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Comparative assessment of the effects of two intrauterine systems for long-term contraception on some haematological, biochemical, and immunological markers

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Abstract
An intrauterine system (IUS) is a type of contraception tool that is used in order to control fertility and prevent conception in women for a long period. The aim of this study was to assess the influence of copper- *versus* levonorgestrel-releasing IUSs on women's health. This is a descriptive cross-sectional study of 75 women that were randomly selected (50 women that used a copper-releasing IUS and the remaining 25 that used a levonorgestrel-releasing IUS) amongst those attending out patient's clinics at Hillah, Iraq, from March to July 2016. All women were between 18 to 46 years of age, and have had an IUS for at least three months. The measurement of serum ceruloplasmin (SCerP), haemoglobin, vitamin D (VD), interleukin-6 (IL-6), and interferon-gamma (IFN-γ) levels was undertaken. Our results revealed that the copper-releasing IUS group has low haemoglobin and VD levels, along with high levels of SCerP and proinflammatory cytokines. One the other hand, the levonorgestrel-releasing IUS group displayed no significant changes on the above markers. We can conclude that the levonorgestrel-releasing IUS is free of any adverse effect when compared to a copper-releasing IUS, at least with regard to the parameters examined by our study.

KEYWORDS
intrauterine system, copper, levonorgestrel, vitamin D, IL-6, IFN-γ

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1. INTRODUCTION

An intrauterine system (IUS) is highly effective contraception, with less than a 1% failure rate. There are two main types: the copper-releasing

and the levonorgestrel-releasing IUS. While both types work similarly in preventing pregnancy, the levonorgestrel-releasing IUS also helps manage heavy menstrual bleeding and offers other health benefits like reducing the risk of endometrial cancer and pelvic inflammatory disease (PID) [1]. Side effects such as irregular bleeding, headaches, and mood changes are usually mild and improve over time with the levonorgestrel-releasing IUS. On the other hand, the copper-releasing IUS may cause heavier bleeding and cramping during periods, but does not affect hormones [2]. However, it may increase the risk of infection, PID, infertility, ectopic pregnancy, or even perforation during insertion. The suitability of the IUS depends on factors like the medical history, the reproductive goals, and the lifestyle, thereby necessitating a thorough discussion with a healthcare provider for proper decision-making [3].

There is an important role for vitamin D (VD) in the body's immune system: its receptors are found in significant concentrations in T-lymphocytes (mostly in the mature CD-8 T-lymphocytes). This suggests that the action of T-lymphocytes might be mediated by VD. In addition, VD is known to block the effects of adaptive immunity, thereby leading to the prevention of autoimmunity [4]. VD can also block the production of pro-inflammatory cytokines such as interleukin-6 (IL-6), the tumour necrosis factor - alpha (TNF-α), and interferon-gamma (IFN-γ); a fact that may also be associated with the stimulation of the production of anti-inflammatory cytokines and the decrease in killer T-cell production [4,5]. On other hand, the deficiency of VD can inhibit the production of B-lymphocytes, thereby leading to the blocking of the production of immunoglobulins [5]. Our study has aimed at assessing the influence of copper- *versus* levonorgestrel-releasing IUSs on women's health, as reflected by the levels of VD and some important immunomodulatory markers (such as IL-6 and IFN-γ).

2. SUBJECTS AND METHODS

Study design: This is a descriptive cross-sectional study of 75 women that were randomly selected (50 women that used a copper-releasing IUS and the remaining 25 that used a levonorgestrel-releasing IUS) amongst those attending out patient's clinics of the Babylon Teaching Hospital for Maternity and Paediatrics and the Al-Hilla Teaching Hospital, at Hillah, Iraq, from March to July 2016. All women were between 18 to 46 years of age, and have had an IUS for at least three months.

Exclusion criteria: Eligible women ought not to document any known chronic diseases (such as diabetes, hypertension, chronic kidney disease, sexually transmitted diseases, or bleeding tendencies). We also excluded women with serious underlying diseases or any gynaecological diseases, and women who were smoking, as these conditions / habits could interfere with the results.

Ethics statement: The study was carried out in compliance with the Declaration of Helsinki principles, and was reviewed and approved by the local research ethics committees of the Faculty of Medicine of the University of Babylon. After gaining the verbal consent from our patients, the data were collected by a well-trained researcher using a standardized questionnaire. Participating women were told that their rejection or withdrawal from the study would have no impact on the medical care they received.

Demographic and clinical variables: These included age, educational level, employment status, pattern of menstrual period, any current vaginal infection, and body mass index (BMI).

Laboratory investigation: We measured the haemoglobin levels, the serum ceruloplasmin (SCerP; which reflected serum copper) levels by using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (E-EL-H6026; Elabscience, USA), VD levels by using ELISA (DE1971; Demeditec Diagnostics, Germany), as well as IL-6 and IFN-γ levels *via* ELISA kits (E-EL-H0192 and E-EL-H0108, respectively; Elabscience, USA).

Statistical analysis: Wherever applicable, a *t*-test was utilized and the significance level was fixed at a $P<0.05$. GraphPad Prism 5.0 on Windows was used in order to conduct all analyses (GraphPad Software, San Diego, CA, USA).

3. RESULTS

The participants of copper-releasing IUS group were mainly between 20 to 30 years of age (52%), while those in the levonorgestrel-releasing group were mainly between 31 to 40 years of age (56%). Most participants in the levonorgestrel-releasing IUS group were higher education graduates (72%), while in the copper-releasing IUS group, the majority of the participants had completed only elementary studies (42%). Most of the levonorgestrel-releasing IUS group women were employed (68%), while in copper-releasing IUS group, the majority were unemployed (62%). The BMI of the levonorgestrel-releasing IUS group's participants was in most cases overweight (40%) or obese (40%), while in the copper-releasing IUS group, most participants were overweight (58%). The coloured vaginal discharge which might be associated with infection was reported by 32% of the

levonorgestrel-releasing IUS group women and by 70% of the copper-releasing IUS group women. Dyspareunia was present in 24% of the participants of the levonorgestrel-releasing IUS group and in 40% of the participants of the copper-releasing IUS group. Finally, menorrhagia was reported by 64% of the women belonging to the copper-releasing IUS group and only by 12% of the women belonging to the levonorgestrel-releasing IUS group (Table 1).

Table 1. General data and data corresponding to serological and immunological tests for the study's two groups of participants bearing an intrauterine system (IUS) in the Babylon Governorate.

General Data of the study's participants			
	Age (number of subjects and percentage)		
	<30 years	**30–40 years**	**>40 years**
Copper-releasing IUS (n=50)	26 (52.0%)	22 (44.0%)	2 (4.0%)
Levonorgestrel-releasing IUS (n=25)	7 (28.0%)	14 (56.0%)	4 (16.0%)
	Educational level (number of subjects and percentage)		
	Elementary	**Secondary**	**Higher education**
Copper-releasing IUS (n=50)	21 (42.0%)	17 (34.0 %)	12 (24.0%)
Levonorgestrel-releasing IUS (n=25)	2 (8.0 %)	5 (20.0 %)	18 (72.0%)
	Employment status (number of subjects and percentage)		
	Employed	**Unemployed**	
Copper-releasing IUS (n=50)	19 (38.0%)	31 (62.0%)	
Levonorgestrel-releasing IUS (n=25)	17 (68.0%)	8 (32.0%)	
	Duration of IUS insertion (number of subjects and percentage)		
	<1 year	**1–2 years**	**>2 years**
Copper-releasing IUS (n=50)	13 (26.0%)	29 (58.0%)	8 (16.0%)
Levonorgestrel-releasing IUS (n=25)	12 (48.0%)	11 (44.0%)	2 (8.0%)
	Body mass index (number of subjects and percentage)		
	Normal (18.5–24.9)	**Overweight (25–29.9)**	**Obese (>30)**
Copper-releasing IUS (n=50)	9 (18.0%)	29 (58.0%)	12 (24.0%)
Levonorgestrel-releasing IUS (n=25)	5 (20.0%)	10 (40.0%)	10 (40.0%)
	Vaginal discharge (number of subjects and percentage)		
	Whitish or transparent	**Coloured (purulent, brownish or bloody)**	
Copper-releasing IUS (n=50)	15 (30.0%)	35 (70.0%)	
Levonorgestrel-releasing IUS (n=25)	17 (68.0%)	8 (32.0%)	
	Dyspareunia (number of subjects and percentage)		
	Presence	**Absence**	
Copper-releasing IUS (n=50)	20 (40.0%)	30 (60.0%)	
Levonorgestrel-releasing IUS (n=25)	6 (24.0%)	19 (76.0%)	
	Menorrhagia (number of subjects and percentage)		
	Presence	**Absence**	
Copper-releasing IUS (n=50)	32 (64.0%)	18 (36.0%)	
Levonorgestrel-releasing IUS (n=25)	3 (12.0%)	22 (88.0%)	
	Haemoglobin levels		
	<12 g/dL	**≥12 g/dL**	
Copper-releasing IUS (n=50)	34 (68.0%)	16 (32.0%)	
Levonorgestrel-releasing IUS (n=25)	9 (36.0%)	16 (54%)	

Serological and immunological tests			
Levels	**Copper-releasing IUS** (n=50)	**Levonorgestrel-releasing IUS** (n=25)	***P*-value**
Serum ceruloplasmin (μg/dL)	121.28 ± 19.73	114.13 ± 11.69	>0.05
Vitamin D (ng/mL)	19.83 ± 3.79	24.65 ± 9.63	<0.01
Interleukin-6 (pg/mL)	314.51 ± 51.21	278.33 ± 38.19	<0.01
Interferon-gamma (pg/mL)	107.80 ± 18.16	91.16 ± 32.51	<0.01

Haemoglobin levels appeared to be mostly normal in the levonorgestrel-releasing IUS group (54%), while in the copper-releasing IUS group they were mostly <12 g/dL (68%). The SCerP levels in levonorgestrel-releasing IUS group were 114.13 ± 11.69 μg/dL, while in the copper-releasing IUS group the same levels were 121.8 ± 19.73 μg/dL (P>0.05). The serum VD levels ranged from 15.18 to 35.5 ng/mL, with the lower levels being observed in the copper-releasing IUS group (19.83 ± 3.79 ng/mL; P<0.01). The range of the IL-6 levels was 240.22 to 365.31 pg/mL, with the mean level being lower in the levonorgestrel-releasing IUS group (278.33 ± 38.19 pg/mL; P<0.01); similarly, the range of the IFN-γ levels was 95.22 to 125.93 pg/mL, with the mean level being lower in the levonorgestrel-releasing IUS group (91.16 ± 32.51 pg/mL; P<0.01) (Table 1)

4. DISCUSSION

Although contraceptive methods are commonly used, their reassessment is still an obligatory action aiming to decrease morbidity for women. This study has compared two commonly used birth control devices, aiming to determine their respective advantages for women and any accompanying conditions. We have identified differences in the impact of clinical and biochemical parameters between women using either levonorgestrel- or copper-releasing IUSs, independent of any underlying conditions that might affect their mode of action [6]. Monocausal theories were insufficient to explain the effects observed, such as the influence of age, BMI, clinical symptoms (such as vaginal discharge and dyspareunia), and duration of insertion; all of which negatively affect women using either type of IUD. Our study has also revealed a significant association between menstrual blood loss (menorrhagia) and the type of IUS used, thereby indicating that the copper-releasing IUS is more likely to cause menorrhagia and greater blood loss, leading to decreased haemoglobin levels and iron deficiency [7]. Additionally, levels of SCerP showed a significant difference, with the copper-releasing IUS having a greater (yet, non-significant) effect on women using it compared to the levonorgestrel-releasing IUS [8].

Our study also examined the physiological alterations associated with the use of IUS, by focusing on the immune system's role and its impact on women's health. The literature highlights the presence of various proteins, cytokines, and cells involved in maintaining immunity, with a particular emphasis on T-helper cells and their potential to trigger autoimmune and inflammatory diseases [9]. Studies suggest that high levels of proinflammatory cytokines (particularly IL-6) are associated with negative health outcomes in women, along with activated T-cells. While there is no significant evidence linking changes in IFN-γ levels with women's health, a recent study suggests a correlation between the VD status, IFN-γ secretion, and women's health and fertility [10]. Our findings suggest a nuanced role for the immune system in women's health beyond inflammation, thereby indicating that low VD levels in copper-releasing IUS users may lead to adverse outcomes and comorbidities. These findings are suggestive of the need for contraception with fewer side effects and greater efficacy.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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