal contraceptives

Exposed and Non-Exposed	Mean ± SEM		t-value	p-value
Parameters	**Users**	**Non-users**		
No of women (%)	40 (55.6)	32 (44.40)		
Age (years)	28.88±1.02	27.31±1.13	1.03	0.31
Age at menarche (years)	13.20±0.24	13.50±0.27	-0.84	0.40
Blood pressure				
Systolic (mmHg)	120.28±2.46	120.06 ± 2.20	0.06	0.95
Diastolic(mmHg)	78.10±2.19	78.25±1.77	-0.08	0.96
Anthropometric measurements				
Weight (kg)	62.50±1.79	54.69±2.10	2.82	0.01[a]
Height (m^2)	1.61±0.01	1.58±0.02	2.06	0.04[a]
BMI (kg/m^2)	23.88±0.59	21.68±0.62	2.53	0.01[a]
History HC use (months)	23.98±1.57	0		
AFP (ng/ml)	2.73±0.58	3.51±1.21	-0.61	0.54

[a] Significant difference were considered at p< 0.05, with 95% CI.

Determination of serum alpha fetoprotein: Table 3 compares serum alpha-fetoprotein (AFP) proportions by hormonal contraceptive type. Progestin-only injectable (POI) users had the highest AFP detection rate (50%). Combined estrogens-progestin injectable (COPI) users had a lower rate (10%). Intrauterine cervical device (IUCD) and implant users had the lowest rates (2.5% and 5%, respectively). However, these differences were not statistically significant (p=0.50).

Table 3: Comparison of serum AFP proportion by hormonal type

Hormonal type	AFP Detected	Chi square	P
POI	20(50%)	5.35	0.50
COPI	4(10%)		
IUCD	1(2.5%)		
Implant	2 (5%)		
Total	**27 (67.5%)**		

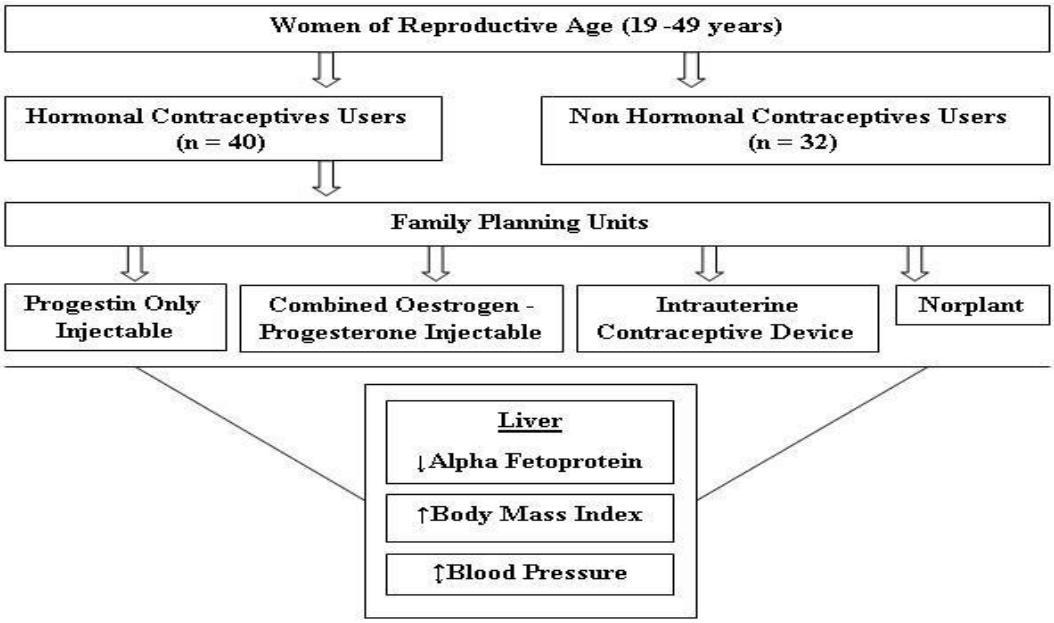
[a] Significant difference were considered at p< 0.05, with 95% CI.POI-progestin-only injectable; COPI-combined estrogens-progestin injectable; IUCD-intrauterine cervical device.

Serum alpha fetoprotein level in hormonal contraceptives users by duration of exposure: Table 4 describes serum alpha-fetoprotein (AFP) levels in hormonal contraceptive users by duration of exposure. The results show that the highest proportion of detected AFP (37.5%) was found among users with 12-24 months of exposure. The proportion of detected AFP decreased with longer duration of exposure, with only 2.5% of users with 37-48 months of exposure having detectable AFP levels. The differences approached statistical significance (p=0.07).

Table 4: Description of serum alpha fetoprotein in hormonal contraceptives users by duration of exposure

Duration (months)	AFP Detected	Chi square	P
<12	5(12.5%)	11.67	0.07
12-24	15(37.5%)		
25-36	6(15%)		
37-48	1(2.5%)		
Total	**27(67.5%)**		

a Significant difference were considered at p< 0.05, with 95% CI.



Graphical abstract: The effects of parenteral hormonal contraceptives on serum alpha fetoprotein level, blood pressure and BMI in reproductive women of child bearing age. ↓, ↑, and ↕ indicate insignificant decrease, significant increase and no effect respectively.

Discussion

The liver is intensely modulated by sex hormones, and long-term use of hormonal contraceptives (HC), as well as exposure to endogenous estrogen and anabolic-androgenic steroids, can provoke both benign and malignant tumors (Odinga *et al.*, 2022). Epidemiologic and experimental animal studies have suggested that men have a higher incidence of hepatocellular neoplastic transformation than women, potentially explained by the stimulatory effects of androgens and the protective effects of estrogens (Wu *et al*., 2023). Moreover, some studies have indicated a direct relationship between alpha-fetoprotein (AFP) and the duration of HC use.

In the present study, progestin-only injectables (POI) and levonorgestrel (LNG)-implant devices may exert a repressive effect on serum AFP synthesis, as no correlations were found between AFP expression and the duration of HC use among respondents using POI and combined oral progestin-estrogen (COPI) contraceptive methods. None of the respondents using LNG-intrauterine contraceptive device (IUCD) or -implant showed changes in serum AFP levels. This observation could be related to the short duration of the survey. However, it is important to note that the side effects of anabolic steroids depend on various factors, including drug formulation, administration route, dosage, duration of use, and individual sensitivity (Liu and Wu, 2019). Furthermore, prolonged use (>5 years) of oral contraceptives or anabolic-androgenic steroids has been linked to the development of hepatocellular carcinoma (HCC) and hepatic adenoma (HA) (Klompenhouwer and IJzermans, 2017). In this study, the presence or absence of HCs in the sera of volunteers did not correlate with the duration of use, serum AFP levels, or predictive value for HCC risk or development. Some reports suggest that progestin-only HCs are protective against HCC evolution (Binette *et al*., 2017). Although the respondents in this study used parenteral HCs, which differ in metabolism and distribution from oral contraceptives, they all bypassed first-pass hepatic metabolism. Reduced involvement of hepatic drug-metabolizing enzymes may decrease steroid-induced gene activation for replication, cell division, proliferation, and differentiation (Shelly *et al*., 2018).

POI exerts a modulatory effect on weight gain, as significant differences in weight by body mass index (BMI) were observed between HC users and non-users. The potential pathway between HC and weight gain involves the lipophilic nature of synthetic steroids, which can enhance fluid retention, reduce sodium excretion, and increase lipid storage (Richard et al., 2020). A 2013 systematic review of progestin-only contraceptives concluded that mean weight gain was <2 kg for most studies up to 12 months, similar to comparable groups using other contraceptives (Lopez *et al.*, 2016). Multiple factors, such as race and individual responses, appear to influence weight gain over time (Lee *et al*., 2019). However, baseline parameters before contraceptive use were not obtained in this study, which is a limitation. No significant difference in weight gain by BMI was observed between POI and COPI users, consistent with findings in DMPA versus estrogen-progestin

contraception studies (Beksinska *et al*., 2021).
The cardiovascular effects of POI, COPI, and LNG-implantable devices showed a slight but statistically significant elevation in mean systolic blood pressure in HC users compared to non-users, while mean diastolic pressure was slightly elevated in non-HC users. Pulse pressures and mean arterial pressures (MAP) were within normal ranges. However, long-term exposure may increase the risk of cardiovascular health alterations. Approximately 80% of HC users were exposed to depot medroxyprogesterone acetate (DMPA), which exhibits progestogenic, anti-gonadotropic, anti-estrogenic, and androgenic effects (Konings *et al*., 2018). DMPA has also been reported to potentially induce elevated blood pressure through glucocorticoid mechanisms with long-term use (Komane *et al*., 2022).

Value to knowledge

In terms of policy implications, the study's findings suggest that healthcare providers should counsel women about the potential risks and benefits of hormonal contraceptives, including the risk of weight gain and increased blood pressure. Additionally, healthcare providers should closely monitor women using hormonal contraceptives for changes in weight and blood pressure.
Furthermore, the study's findings highlight the need for further research on the effects of hormonal contraceptives on women's health, particularly in relation to liver health and cardiovascular risk factors. This research should inform the development of evidence-based guidelines for the use of hormonal contraceptives.

Policy recommendations

To ensure that women receive optimal care when using hormonal contraceptives, several measures are necessary. Firstly, healthcare providers should receive comprehensive education and training on the potential risks and benefits of hormonal contraceptives. This education should encompass the risk of weight gain and increased blood pressure associated with hormonal contraceptive use.
In addition to educating healthcare providers, it is essential that women are thoroughly counseled about the potential risks and benefits of hormonal contraceptives. This counseling should include information about the risk of weight gain and increased blood pressure, enabling women to make informed decisions about their reproductive health.
Furthermore, healthcare providers should closely monitor women using hormonal contraceptives for changes in weight and blood pressure. Regular monitoring will facilitate early detection of any adverse effects, ensuring that women receive timely interventions to mitigate potential health risks.
Finally, further research is necessary to fully elucidate the effects of hormonal contraceptives on women's health, particularly in relation to liver health and cardiovascular risk factors. This research will provide valuable insights, informing the development of evidence-based guidelines for the use of hormonal contraceptives and ensuring that women receive safe and effective care.

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Conflict of interest

Authors have declared that no potential conflicts of interest exist.

Authors' contributions

ASA, EBO, JOF and HAA conceived and designed the study. HAA, SIL and HAA carried out the study. ASA, ALA and HAA conducted AFP analysis. IB, HAA, SIL and NAO analyzed and interpreted the data. NAO and HAA designed graphical summary. HAA, NAO, HAA, SIL and ABN drafted the manuscript. ASA, EBO, JOF, HAA and ABN revised the manuscript. All authors read and approved the final manuscript to be published.

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