International Scholars Journals

International Journal of Obstetrics and Gynecology ISSN 2736-1594, Vol. 10 (8), pp. 001-007, August, 2022. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Metabolic and inflammatory consequences in women using selected methods of contraception

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Accepted 11th August, 2022.

Abstract

Hormonal contraception is associated with increased risk of obesity and cardiovascular diseases in women. We therefore studied the effect of different methods of contraception on insulin resistance and an inflammation biomarker. A total of ninety women were recruited - 25 implant contraceptive (IMC) users, 25 injectable contraceptives (INC) users, 10 oral contraceptive (OC) users and 10 intrauterine contraceptive device (IUCD) users, 20 non contraceptive users who served as controls. Anthropometric measurements were made and blood samples were collected for the determination of fasting plasma glucose (FPG), serum insulin and high sensitivity C-reactive protein (hsCRP), while Homeostasis model of assessment of insulin resistance (HOMA-IR) was calculated. We observed a significantly decreased HOMA-IR and serum insulin, in the IMC, INC and OC groups compared with the control. There was also significantly elevated waist circumference, waist-hip ratio and diastolic blood pressure in the test groups compared with the controls. In implants users, hsCRP showed a significant positive correlation with WC and FPG. In injectable users, hsCRP showed a significant positive correlation with BMI and WC. This study showed decreased serum insulin concentration among women using hormonal contraceptives and an association between serum hsCRP level and Waist circumference in them.

Key words: *Contraception, Insulin resistance, anthropometric variables, inflammatory markers.*

INRODUCTION

Background

Contraception is the intentional prevention of conception using various pharmaceutical and non-pharmaceutical interventions as well as modified sexual practices (Centers for Disease Control and Prevention, 2019). Through the use of contraceptive devices, couples and individuals have demonstrated their basic right to decide freely and responsibly if, when and how many children to have. The emergence of contraceptive methods has resulted in not only improved health-related outcomes such as reduced maternal mortality and infant mortality, but also improved socio-economic outcomes, especially for girls and women

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(Duane *et al*., 2022).

Apart from preventing unintended pregnancy, hormonal contraceptives (HCs) are also used in minimizing the risk of gynaecological (i.e. ovarian and endometrial) cancers, regulating the menstrual cycle, controlling acne as well as pre-menstrual and menstrual symptoms (Michels et al.,2018; Chikandiwa et al., 2018; Smith 2019; Huber, 2008). In 2015, the global prevalence of contraceptive use among married or in-union women was 64%, with a much lower incidence in the least developed countries (40 per cent) and particularly low in Africa (33%) (United Nations, 2015). Also, a Nigerian study revealed that 44% and 59% incidences of current history of contraceptive use respectively (Bertrand *et al*., 2014). The active components of HCs are mainly progesterone and oestrogen with the resultant effect of gonadal suppression preventing ovulation and inhibition of sperm penetration by increasing cervical mucus viscosity (Nelson and Cwaik, 2011; Speroff and Darney, 2011).

A number of complications and side effects have been reportedly associated with the use of HCs (Sabatini *et al.,* 2011; Stoco *et al.,* 2013; Cagnacci and Biasioli, 2021). These include tolerability issues, nausea, breast tenderness, weight gain, menstrual cycle disturbances, water retention, perimenstrual symptoms and hypertension (Leo *et al.,* 2018); as well as venous and arterial cardiovascular complications (Kasal and Lorenzo, 2020). These side effects are of great clinical importance and have over the years resulted in many important changes in the composition and use of these preparations to reduce the side effects. Amongst all the side effects, young women are especially concerned with issues of weight gain. HC use have also been linked to a greater risk of cardiovascular disease, dyslipidemia, myocardial infarction, venous thromboembolism (Khader *et al.,* 2003, Baillargeon *et al.,* 2005, Kluft, 2007).

Insulin resistance (IR), a reduced physiological response of peripheral tissues to the action of insulin, is significantly associated with obesity, type 2 diabetes mellitus (T2DM) and plays a critical role in the pathogenesis of cardiovascular diseases (CVDs) (Ginsberg and Mac Callum, 2009; Deveci *et al*., 2009). It manifests as decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle as well as impaired suppression of hepatic glycolysis (Reaven *et al*., 2006). These functional defects may result, in part, from impaired insulin signaling in all three target tissues and, in adipocytes, also from down-regulation of the major insulin-responsive glucose transporter, GLUT4 (Griffin *et al*., 2000). Attendant features associated with insulin resistance include dyslipidaemia and oxidative stress which may have a propensity towards a proinflammatory state or acute phase response.

The homeostasis model of assessment of insulin resistance (HOMA-IR), a mathematical model that includes interactions between fasting plasma insulin and fasting plasma glucose concentrations, has proven to be a reliable tool for the assessment of insulin resistance (Antunes *et al.*, 2016). It is an alternative to the glucose clamp and is the most commonly used surrogate measure of insulin resistance in vivo (Alireza *et al.,* 2007; Cazzo *et al.,* 2017). Measurement of the inflammatory biomarker High sensitivity C-reactive protein (hsCRP) has been proposed for assessment of risk for cardiovascular disease.

The higher risk of cardiovascular events has been associated with changes in lipid metabolism through the modification of low-density lipoprotein (LDL) and high-density lipoprotein cholesterol (HDL-C) levels (Fazio *et al.,* 2010) and the chronic subclinical inflammation (Petto *et al.,*2013).

High-sensitivity C-reactive protein (hsCRP) is the best biomarker of chronic subclinical inflammation and is associated with the risk of cardiovascular diseases (Fonseca and de Oliveira-Izar, 2016). It has been reported to be a strong and independent predictor of myocardial infarction, ischemic stroke, type 2 diabetes, and hypertension (Li *et al*., 2016). An emerging body of evidence documents associations of elevated CRP concentrations in individuals with IR (Kanmani *et al.,* 2019; Missel *et al*., 2021)

Hormonal contraceptives are widely used with notable metabolic side effects of obesity and increasing cardiovascular disease risk. It is therefore important to determine relationship between insulin resistance and inflammatory biomarkers in users of hormonal contraceptives.

This study is therefore aimed at assessing the relationship between hsCRP and insulin resistance in women using hormonal contraceptives.

MATERIALS AND METHODS

Subjects

A total of ninety (90) participants were recruited for this study after obtaining ethical clearance from Babcock University Health Research and Ethics Committee as well as the Ethical Committee of Lagos State Primary Health Care Board.

Purposive random sampling technique was used to recruit women of reproductive age (20 – 45 years) comprising twenty five (25) using progestin-only implant contraceptives; twenty five (25) using progestin-only injectable contraceptives; ten (10) using combined oral contraceptives (Progestin/estrogen); ten (10) using Copper T 3804 intrauterine contraceptive device (non-hormonal); and twenty (20) not using any of these contraceptive methods who served as controls. The contraceptive users have been on specified contraceptives for up to 48 months (60.2 ± 5.8 months). The control subjects were ensured to be age-matched, apparently healthy, non-pregnant women from the same locality. All subject consented to participate in the study

through writing.

Sample Collection and Biochemical Analyses

Venous blood sample (4mL) was collected from each of the study participants, after overnight fast which lasted for 10-12 hours. Two millilitres of blood sample was dispensed into fluoride oxalate bottle for the assay of fasting plasma glucose (FPG) which was performed within 6 hours of sample collection, while the remaining 2mL was dispensed into plain bottle and was centrifuged at 4000 rpm for 3 minutes to obtain serum which was aliquoted into small vial and stored at -20°C until the time of analysis for serum insulin. Plasma glucose was determined by the glucose oxidase method (Randox Laboratories Ltd., UK). Serum insulin was determined using ELISA (Calbiotech, USA) as previously described (Adediji *et al*., 2016).

Principle of ELISA

In this assay, the antigen – insulin or CRP present in each sample reacts with its corresponding antibody adsorbed to the surface of solid-phase polystyrene microtitre wells. On removal of unbound proteins by washing, the antibodies conjugated with horseradish peroxidase (HRP) form complexes with the previously bound antigen following the addition of a chromogenic substrate, 3, 3, 5, 5-tetramethylbenzidine (TMB). The absorbance at 450 nm is a measure of the concentration of the 'antigen' in the test sample.

ELISA Procedure

A gradient of standard concentrations were prepared from the concentrated standard through serial dilution to cover the expected assay range. One hundred microliters of the standards and sera were pipetted into microwells already coated with specific antibodies and incubated at 37°C for 90 min.

Following incubation, the wells were aspirated of their contents without washing and 100µl of biotinylated detection antibody was added to each well and incubated for 60 minutes at 37°C, after which each well was completely filled with appropriate wash solution. The plate was washed three times. One hundred microliters of appropriately diluted enzyme–antibody conjugate was pipetted into each well and the plate was incubated at 37°C for 30 minutes. After incubation, another process of washing was performed as described above and 90µl of TMB substrate solution was added to each well. This was followed by incubation for 15 minutes at 37°C after which 50µl of stop solution was added to each well. The absorbance (at 450 nm) was determined using ELISA reader. Concentration of analytes in each specimen was determined by tracing the absorbance from the calibration curve.

HOMA-IR and Biophysical Parameters

HOMA-IR was calculated using the formula as described by Matthews *et al*. (1985): HOMA-IR = fasting plasma insulin (µIU/mL) x fasting plasma glucose (mmol/L)/22.5.
Waist circumference (WC), and hip circumference (HC) were measured using a meter tape; height was measured using a stadiometer, and weight measured using a clinical weighing scale. All measurements were taken with appropriate precautions to minimize errors of measurement. Waist-hip ratio (WHR) was determined as waist circumference divided by hip circumference, while body mass index (BMI) was calculated as BMI = weight (kg) / height^2 (Kg/m^2).

The Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) of subjects were measured using the auscultatory method of Korotkoff with a mercury in-glass sphygmomanometer and recorded as phase I and phase IV Korotkoff sounds respectively.

Data Analysis

Data analysis was done using SPSS version18.0. All values were expressed as mean±standard deviation for test and control groups. Comparison of variables was done using ANOVA, Post-hoc test and Pearson's correlation was used to determine the relationship between variables. $P < 0.05$ was considered to be statistically significant

RESULTS

Table 1. shows the anthropometric and biophysical parameters in the study participants. The results obtained showed statistically significant increases in the mean waist circumference and waist hip ratio among the various groups of contraceptive users compared with the controls. Also, systolic blood pressure and diastolic blood pressure were higher in those who used implants and injectable contraceptives than in those who used IUCD, oral contraceptives and controls. There was however, no significant difference in BMI among the various groups.
Table 2. shows biochemical parameters in the study participants. There was a statistically significant decrease in the HOMA-IR and serum insulin in the Implant users, injectable users and oral contraceptive users compared with the control group, while IUCD users had higher values compared with the controls. There were no significant differences in hsCRP and FPG among the various groups.
Table 3. shows correlation between hsCRP, anthropometric and other biochemical parameters in users of implants. There was a significant positive correlation between hsCRP and waist circumference ($r=0.784$, $p<0.005$) and also a positive correlation between hsCRP and fasting blood glucose ($r=0.939$, $p<0.005$). There was no significant correlation between

Table 1: Biophysical parameters in study participants

Parameters	Implant N = 25	Injectables N = 25	IUCD N = 10	Oral N = 10	Control N = 20	P – value
BMI (kg/m²)	25.3 ± 4.2	25.5 ± 4.5	25.7 ± 4.3	27.1 ± 5.0	24.3 ± 3.6	0.557
WC (cm)	85.5[a] ± 11.5	86.0[a] ± 13.0	87.5[a] ± 12.2	87.8[a] ± 10.1	75.7 ± 7.0	0.008*
WHR	0.80[a] ± 0.06	0.79[a] ± 0.07	0.81[a] ± 0.07	0.80[a] ± 0.06	0.73 ± 0.04	0.001*
SBP (mmHg)	120[a,b,c] ± 16.3	119[a,b,c] ± 12.2	113 ± 12.5	115 ± 10.7	113 ± 11.0	0.038*
DBP (mmHg)	80[a,b,c] ± 11.4	80[a,b,c] ± 8.1	72 ± 12.4	71 ± 9.1	75 ± 7.6	0.048*

* Statistically significant at P < 0.05
a- Significantly different from Control
b- Significantly different from IUCD
c- Significantly different from Oral

Table 2: Biochemical parameters in study participants

PARAMETERS	Implant N = 25	Injectables N = 25	IUCD N = 10	Oral N = 10	Control N = 20	P – value
HOMA-IR	2.72 ± 0.36[a,b,c,d]	4.52 ± 0.62 [a,b,c]	7.06 ± 0.43 [a,c]	3.23 ± 0.39 [a]	5.24 ± 0.28	.038*
hsCRP (mg/L)	0.3 ± 0.03	0.3 ± 0.04	0.3 ± 0.03	0.4 ± 0.04	0.2 ± 0.02	.451
FPG (mmol/L)	4.0 ± 0.60	4.7 ± 1.08	4.83 ± 1.23	4.17 ± 0.64	4.1 ± 0.50	.548
Insulin (µIU/ml)	15.3 ± 2.20[a,b,c,d]	21.7 ± 3.20[a,b,c]	32.9 ± 3.42[a,c]	17.6 ± 1.47[a]	29.0 ± 1.92	.048*

* Statistically significant at P < 0.05
[a]- Significantly different from Control
[b]- Significantly different from IUCD
[c]- Significantly different from Oral
[d] – Significantly different from injectable

Table 3: Correlation between hsCRP, anthropometric and other biochemical parameters in implants

hsCRP	R	p-value
BMI	0.159	0.449
WC	0.784	0.042*
WHR	0.266	0.198
SBP	0.146	0.487
DBP	0.196	0.348
FPG	0.939	0.016*
Insulin	0.105	0.618
HOMA-IR	0.105	0.616

Table 4: Correlation between hsCRP, anthropometric and other biochemical parameters in injectables

hsCRP	R	p-value
BMI	0.601	0.001*
WC	0.467	0.019*
WHR	0.219	0.293
SBP	0.785	0.057
DBP	0.228	0.274
FBG	0.246	0.236
Insulin	0.092	0.663
HOMA-IR	0.119	0.572

hsCRP and body mass index, waist hip ratio, systolic blood pressure, diastolic blood pressure and insulin.

Table 4. shows correlation between hsCRP, anthropometric and other biochemical parameters in users of injectable contraceptives. There was a significant positive correlation between hsCRP and waist circumference (r=0.467, p<0.005). There was no significant correlation between hsCRP and body mass index, waist hip ratio, systolic blood pressure, diastolic blood pressure, fasting blood glucose and insulin.

DISCUSSION

In this study, we evaluated selected biochemical and biophysical parameters of women using hormonal contraceptives and non-hormonal IUCDs. These were measured to assess the effect of different methods of contraception on adiposity, insulin resistance and an inflammatory biomarker - hsCRP.

In women using progestin-only implants, there was no significant difference in FPG, while serum insulin was significantly lower compared to control group. This contradicts previous reports in which it was noted that the synthetic progestins are structurally similar to testosterone and therefore produce androgenic side effects with effect on metabolism as reduced insulin sensitivity and glucose tolerance (Turner *et al*., 2019). Surprisingly, we observed a reduced HOMA-IR in this group of subjects compared with controls. A similar pattern was seen among the oral and injectable contraceptives group which had no significantly different FPG, lower serum insulin and lower HOMA-IR compared with controls. However in the IUCD group, serum insulin is significantly higher compared with the other test groups and the control group and the mean FPG was higher but not statistically different when compared with other groups. This could be due to the non-hormonal origin of IUCD as the other methods of contraception are hormone based.

In women who used combined oral contraceptive pills, FPG value was increased but not statistically significant when compared with control and other test groups, while insulin was decreased, and the mean value of HOMA-IR was significantly decreased compared to the control group and IUCD users. The comparable findings of FPG, serum insulin and HOMA-IR observed in women on progestin-only contraceptives (implants and injectables) as well as those on combined oral contraceptives showed that despite their differing composition (progestin-only versus progestin with oestrogen) and the route of delivery (oral versus parenteral), similar glycaemic levels were observed. Since these are hormone-based contraceptives, it could be concluded that the effects are observable in hormonal contraception methods. Also, since insulin resistance is a feature of dysglycaemia, it could be hypothesized that the use of hormonal contraceptives can help mitigate hyperinsulinaemia associated with metabolic disorders.

In women using IUCDs, the mean value of insulin and HOMA-IR was significantly increased compared to that of the controls and other test groups. The increased FPG and decreased insulin levels observed among IUCD users, were not statistically significant when compared with control. This is in agreement with the results from the study by Jamil *et al*. (2017) in which 54 women on IUCD were examined and was reported to have high FPG and low insulin level.

High sensitivity C-Reactive Protein (hsCRP) across the test groups and control groups were similar and not significantly different. This implies that the use of contraception cannot be said to predispose one to inflammatory conditions. However, Guedes *et al*. (2018) reported an increase in the level of hsCRP in users of hormonal contraceptives compared to non-users which could indicate a subclinical inflammatory process. Users of contraceptives should therefore pay attention to this risk.

Also in this study, it was revealed that the mean values of WC and WHR for the 4 test groups (oral, IUCD, implants and injectable) although similar to each other were significantly higher compared to the control group in this study. Significantly higher values of SBP and DBP were observed in users of implants and injectable contraceptives compared to the control. The mean value of SBP in OC users was higher than the control group but it was not statistically significant. This agrees with the study of Haroon and Naveed (2014) in which 90 women examined were found to have higher SBP and DBP were significantly higher in users of contraceptive compared to the control groups. This further emphasizes that the use of hormonal contraceptives leads to a steady increase in SBP and DBP as reported by Kalenga *et al* (2022).

A positive correlation was observed between waist circumference (WC) and hsCRP, and this is in agreement with the study of Fatma *et al.* (2010) which reported that systemic inflammation is associated with greater adiposity as measured by waist circumference. Several studies have shown that hsCRP is associated with most obesity markers. The high fat mass in the abdominal region measured by the waist circumference might lead to the increased production of TNF-α and IL-6, which in turn increase hepatic production of hsCRP (Marques *et al*., 2012). The findings from this study also revealed a positive correlation between hsCRP and FPG which is consistent with a study reported by Du *et al*. (2005).

CONCLUSION

This present study showed that reduced serum insulin is associated with the use of hormonal contraceptives which might reveal insight into their use in the management of dysglycaemic disorders. Also, there is an association between serum hsCRP level and WC among women using hormonal contraceptive. This shows that hormonal contraception is associated with metabolic and inflammatory consequences, evidenced through increased adiposity which might predispose users to reduced insulin sensitivity as well as subclinical inflammation.

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