DO THE COMMONLY USED CONTRACEPTIVE METHODS HAVE A ROLE ON THE ACTIVITY OF RHEUMATOID ARTHRITIS?

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ABSTRACT:

Background: *Rheumatoid arthritis (RA) is one of the most common autoimmune diseases of connective tissue. Women are affected by RA 3 times more than men, and because most of them are in the reproductive age and they have to be on a teratogenic drugs (disease modifying antirheumatic drugs DMARDs as methotrexate, leflunamide) for a long periods, so there is a big need to clarify the contraceptive method that should be used by those women.*

Aim of the Work: *we aimed to explore the association of the RA activity and the commonly used female contraceptive methods in a sample of Egyptian females.*

Patients and Methods: *Fifty female RA patients were enrolled and divided into two groups; contraceptive methods users(40 patients), which was further subdivided into intra uterine cupper device (IUCD) users(15 patients),oral contraceptive pills(OC) users(13pateints) and injectables users(12 patients), and non-contraceptive methods users(control group) (10 patients). All patients underwent thorough history taking with special emphasis on contraception history, clinical examination, and assessment by routine laboratory tests, rheumatoid factor (RF) and antibodies to citrullinated protein antigens (ACPA). Rheumatoid arthritis disease activity was assessed using Disease Activity Score 28 using CRP (DAS28/ CRP), while RA disease severity was assessed using Rheumatoid Arthritis Severity Scale (RASS).*

Results: *The RASS was significantly higher in injectables-users in comparison to other methods-users followed by the IUCD-users with the highest significant difference between the injectables and OCs (P=0.002), and the DAS28\CRP was significantly higher in IUCD users followed by the injectables users with the highest significant difference between the IUCD and OCs (P=0.009). the highest CRP and ACPA was among the IUCD users with the highest significant difference in CRP level between the IUCD users and the control group (P=0.030) and the highest significant difference in ACPA level between the IUCD users and the OCs users (P=0.004). About 64 % of all patients used IUCD prior to the onset of RA, The RA patients who used IUCD prior to the onset of RA had a higher ACPA titers than those with disease onset preceding IUCD use with high statistical significance(P=0.004), Also, on performing a correlation between the duration passed since first use of IUCD and the disease duration, There was a significant positive correlation between them (i.e. the earlier the first exposure to IUCD the longer the disease duration) (r=0.425)*

Conclusion: *There's a relation between RA activity and the currently used contraceptive methods. the IUCD could increase the severity and activity of RA.OCs could decrease the disease activity and severity.*

Keywords: *Rheumatoid Arthritis Severity Scale, total leucocytic count, Rheumatoid Arthritis, intrauterine device, oral contracaptive pills.*

INTRODUCTION:

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases of connective tissue and is considered as a rheumatic disease. Women, especially in the third to the fifth decades of life, are affected by RA 3 times more than men[1]. This tendency to affect women more than men suggests that sex hormones may have an influence on disease. In a broad manner, it has been suggested that estrogens have a pro-inflammatory and androgens exert an anti-inflammatory effect[2].

Because most of these women are in the reproductive age and they have to be on a teratogenic drugs for a long periods as DMARDs and nonsteroidals anti inflammatory drugs, so there is a big need to clarify the contraceptive method that should be used by women with RA and other than the use of this contraceptives carry risks or not on the RA activity and severity[3] .

The different contraceptive methods influence:

A) Combined Oral contraceptive pills (OC):

Recently, considerable interest has focused on whether oral contraceptives (OCs) are protective against the risk of developing RA. The results have been contradictory, as there's a study that indicate that there was not any association between using OCPs and RA severity[4]. But there another study of Swedish Epidemiological Investigation of RA (EIRA), revealed that the ever and past OC use decreased the risk of RA, especially ACPA-positive RA. A long duration of OC use decreased the risk of both disease subsets. There is no evidence to suggest that the OC use would exacerbate disease [5].

B) Intra uterine cupper device (IUCD):

Although the real mechanism is not yet clear, there are some possible mechanisms of cupper-containing IUDs for inducing inflammation. The IUCDs are considered as a foreign body inside the uterine cavity producing varying degrees of foreign body reactions which result in inflammation because of short-term inflammatory reaction that results from transient low-grade bacterial infection of the endometrial cavity following insertion of an IUFB produce a more rapid influx of intrauterine inflammatory cells than would normally occur if no IUFB were present. Also, there's a long-term inflammatory reaction that results from the cyclic decidualization of the endometrial surface, the foreign body reaction is continually renewed. This cyclic chronic inflammation may well explain the nonprogressing endometritis produced by the IUD[6].

Additionally, there's an increased risk of anti-citrullinated protein antigen (ACPA) positivity in females who are using IUCD and they are in a first degree relativity of RA patients, this make them in high risk to become RA patients and that was suggested in the Studies of the Etiology of RA (SERA). This is theoretically attributed to the IUCD-induced endometrial inflammation that may be a potential mucosal trigger of RA-related antibodies. These suggestions may make the IUCD choice an unfavorable one in RA

patients if it shows a future relation between RA activity and IUCD use [7].

C) The Injectable Depomedroxy-progesterone Acetate (DMPA):

As regards the use of injectables, it is associated with important, but generally reversible, changes in bone mineral density. As it decrease the bone density which lead to increasing fracture risk due to inhibition of ovulation in the early months of use.

So, it's not seems to be a good long-term choice for the RA patient especially those receiving long-term corticosteroid therapy with a history of, or with risk factors for, non-traumatic fractures[8] .

AIM OF WORK:

This study explored the association of the RA activity and the commonly used female contraceptive methods in a sample of Egyptian females. We aimed to help RA patients to choose a suitable contraceptive method which will not deteriorate their disease activity and severity.

PATIENTS AND METHODS:

In this Cross-sectional study, we enrolled 50 female patients with RA from the outpatient clinic of rheumatology and rehabilitation department of El Sahel teaching hospital, who were divided into two groups: contraception users (40 patients), which was further subdivided into IUCD users(15 patients), OC users(13pateints) and injectables users(12 patients), and non-contraception users(control group) (10 patients).

Inclusion criteria:

1. Female patients diagnosed as RA and fulfilling the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) classification criteria 2010[9] , which is a score-based algorithm, with four categories A–D; a score of 6/10 is needed for classification of a patient as having definite RA.
2. Age ≥ 18 years.
3. Two years after menarche.

a. For contraceptive method users: used the same specific method for contraception for at least 6 months.

b. For non-contraceptive method users: they were on no contraception method for at least 6 months.

4. Patients treated by DMARDs ,with or without steroidals and nonsteroidals anti-inflammatory drugs

Exclusion criteria

1. Age < 18 years.
2. Onset of menarche of less than 2 years.
3. Use of specific contraceptive method for less than 6 months.
4. Irregular use of contraception method within the studied 6 months.
5. Severe liver dysfunction, because diagnosis and treatment of liver disease in RA patients can significantly influence the course and outcome of rheumatoid arthritis.
6. Any sort of malignancies or treatment with chemotherapy, as the RA severity correlates with more intense use of immunosuppressive medications which are used in treatment of malignancies[10] .
7. Pregnancy or lactation, as all this cases affect the hormonal state of the patient.
8. Patients with morbid obesity (BMI > 40),as morbid obesity has been observed to be associated with greater subjective measures of disease activity and poor treatment response, but also with a decreased risk of joint damage and lower mortality[11] .
9. Post-menopausal females.
10. Patients treated by biological treatment.

A written consent was taken from patients for their participation on this study, and approval from ethical committee.

All patients were subjected to:

I. Full general and medical history.

Including history of drug intake, family history and past history.

II. History of contraception:

Previously and Currently used contra-ceptive methods (IUCD, OC, inject-ables or non-user) and it's duration of use.

III. Full clinical examination with particular attention to extra-articular manifestation of RA, Full joint examination including tender joints count(TJC), swollen joints count (SJC), and deformity.

IV. Laboratory measures: Complete blood count**.** Erythrocyte sedimentation rate (ESR) in mm/ hour. C - reactive protein (CRP). Liver function test: serum alanine transaminases (ALT), aspartate transaminase (AST). Serum creatinine level. Rheumatoid factor (RF). Antibodies to cyclic citrullinated peptides (ACPA).

V. Imaging:

Patients were subjected to plain x-ray on the affected joints to asses' erosions that indicate the level of anatomical damage to the joints, that was assessed by the third visual analogue in rheumatoid arthritis severity scale (RASS).

VI. Disease activity score DAS28 /CRP:

To measure the RA activity[12].

VII. Rheumatoid Arthritis Severity Scale (RASS):

To assess the RA severity. This scale asses disease activity, functional impairment and physical damage by it's three visual analouges[13].

Statistical Analysis:

The data were coded, entered, and analyzed by SPSS program version 20 (statistical package for social sciences) data were summarized as mean ± Standard deviation and percentage. T test was used for comparison of mean of the four groups, A one-way analysis of variance (ANOVA) when comparing between more than two means, Comparisons between quantitative variables were done using the nonparametric Mann-Whitney test. Chi Square for comparison of qualitative data. Pearson's correlation test was used to test relation between two numeric variables Cut off level: P≤ 0.05= Significant (), P≤ 0.001= highly significant (*) P-value >0.05=insignificant

Correlation analysis (using Spearman correlation coefficient) was used to assess the strength of association between two quantitative variables.

RESULTS:

In this Cross-sectional study, we enrolled 50 female patients with RA who were divided into two groups; contraceptive methods users were 40 patients (80%).which was further subdivided into IUCD users were 15 patients (30%), OC users were 13 patients (26%) and injectables users were 12 patients (24%),and non-contraceptive users were 10 patients (20%)

Their age ranged between (26-50) years, with no statistical significant difference between the four groups, the educational state has a statistical significance (P value 0.012) between the four groups, as the injectable users group has the lower educational level in comparison to the other groups, The body mass index (BMI) ranged between (18-35), and menarche age ranged from (9-16) years with no statistical difference between the four groups. past and family history were taken and it was irrelevant to our results.

On clinical assessment, the swollen joint count (SJC) and morning stiffness (M.S) showed no statistical significance between the four groups, while the tender joint count (TJC) shows statistical significance between

the four groups with the highest median in TJC in the IUCD users group followed by the injectable users then OC users then the control group (P value 0.018) **(Table 1)**.

Table (1): Clinical articular manifestations of patients with various contraceptive methods.

Clinical manifestations articular		Control group	IUCD users	Injectables users	Oral contraception	Test value	P-value	Sig.
		No. = 10	No. = 15	No. = 12	No. = 13			
SJC	Median (IQR)	4 (1.5 – 7)	8 (4 – 14)	7.5 (3 – 9)	3 (1 – 14)	2.419	0.490	NS
	Range	1 – 15	1 – 21	0 – 14	1 – 15			
TJC	Median (IQR)	7 (2 – 13)	14 (8 – 17)	12 (6.5 – 15.5)	4 (2 – 6)	10.086	0.018	S
	Range	1 – 20	2 – 33	3 – 30	1 – 20			
M.S min	Median (IQR)	15 (15 – 40)	30 (20 – 50)	30 (17.5 – 60)	15 (12.5 – 20)	6.754	0.080	NS
	Range	10 – 50	10 – 60	10 – 60	10 – 50			

‡: Kruskal Wallis test *IQR: interquartile range, it describes the middle 50% of values when ordered from lowest to highest

On comparing the disease activity DAS28/CRP of RA patients among the four different groups there was a high statistical difference between the four groups with the highest median in the ICUD users group followed by the injectable users then the control group then OC users (P value 0.004) (table 2) (diagram 1)

As for the severity of RA by RASS among the four groups, there was a high statistical difference between them with the highest median score among the injectable users followed by the IUCD users then the control and the OC users (P value 0.002) (table 2) (diagram 2)

Table (2): DAS28/CRP and RASS among the four different groups:

		Control group	IUCD users	Injectables users	Oral Contraception	Test value	P-value	Sig.
		No. = 10	No. = 15	No. = 12	No. = 13			
DAS 28/CRP	Median (IQR)	4.13 (2.81–5.18)	5.85 (4.52–6.78)	5.08 (3.91–6.18)	2.94 (2.37–3.59)	13.535	0.004	HS
	Range	1.84 – 7.18	3.1 – 7.25	2.69 – 7.01	1.85 – 6.55			
RASS	Median (IQR)	60 (30 – 104)	145 (75 – 180)	145 (105– 195)	25 (20 – 55)	14.656	0.002	HS
	Range	15 – 232	17 – 245	20 – 235	10 – 210			

‡: Kruskal Wallis test

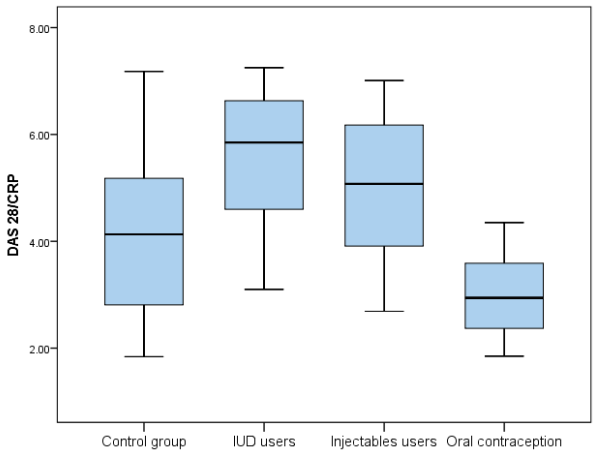

Diagram (1): Shows the DAS28/CRP among the four groups

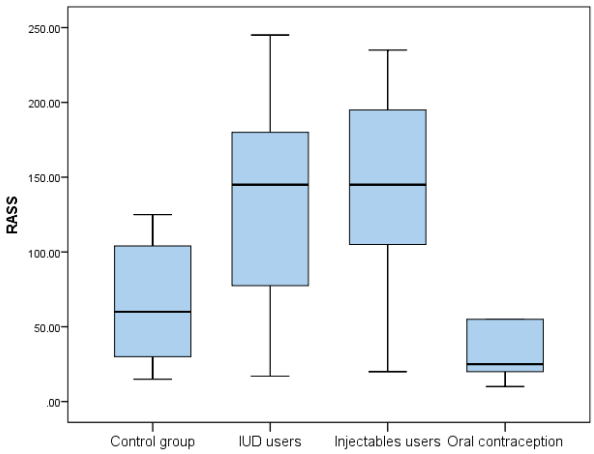

Diagram (2): Shows the RASS among the four groups

Diagram (1): shows that the highest DAS 28\CRP was in the ICUD users group followed by the injectable users then the control group then OC users.

Diagram (2): shows that the highest RASS score was in the injectable users followed by the IUCD users then the control and the OC users

Common expressed clinical extra articular manifestations by the studied patients were subcutaneous nodules, fever, weight loss, thromboembolic manifestations and sicca manifestations, there was no statistical significant difference between the four groups.

As for laboratory data, OC users had the highest total leucocytic count (TLC) in comparison to other groups in overall. The TLC count was significantly higher in OC users compared to IUCD users, erythrocyte sedimentation rate (ESR) was significantly different among the four groups, with the highest median in ESR level in injectables followed by IUCD users then the control group and OC users group. While on comparing between the four groups regarding Rheumatoid factor(RF) there was no statistical difference between the four groups, while C-reactive protein (CRP) had a statistical difference between the four groups (P value 0.038), with the highest median in CRP level in the IUCD users group followed by the injectable users, the control group then OC users.

Also, anticitrullinated peptide antibody (ACPA) titer had a statistical difference between the four groups (P value0.005) with the highest median in ACPA level in the IUCD users group followed by the injectable users, the control group then OC users(as the CRP level) (table 3). Otherwise, there were no statistically significant differences in other laboratory parameters.

Table (3): Laboratory investigations among the four groups.

Laboratory evaluation		Control group	IUD users	Injectables users	Oral contraception	Test value	P-value	Sig.
		No. = 10	No. = 15	No. = 12	No. = 13			
CBC								
HB (gm\dl)	Mean ± SD	11.37 ± 0.77	11.48 ± 1.18	11.28 ± 1.36	12.18 ± 1.29	1.470	0.235	NS
	Range	9.8 – 12.3	9.2 – 13.7	8.9 – 13.3	9.4 – 14.1			
TLC (per mm3)	Mean ± SD	5.35 ± 1.32	6.11 ± 2.32	5.48 ± 2.17	9.18 ± 4.03	5.477	0.003	HS
	Range	3.5 – 7.1	2.1 – 10	3 – 10.5	3.2 – 16.3			
Platelets (per mm3)	Mean ± SD	271.70 ± 55.60	308.87 ± 80.20	302.83 ± 59.52	291.23 ± 97.31	0.523	0.669	NS
	Range	193 – 392	180 – 457	166 – 380	168 – 540			
ESR (mm\h)	Median (IQR)	28.5 (23 – 56)	52 (36 – 78)	53 (37.5 – 68.5)	23 (18 – 28)	10.320	0.016	S
	Range	15 – 142	8 – 156	10 – 110	7 – 98			
Liver function								
SGOT (U\L)	Mean ± SD	21.70 ± 10.37	27.24 ± 10.45	20.92 ± 7.86	19.77 ± 6.71	1.935	0.137	NS
	Range	9 – 38	12 – 47	11 – 38	10 – 37			
SGPT (U\L)	Mean ± SD	21.40 ± 8.50	26.33 ± 11.21	22.50 ± 7.14	18.77 ± 7.15	1.768	0.166	NS
	Range	11 – 34	12 – 48	14 – 35	11 – 35			
S. creatin (mg\dl)	Mean ± SD	0.87 ± 0.21	0.89 ± 0.24	0.82 ± 0.13	0.86 ± 0.28	0.267	0.849	NS
	Range	0.6 – 1.2	0.6 – 1.4	0.6 – 1	0.6 – 1.4			
RF (IU\ml)	Median (IQR) Range	13 (6-16) 2 - 2	6 (4-32) 2 - 139	4.5 (2.65- 8.5) 1 – 160	12 (8-18) 2 – 32	4.338	0.227	NS
CRP (mg\L)	Median (IQR)	4.5 (1 – 9)	23 (8 – 42)	8.2 (4.5 – 23.15)	4 (3 – 11.5)	8.434	0.038	S
	Range	0 – 56	1.7 – 79	1.2 – 128	0.6 – 18			
ACPA (EU\ml)	Median (IQR)	25.5 (8 – 40)	58 (43 – 92)	21 (15 – 42)	7 (2.8 – 46)	12.690	0.005	HS
	Range	1 – 46	13 – 92	0.36 – 180	0.8 – 341			

•: One Way ANOVA test; ‡: Kruskal Wallis test *CBC: complete blood picture *HB: haemoglobin *S.creatnin: serum creatnin *SGOT: serum glutamic-oxaloacetic transaminas *SGPT: serum glutamic pyruvic transaminase

As for DMARD used by patients, 76 % of them were using Methotrexate (MTX), 38 % on Sulfasalazine (SSZ), 30% on leflunomide and 56 % on hydroxyl-chloroquine (HCQ) with no statistical significance between the four groups, corticosteroid was used by 90% of the patients,with statistical difference between the four groups(P value 0.031) as it's more used in IUD users followed by the injectable users (table 4)

Table (4): DMARDs and corticosteroids used by the four groups.

Current treatment		Control group	IUD users	Injectables users	Oral contraception	Test value	P-value	Sig.
		No. = 10	No. = 15	No. = 12	No. = 13			
MTX	No	2 (20.0%)	6 (40.0%)	3 (25.0%)	1 (7.7%)	4.095	0.251	NS
	Yes	8 (80.0%)	9 (60.0%)	9 (75.0%)	12 (92.3%)			
Duration (year)	Median (IQR)	4 (2 – 5)	5 (2 – 7)	6 (4 – 8)	3 (1.5 – 5.5)	3.668	0.300	NS
	Range	1 – 6	1 – 10	2 – 10	1 – 13			
Dose(mg)	Median (IQR)	13.75 (12.5–15)	12.5 (12.5– 15)	12.5 (12.5– 25)	12.5 (12.5–13.75)	1.246	0.742	NS
	Range	12.5 – 25	10 – 25	10 – 25	10 – 25			
Leflunomide	No	8 (80.0%)	9 (60.0%)	9 (75.0%)	9 (69.2%)	1.337	0.720	NS
	Yes	2 (20.0%)	6 (40.0%)	3 (25.0%)	4 (30.8%)			
Duration (year)	Median (IQR)	3.5 (2 – 5)	5.5 (3 – 7)	3 (3 – 4)	2 (2 – 2.5)	5.525	0.137	NS
	Range	2 – 5	2 – 7	3 – 4	2 – 3			
Dose(mg)	Median (IQR)	20 (20 – 20)	20 (20 – 20)	20 (20 – 20)	20 (20 – 20)	0.000	1.000	NS
	Range	20 – 20	20 – 20	20 – 20	20 – 20			
SSZ	No	5 (50.0%)	9 (60.0%)	9 (75.0%)	8 (61.5%)	1.499	0.683	NS
	Yes	5 (50.0%)	6 (40.0%)	3 (25.0%)	5 (38.5%)			
Duration (year)	Median (IQR)	5 (4 – 5)	5 (2 – 5)	6 (1 – 8)	2 (2 – 3)	1.340	0.720	NS
	Range	2 – 5	2 – 7	1 – 8	1 – 10			
Dose(mg)	Median (IQR)	2000 (2000 – 2000)	2000 (1000 – 2000)	2000 (2000– 3000)	2000 (1500–2000)	2.487	0.478	NS
	Range	10002000	1000 – 2000	2000 – 3000	10003000			
HCQ	No	7 (70.0%)	3 (20.0%)	5 (41.7%)	7 (53.8%)	6.788	0.079	NS
	Yes	3 (30.0%)	12 (80.0%)	7 (58.3%)	6 (46.2%)			
Duration (year)	Median (IQR)	2 (1 – 2)	5 (3.5 – 5.5)	4 (3 – 5)	3.5 (2 – 5)	7.415	0.060	NS
	Range	1 – 2	2 – 7	3 – 10	2 – 8			
Dose(mg)	Median (IQR)	400(400– 400)	400(400– 400)	400(400– 400)	400(400– 400)	0.000	1.000	NS
	Range	400 – 400	400 – 400	400 – 400	400 – 400			
Corticosteroids	No	0 (0.0%)	1 (6.7%)	0 (0.0%)	4 (30.8%)	8.860	0.031	S
	Yes	10 (100%)	14 (93.3%)	12 (100%)	9 (69.2%)			
Duration (year)	Median (IQR)	2 (2 – 2)	4.5 (2 – 5)	3 (2 – 4)	2 (2 – 3)	3.747	0.290	NS
	Range	1 – 5	1 – 8	2 – 6	1 – 10			
Dose(mg)	Median (IQR)	5 (5 – 5)	7.5 (5 – 10)	7.5 (5 – 10)	5 (5 – 5)	8.979	0.030	S
	Range	5 – 10	5 – 30	2 – 20	5 – 5			

*: Chi-square test; ‡: Kruskal Wallis test

About 64 % of all patients used IUCD prior to the onset of RA. The median duration of IUCD first use before the onset of RA was 3 years with a range of (2-5) years, and 12% of patients had the onset of RA before the prior use of IUCD while 12% of patients did not use IUCD ever in their lives.

The RA patients who used IUCD prior to the onset of RA had a higher ACPA titers than those with disease onset preceding IUCD use with high statistical significance (table 5).

Table (5): Onset of RA in relation to prior IUCD use.

IUCD	ACPA (EU\ml)		Test value	P-value	Sig.
	Median (IQR)	Range			
No IUCD usage	6.30 (1.80 – 22)	0.36 – 52	11.286	0.004	HS
Start using IUD before RA onset	52 (16 – 92)	2.7 – 341			
RA onset before IUD	16 (16 – 18)	1 – 31			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) ‡: Kruskal Wallis test

On performing a correlation between first exposure of IUCD and DAS 28/CRP and RASS there's no statistically significant correlation between them.

On performing correlation between (DAS 28/CRP, RASS, and ACPA) and patient's demographic data (age, BMI, menarche age, disease duration, there was no significant correlation between them.

On performing a correlation between ACPA and the duration passed since first exposure to IUCD There was a significant positive correlation between them (diagram 3)

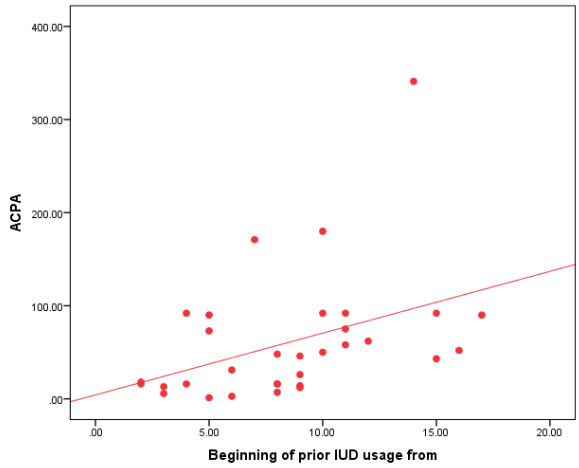

Diagram (3): Scatter figure showing positive correlation between ACPA and the duration passed since first exposure to IUCD

Also,on performing a correlation between the duration passed since first use of IUCD and the disease duration,There was a significant positive correlation between them (i.e. the earlier the first exposure to IUCD the longer the disease duration) (p value 0.015 and r 0.425). (diagram 4) (table 6).

Table (6): Correlation between Disease duration and Beginning of prior IUCD usage from.

Correlation between Disease duration and Beginning of prior IUCD usage	Disease duration	
	r	P-value
Beginning of prior IUCD usage from	0.425*	0.015

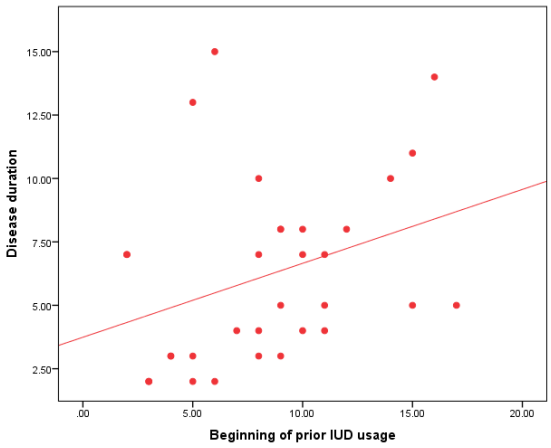

Diagram (4): Scatter figure showing positive correlation between the duration passed since first exposure to IUCD and the disease duration.

DISCUSSION:

We found in our study that there's a relation between RA activity and the currently used contraceptive methods as:

The OCs could decrease the disease activity and severity.

As on studying the four groups we found that the OCs users group had the lowest RASS, DAS28/CRP and ACPA titre and the lowest TJC compared to other methods users, and this go in accordance with Amini and his colleagues[1], that discussed the effect of oral contraception on rheumatoid arthritis disease activity in women, their study showed that the oral contraception users group has a lower TJC than the control group(RA patients with no contraception) with a statistical significant difference. Also in a study of the OCs effect on RA activity[14] revealed that using OCs significantly reduced the clinical manifestations, and Women who are on OCs presented with less morning stiffness and arthritis than the control group. Also he revealed that current users of OCs had significantly low DAS28 scores in comparison to non-users.

Although DAS28\CRP ,RASS and ACPA are low in the OC users,but we found in our results TLC count was significantly higher in OC users compared to the other users (however it was expected that OC users have normal TLC as it's a sign of inflammation and this group has the lowest signs of inflammation), and this goes in accordance with the observations obtained firstly by a research which studied the effect of OCs on the normal leucocytic count[15] and revealed that oral contraceptives increase the neutrophil count, and to a lesser extent the lymphocyte count resulting in higher TLC count than other females not on them[16]. So that this finding is still under investigations to explain this sign.

The IUCD and injectables could increase the severity and activity of RA:

As on studying the four groups, we found that the IUCD users groups had the highest RASS and DAS28/CRP followed by injectable users , while in a study of the relation of RA and the commonly used contraceptive method[17], his results showed that the injectable group had the highest RASS and DAS28/CRP followed by the IUCD users.

Also we found that the IUCD users groups had the highest ACPA titre compared to other methods users, and this go in accordance with a study of the relation of RA and the commonly used contraceptive

method[17] who showed that the RA patients who used IUCD had the highest ACPA titre among the other different contraceptive users.

we found that About 64 % of all patients used IUCD prior to the onset of RA. The median duration of IUCD first use before the onset of RA was 3 years with a range of (2-5) years, moreover, The RA patients who used IUCD prior to the onset of RA had a higher ACPA titers than those with disease onset preceding IUCD use with high statistical significance**,** and this go with the study of American College of Rheumatology (ACR,2014) that shows that Women using IUCD may be at increased risk for producing autoantibodies related to the risk of developing rheumatoid arthritis[7] .

Taken that the IUD might be a potent environmental trigger in susceptible females, by being able to induce chronic subtle renewed tissue injury ending at citrullination at the site of the endometrium prior to onset of RA. So, the choice of contraception may influence rheumatoid arthritis autoimmunity risk, with the biggest risk coming from IUD, whether a cupper IUD(IUCD) or a hormonal IUD[7]**.**

ACPA is considered a predictive antibody to detect individuals at risk for RA. It is also considered as a prognostic factor that is correlated with disease activity parameters. It has been proven that there is a strong correlation between greater disease activity and degree of radiographic damage and anti-CCP positivity[18] and this go in accordance with a study of the relation between the contraceptive factors which associated with serum antibodies and citrullinated protein antigens in women at elevated risk for future rheumatoid arthritis[7], showed that there was an association of an increased risk of ACPA positivity with IUCD use, suggesting avoidance of use in first degree female relatives (who are not RA patients).

As regarding the injectables group, we found in our results that this group had the highest ESR level among the four groups. We explained this by that the DMPA injectables induces ovarian oxidative stress[19] which can promote inflammation in the ovaries leading to pro-inflammatory cytokine secretion (IL-1β and IL-18) and induce the activation of nuclear factor kappa B (NF-κB), a crucial mediator of inflammatory responses which lead to increase ERS level[20].

Also, there's a study of the effect of injectables on bone density[21] which revealed that injectables are associated with a small reduction in bone mineral density due to its hypo-estrogenic effect. This form of contraception is therefore not a first-line choice in people aged under 18 years as there are concerns that it may influence peak bone mineral density[21]. But as we did not investigate bone density in all patients, so we cannot generalize this observation.

Conclusion:

There's a relation between RA activity and the currently used contraceptive methods. As we can conclude the results as follows:

In the IUD users group, we found that this group has the highest disease activity (DAS 28\CRP) ,the highest TJC, and it has the second highest disease severity (RASS score) (injectables users had the highest RASS score),

Also, IUD users has the highest RF, CRP, and ACPA among the four groups.

So, in our results we found that using IUD in RA patients increase disease severity and activity.

While in the OCs users group, we found that this group has the lowest disease activity (DAS 28\CRP), the lowest TJC, and the lowest disease severity(RASS score), even below the non contraceptives users group.

Also, OCs users has the lowest ESR, RF, CRP, and ACPA among the four groups.

So, in our results we found that using OCs in RA patients enhance disease severity and activity even more than RA patients that were not using any contraceptive methods.

As regarding the injectables users group, we found that this group has the second highest disease activity (DAS 28\CRP) after the IUD users, the second highest TJC, and the highest disease severity (RASS score), the highest ESR level.

So, in our results we found that using injectables in RA patients increase disease severity and activity.

So, we summarize our conclusion that the use of IUCD and injectables could increase the severity and activity in RA patients. however, the usage of OCs could decrease the severity and activity in RA patients who are using it.

Recommendations:

We recommend according to our findings that cessation of IUD use in RA patients might improve their current state of disease, but this requires larger scale studies to understand the exact pathogenesis as these differences could be due to other variables that were not studied. The use of IUD in ACPA sero-positive patients should be under strict observation. Future large-scale population- based studies are needed to evaluate the effect of long term contraceptive use in relation to RA activity and severity.

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هل يوجد تأثير فعال لوسائل منع الحمل الشائع استخدامها علي نشاط مرض الروماتويد المفصل

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نبذه عن البحث: التهاب المفاصل الروماتويدي هو مرض التهاب مزمن يتميز بتاكل العظام والغضاريف ، وتسلل الخلايا الليمفاوية إلى النسيج الزليلي ، والإفراط في إنتشار الخلايا الليفية الزليلية ، التي تنتج الإنزيمات والسيتوكينات المسببة للالتهاب ، وهي تعد من اهم اسباب تفاقم المرض . في دراستنا ، نشمل مسألة وسائل منع الحمل لأنها لها أهمية كبيرة في المرضى الذين يعانون من التهاب المفاصل الروماتويدي بسبب حقيقة أن بداية المرض تحدث في كثير من الأحيان خلال سنوات الإنجاب. بالإضافة إلى ذلك ، بعض العقارات المعالجه للمرض مثل ميثوتريكسات ولفلونوميد هي مسببه للعيوب الخلقيه، مما يستلزم وسائل منع حمل عالية الفعالية للإناث اللاتي في فتره النشاط الجنسي.

الهدف من البحث: في هذه الدراسة سوف نستكشف العلاقة بين نشاط التهاب المفاصل الروماتويدي وطرق منع الحمل الشائع ستخدامها في مصر. نحن نهدف إلى سد الثغرات في المعرفة حول اختيار أفضل وسائل منع الحمل (التي يمكن استخدامها من قبل مرضى الروماتويد من الإناث) والتي يمكن أن تحسن درجة نشاط المرض أو على الأقل لا تؤدي الي تدهوره.

طريقه البحث:يتضمن البحث ٥٠ مريضه بالروماتويد المفصلي تم تشخيصهم طبقا للكلية الأمريكية لأمراض الروماتيزم ومعايير تصنيف الاتحاد الأوروبي ضد الروماتيزم و تم تقسيمهم الي مجموعتين , مجموعه لا تستخدم اي من وسائل منع الحمل و مجموعه تستخدم وسيله من وسائل منع الحمل (اللولب, حبوب منع العمل و الحقن) و تم تقييم نشاط المرض عن طريق معدل نشاط المرض ٢٨ علي اساس البروتين (RASS). التفاعلي و مقياس شده المرض

النتائج: ان هناك علاقه بين استخدام وسائل منع الحمل المختلفه و نشاط و حده الروماتويد المفصلي في النساء, حيث ان نتائج البحث لدينا تثبت ان استخدام اللولب و الحقن الهرمونيه تزيد من نسبه نشاط و حده مرض الروماتويد المفصلي, بينما استخدام حبوب منع الحمل تؤدي الي انخفاض شده و حده المرض في مستخدميها .

الخلاصه:بما ان مرضي الروماتويد المفصلي اكثرهم من النساء اللاتي في سن الانجاب ,لذا يجب توخي الحذر في استخدام وسائل منع الحمل المختلفه بسبب تأثيرها القوي علي نشاط و حده الروماتويد المفصلي في مستخدميها.