Impact of Various Contraceptive Methods on Immunological Profiles in Women: A Serological Analysis in Diyala Governorate

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Abstract

Introduction: Both hormonal and non-hormonal contraception methods are highly effective and used globally. Our study aimed to examine the immune factors in women using contraceptives, providing insights into the complexities involved. Ninety women participated, with 50 using contraceptives (study group) and 40 not using any (control group), all considered healthy individuals. Venous blood samples, drawn using sterile single-use medical syringes, were 5 ml each. **Methods:** The study used an inclusive approach, employing techniques like Indirect Sandawish ELISA to assess CD4, CD8, IL16, and IL27 levels, and Single Immunodiffusion (SRID) for IgG, IgM, and IgA determination. **Results:** Analysis revealed significantly higher levels of IgG, IgM, IgA, and IL16 in contraceptive users compared to non-users. However, CD4 and IL27 levels showed a marked reduction in patients compared to healthy controls. Notably, there were no statistically significant differences (P>0.05) in immune variables between different contraceptive types, except for IgA, which was highest in injection users and lowest in oral contraceptive users. Further scrutiny found no significant variations (P>0.05) between immune variable levels and hormonal/non-hormonal contraceptives, except for IL16 (P>0.01). **Conclusions:** The study concludes that various contraceptive methods (tablets, injections, copper IUDs) lead to increased levels of immunoglobulins (IgG, IgM, IgA). Importantly, changes in contraceptive type (tablets, injections, IUDs) had minimal impact on immune variables, except for increased IgA in injection users. Hormonal or non-hormonal contraceptives showed no noticeable influence on immune indicators, except for IL16, which exhibited a significant increase.

Keywords: Contraceptives, Copper IUD, Ovulation, Hormonal, Estrogen, Progesterone.

Significance | The immune system is influenced by hormonal contraceptives, leading to a reduction in thyroid activity. Additionally, progesterone might affect T cells and elevate the risk of autoimmune diseases.

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1. Introduction

Contraceptiones, the intentional prevention of fertilization, has evolved significantly, offering women greater control over reproductive health and family planning. This progress, especially in the 20th century, introduced safe and effective contraceptive methods (Apter, 2016). Contraceptives are broadly categorized into hormonal and non-hormonal types. Hormonal contraceptives, containing estrogen and progesterone, influence the uterine environment, hindering sperm entry or preventing ovulation (Mawet et al., 2015). However, studies highlight potential risks, such as a heightened chance of diseases like breast cancer, irregular bleeding, myocardial infarction, and stroke (Geampana A., 2016; Peter, 2013). Age, chronic conditions, and

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smoking status must be considered when prescribing hormonal contraceptives. Non-hormonal contraceptives encompass various methods like the cervical cap, spermicides, vasectomy, intrauterine contraception (ICU), and IUD (Dreskin, 2012). Hormonal contraceptives, including birth control pills and patches, can impact the immune system, leading to decreased thyroid activity and associations with conditions like ulcerative colitis and lupus erythematosus (Ågren, 2011). Progestogen-only contraceptives may induce dermatitis, affecting T cells and sub-T cells, and influencing cellular proliferation and antibody secretion (Mosher and Jones, 2010; Islam, 2020). In a recent study, it was found that hormonal contraceptives can inhibit pituitary gonadotropin (Jaing et al. 2022). This inhibition occurs through the expression of gonadotropin-releasing hormone (GnRH) and its receptors in specific immune cell subsets. Additionally, there is a clear link between gender and autoimmune diseases. Females are more prone to conditions such as lupus erythematosus (SLE), rheumatoid arthritis (RA), and autoimmune thyroid disease, attributed to the secretion of progesterone and estrogen. Interestingly, some hormonal contraceptives may increase the risk of these diseases, while also serving as a treatment for interstitial cystitis (Symmons et al. in 2011).

The study aimed to explore the impact of contraceptives on immune variables (CD4, CD8, IL16, IL27, IgA, IgM, and IgG) among women in Diyala Governorate. Hormonal contraceptives' ability to suppress pituitary gonadotropin and influence immune cells is a focal point (Jaing et al., 2022). Considering the gender-immune system connection, hormonal contraceptives may contribute to autoimmune diseases due to progesterone and estrogen secretion, while potentially acting as a treatment for interstitial cystitis (Symmons et al., 2011). This research seeks to shed light on the intricate relationship between contraceptives and immune variables, offering valuable insights into the potential repercussions of contraceptive choices on women's health in Diyala Governorate.

Materials and Methods

Study design

In this study, conducted from July to October 2023, samples were gathered from Al-Batoul Teaching Hospital (Family Planning Department), private clinics, and health centers. The study included a total of 90 women meeting the inclusion criteria. Of these, 50 women comprised the study group, using contraceptives, while the remaining 40 females constituted the control group, representing healthy women not using any contraceptive method. A personalized interview was conducted, and a questionnaire was filled out, capturing information such as name, age, type of contraceptive used (pills, injections, IUD, strip), duration of contraceptive use, number of children, presence of other diseases, and the use of additional medications. Additionally, blood samples were collected by drawing 5 ml of venous blood using a sterile, single-use medical syringe. The blood was then placed in a gel tube and centrifuged at 3000 rpm for 15 minutes to obtain blood serum. The study received approval from the Scientific Ethical Committee at the University Of Anbar, adhering to Helsinki Declaration guidelines. Reporting in this article aligns with CONSORT standards.

ELISA

The blood supernatants were used to quantify cytokine expression according to manufacturers' instructions for human CD4, CD8, IL16, IL27 in fifty women (contraceptives user) and forty healthy group samples with ELISA (Biotek USA). All supernatants were either undiluted or diluted 1:2 and 1:5 and were run on the same plate to ensure the readings were comparable. Absorbance was measured with the BioTek ELx800 Microplate Reader (Winooski, VT, USA) at 450 nm. Graphic data present the mean ± SEM, and n values for each experiment are indicated in figure legends.

Assessment of serum immunoglobulins

Blood samples collected at study entry were stored in ethylenediamine tetra-acetic acid (EDTA)-treated containers and frozen at -80 °C, according to standard procedures. From 2016 to 2018, these samples were thawed for analytic purposes. A single radial immunodiffusion method (SRID) using a kit (sanofi Diagnostics France) was used to measure serum IgA, IgG, and IgM levels. The manufacturer's protocol provided reference ranges of serum immunoglobulins for adults, which were 0.7–4.0 g/L for IgA, 7.0–16.0 g/L for IgG, and 0.4–2.3 g/L for IgM. Reference ranges for our study population, based on the 2.5th-97.5th percentiles (in accordance with practice in clinical chemistry) (Khan SR et al., 2021) were: 0.86–4.76 g/L for IgA, 6.20–15.10 g/L for IgG, and 0.28–2.64 g/L for IgM.

Statistical Analysis

We analyzed data using SPSS v. 25, GraphPad Prism v.6, and Excel 2013. We presented ordinal and nominal data as numbers and percentages, comparing percentages with the chi-square test. Quantitative data was described The Least Significant Difference (LSD) test compared arithmetic means. We used the Pearson correlation coefficient to assess the relationship strength between immune variables. Significant differences were considered at $P \leq 0.05$.

Results and discussion

Immune Response Discrepancies in Women Using Contraceptives

The research compared the levels of various immune variables in two study groups: patients and healthy individuals. We determined significant differences ($p<0.05$) in IgG, IgM, IgA,

CD4, IL16, and IL27 levels between the two study groups. Patients had higher quantities of IgG, IgM, IgA, and IL16, while CD4 and IL27 levels were lower than those of healthy individuals. No significant differences (P>0.05) in CD8 levels between the two groups were observed (Table 1).

These results align with a previous study suggesting that immunoglobulin proteins increase as part of an immune response to copper IUD usage. Copper IUDs enhance local secretory responses, releasing proteins like lysozyme, lactotransferrin, and immunoglobulin. The IUD's irritation stimulates prostaglandin release, hindering fertilization. The IUD also induces the release of prostaglandins, leading to muscle contractions that hinder fertilization. Additionally, the copper IUD triggers a local immune response that prevents germination after fertilization. Additionally, copper toxicity to sperm and inflammatory responses contribute to contraceptive effectiveness (Silvia, 2019).

A study indicated lower immunoglobulin and trace element levels in individuals with preeclamptic preeclampsia, suggesting micronutrient deficiencies and low immunoglobulins as potential risk factors for hypertension and preeclampsia (Nwatah et al., 2022).

The findings of our research revealed a notable decrease in CD4 levels among women utilizing contraceptives in comparison to healthy controls. Interestingly, our results contradicted a study conducted by Omollo in 2021, which suggested that women using hormonal contraceptives, such as pills and injections, exhibited higher rates of CD4 and CD8 T-cell expression among healthy women. This implies that contraceptives, particularly hormonal methods, may contribute to increased inflammation and activation signs on HIV target cells in both the bloodstream and the reproductive system.

Furthermore, the authors observed a decline in the concentration of T cells producing CD4 and CD8 after 180 days of using DMPA. Recent research also suggests variations in the functioning of natural killer cell subpopulations in the altered immune state characteristic of early-onset preeclampsia. Different subpopulations may play a role in compensating or maintaining Th1 dominance, as indicated by Meggyes et al. in 2023.

The CD4/CD8 ratio emerges as a crucial measure of the immune system imbalance in a patient, capturing essential information about disease progression. This ratio assesses two significant subtypes of white blood cells: CD4+, responsible for infection protection, and CD8+, responsible for eliminating malignant cells and other harmful substances, as highlighted by Fawzy et al. in 2022.

Intriguingly, variations in a woman's environment may trigger the protective system, influencing the size and function of CD8 and CD4 T lymphocytes. Additionally, CD8 and CD4 expression could indicate pregnancy screening in animals, as suggested by Islam et al. in 2020.

In South Africa, a study on women using DMPA injections, IUDs, and implants revealed an increase in interleukin IL16 levels among those using contraceptive pills, injections, and strips. This points to differences in inflammatory profiles influenced by environmental or genetic factors, as indicated by Nina et al. in 2022. Some studies even suggest that changes in cytokines in contraceptive users may lead to alterations in inflammation, potentially compromising the integrity of the mucus barrier and making the reproductive system more vulnerable to invasion by HIV and other sexually transmitted agents, as noted by Arnold et al. in 2016.

Contrary to a study on 128 women using DMPA hormonal contraceptives, our results did not align with the decrease in cellular mediators and soluble factors such as IL16, IL10, growth factor, and chemokines, as reported by Silvia B. in 2019. However, they did align with a study by Dabee et al. in 2019, which demonstrated a significant increase in cytokine concentration and soluble inflammatory factors with hormonal contraceptives like DMPA. This suggests that DMPA creates an immune environment, facilitating the recruitment of target cells and inhibiting antiviral activity.

Our study found higher levels of IL-27, in line with Jahantigh et al.'s findings in 2019 comparing women using contraceptives to healthy subjects,. IL-27, with its pro- or anti-inflammatory properties, is crucial in maintaining immunological balance during pregnancy, as highlighted by Hu et al. in 2020. The occurrence of pregnancy problems can be influenced by changes in IL-27 levels, with reduced quantities linked to repeated miscarriage during early pregnancy stages. This reduction diminishes IL-27's beneficial effects on anti-inflammatory IL-10 release by CD4+ Treg cells and its inhibitors on pro-inflammatory IL-17 generation by CD4+ Th17 cells. Elevated peripheral blood levels of IL-27 in late pregnancy may initiate a systemic inflammatory state leading to preeclampsia, as demonstrated by Ran et al. in 2021.

The study results also suggest that IL-27 may inhibit trophoblast cell migration and invasion by influencing epithelial–mesenchymal transition (EMT) through the STAT1-dominant pathway in preeclampsia, as outlined by Ge et al. in 2019.

Our study, which showed higher levels of IL-16 in women using contraceptives compared to healthy controls, is consistent with Jiang et al.'s findings in 2022. Increased atonic bleeding after delivery was linked to greater amounts of IL-16 in the latter half of the third trimester of pregnancy. These indicators could potentially serve as predictive markers for atonic bleeding after delivery in the future.

Table 1. Comparison of levels of immune variables between the two study groups

Groups		N	Mean	Std. Deviation	P value
IgG (mg/dl)	Patients	50	2443.61	825.72	p<0.001***
	Healthy	40	337.52	75.97	
IgM (mg/dl)	Patients	50	1549.66	600.90	p<0.001***
	Healthy	40	54.02	10.19	
IgA (mg/dl)	Patients	50	1043.21	511.43	p<0.001***
	Healthy	40	120.88	44.78	
CD4 (pg/ml)	Patients	50	0.39	0.14	P<0.05*
	Healthy	40	0.50	0.22	
CD8 (pg/ml)	Patients	50	0.41	0.15	p>0.05
	Healthy	40	0.40	0.12	
IL16 (pg/ml)	Patients	50	0.94	0.38	P<0.05*
	Healthy	40	0.82	0.36	
IL27 (pg/ml)	Patients	50	0.35	0.13	p<0.05*
	Healthy	40	0.55	0.14	

Table 2. Comparison of levels of immune variables with the type of contraceptive substance

Contraceptive Types		N	Mean	Std. Deviation	P value
IgG (mg/dl)	Injection	4	2533.43	855.68	p>0.05
	Oral tips	27	2481.62	813.06	
	Intrauterine Device	19	2370.68	877.25	
IgM (mg/dl)	Injection	4	939.35	321.31	p>0.05
	Oral tips	27	1593.70	723.72	
	Intrauterine Device	19	1615.57	723.13	
IgA (mg/dl)	Injection	4	2938.53	811.80	p<0.01**
	Oral tips	27	863.72	422.48	LSD=651
	Intrauterine Device	19	899.27	342.23	
CD4 (pg/ml)	Injection	4	0.23	0.09	p>0.05
	Oral tips	27	0.40	0.18	
	Intrauterine Device	19	0.40	0.19	
CD8 (pg/ml)	Injection	4	0.27	0.11	p>0.05
	Oral tips	27	0.42	0.14	
	Intrauterine Device	19	0.39	0.15	
IL16 (pg/ml)	Injection	4	0.72	0.49	p>0.05
	Oral tips	27	0.97	0.39	
	Intrauterine Device	19	0.94	0.35	
IL27 (pg/ml)	Injection	4	0.24	0.13	p>0.05
	Oral tips	27	0.34	0.12	
	Intrauterine Device	19	0.39	0.15	

Table 3. Comparison of levels of immune variables with contraceptives (hormonal and non-hormonal)

Contraceptives		N	Mean	Std. Deviation	P value
IgG (mg/dl)	Hormones	30	2531.15	887.79	P>0.05
	Un hormones	20	2312.29	724.64	
IgM (mg/dl)	Hormones	30	1676.31	711.60	P>0.05
	Un hormones	20	1359.70	523.30	
IgA (mg/dl)	Hormones	30	1160.84	512.17	P>0.05
	Un hormones	20	866.78	421.00	
CD4 (pg/ml)	Hormones	30	0.40	0.16	P>0.05
	Un hormones	20	0.37	0.14	
CD8 (pg/ml)	Hormones	30	0.41	0.13	P>0.05
	Un hormones	20	0.39	0.16	
IL16 (pg/ml)	Hormones	30	1.13	0.33	P<0.001***
	Un hormones	20	0.65	0.25	
IL27 (pg/ml)	Hormones	30	0.35	0.14	P>0.05
	Un hormones	20	0.36	0.13	

In examining IL-16 expression in the systemic arteries of mothers, scientists discovered significant IL-16 staining in the vascular endothelium of both arteries and venules in preeclamptic women. This reinforces the notion of an elevated inflammatory reaction in the mother's systemic blood vessels in preeclampsia, suggesting that leukocytes in circulation and vascular endothelium may interact in immune reactions. This interaction may be connected to the recruitment of leukocytes and permeation into interstitial tissues, possibly contributing to delayed apoptosis in preeclampsia, as proposed by Guo et al. in 2023.

In conclusion, our study contributes valuable insights into the complex interplay between contraceptive use, immune system dynamics, and pregnancy outcomes. The varied findings across different studies underscore the need for further research to comprehensively understand the intricate mechanisms at play in these complex biological processes.

The effect of types of contraceptives on immune variables

Our study results indicate no statistically significant differences ($P>0.05$) in immune variables based on the type of contraceptive substance patients use, except for IgA. IgA levels were highest in women using injections (2938.53 ± 811.80) and lowest in those using oral contraceptives (863.72 ± 422.48) (Table 2).

Hormonal contraceptives are widely used for birth control, but their unexpected negative consequences are not well understood. A prior study found that women taking oral hormonal contraceptives exhibited higher levels of plasma cortisol, CRP, stress, and despair compared to those with regular cycles. Such findings can help young women contemplating hormonal contraceptive use make informed decisions by highlighting the physiological consequences (Masama et al., 2022).

Studies on humoral factors of immunity have explored compensatory-adaptive reactions, with cytokines IL-1β and IL-8 having diagnostic and prognostic value in operative delivery and intrauterine contraceptive insertion. The IL-1β/IL-8 ratio serves as a crucial prognostic marker, predicting compensation levels and indicating the degree of the inflammatory process. Postoperative intrauterine contraception leads to changes in immune mediators proportional to the inflammatory process (Azizovna, 2021).

Research on combined contraceptive vaginal rings (CCVR) revealed altered endogenous hormone levels and a stronger link between cervical Th17 cell frequencies and CCVR use compared to norethisterone oenanthate (NET-EN) or combined oral contraceptive pills (COCPs). While Th17 cells were more active, concentrations of Th17-related cytokines were elevated, suggesting that CCVR may influence HIV risk through Th17 regulation (Konstantinus et al., 2020).

In addition, a study demonstrated that oral contraceptives (OC) can modify the number and phenotype of T regulatory cells in peripheral blood, raising the possibility that regulatory T cells contribute to the physiological changes and altered disease susceptibility associated with OC use (Moldenhauer et al., 2022).

The effect of hormonal and non-hormonal contraceptives on immune variables

The findings of our report reveal no significant variations ($p>0.05$) in the levels of immune variables concerning different contraceptives (both hormonal and non-hormonal), except for IL16, which showed significance at $p>0.01$ (Table 3).

Previous research has indicated that the use of hormonal contraceptives can impact the production of immune-mediated substances in both the reproductive and systemic systems, along with affecting the activity of plasmacytoid dendritic cells (pDCs). This study contributes to the expanding body of research on the biological impact of progestins on the body's immune system, particularly in the lower female reproductive tract (FRT) (Murphy et al., 2014). However, the broader question remains unanswered – whether the systemic and reproductive immune processes altered by contraceptives, as discussed in this study and others, have an impact on an individual's susceptibility to HIV-1 and other infections. For women at risk of contracting HIV-1, making informed choices about effective contraceptive methods is crucial. Further investigation into the biological impact of hormonal contraceptives on the immune system is warranted. WHO guidelines recommend counseling women taking hormonal contraceptives to also use both male and female condoms and adopt other HIV prevention measures (Michel et al., 2015).

A prior study has demonstrated that in vivo exposure of CD4, CD8, and T cells to normal pharmacological concentrations of depot medroxyprogesterone (DMPA) does not result in broad agonist suppression. However, prolonged use of medroxyprogesterone (DMPA) may lead to exhaustion of certain cytokine-producing T cells (Matubu et al., 2021).

In the context of a previous research finding, IL-27 is produced in the endometrium as part of the antiviral response, enhancing the body's reaction to viral ligand activation. The influence of E2 suggests that IL-27 may regulate immunological responses to invading pathogens and contribute to immune defense throughout the menstrual cycle. Given the widespread use of hormonal treatments and chemical contraceptives globally, it remains crucial to determine if other estrogenic elements, including ethinyl estradiol used in contraceptives, or selective ER modulators, affect IL-27 production and sensitivity (Patel et al., 2018).

In summary, our study adds valuable insights by highlighting the lack of significant variations in most immune variables concerning different contraceptives. However, the exception of IL16 suggests the need for further exploration. The impact of hormonal contraceptives on the immune system and susceptibility to infections remains a complex and evolving area of study, emphasizing the importance of continued research and informed

decision-making for individuals, especially those at risk of HIV-1.

Conclusions

In conclusion, different contraceptive methods, including tablets, injections, and copper IUDs, elevate immunoglobulins IgG, IgM, and IgA. The alteration in the choice of contraceptive material (tablets, injections, IUD) did not influence any of the immune variables, except for IgA, which exhibited an increase in women using injections. Notably, whether hormonal or non-hormonal inhibitors were employed, they did not impact any immune indicators except for IL16, which showed a significant increase.

Author contribution

S.M.A. performed analyses, and analyzed data, M.F.N. conceptualized and wrote the paper. A.F.M. collected data and performed an analysis.

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Competing financial interests

The authors have no conflict of interest.

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