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Commercial Hormone Replacement Therapy Jeopardized Proinflammatory Factors in Experimental Rat Models

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Abstract

BACKGROUND: Hormonal contraceptive therapy is considered the easiest and most convenient contraceptive method. Commercially, available contraceptive combination differs in their composition and concentration of combined constituents. These variations make some of these products preferred over others by consumers based on their side effects profile.

AIM: The objective of the current research was to ascertain the proinflammatory influences of commercially available products.

METHODS: To do so, five groups of rats (ten rats in each group) were exposed to Microgynon, Depo-Provera, marvel on, and Yasmin compared to the control non-treated group. We measured proinflammatory markers including d-dimer, TNF-α (tumor necrosis factor-alpha), IL (interleukin)-6, IL (interleukin)-1B, and c-reactive protein.

RESULTS: The results confirmed that Yasmin has induced the most deleterious effects on proinflammatory markers indicated by significant elevation of IL1B.

CONCLUSION: Hormone replacement therapy should be critically indicated and precautions raised inpatient with subclinical diseases, especially cardiovascular ones.

Introduction

Estrogen therapy during the postmenopausal increases the hepatic production of C-Reactive Protein (CRP) [1], and the representation of IL-6 increases and plays an inflammatory role [2]. It has illustrated the contrary results for Estradiol [3], [4] used in postmenopause. Bestowing to an earlier conducted study progesterone increases the sequel of experimental stroke [5]; however, an alternative study clarifies that progestins resolve "oxidative stress" and relegates generating of IL-6 and TNF-α [6].

In the western world, vascular diseases are a huge health care burden and a considerable increase in aging is observed [7]. This risk is increased only in women alongside aging without caring about the well-known sex difference in cardiovascular diseases [8], [9]. The postmenopausal decrease in ovarian hormones can also be a contributing factor, which can have an impact on many tissues alongside vasculature [7], [10]. The beneficial effect of estrogen on "cerebrovascular function" has constantly been shown in observational studies and experimental animal research [10]. However, a large number of "randomized clinical trials" raised questions about the benefits of "hormone-replacement therapy (HRT)," and in fact, they detect an increase in stroke [11], [12], [13].

These diversified verdicts played a role to mention the necessity for improved comprehension of vascular actions of "ovarian hormones" alongside the understanding of "medroxyprogesterone acetate (MPA)"; a "synthetic analogue of progesterone." It is usually instructed to use in a mixture with estrogen for the treatment of "perimenopausal symptoms." Having benefits, MPA also has some back draws. According to some studies, MPA can also withstand the favorable influences of "estrogen on cardiovascular" functions and operations [14], [15], [16]. Talking about example, MPA has positive effects on estrogen biomedical metabolism, vasculature system, and advancement of atherosclerosis [14].

The pathogenesis of "cerebral ischemia" [17] is mainly caused by "cerebrovascular inflammation" [18]. The induction of promotion of inflammation mediators alongside the inclusion of inducible nitric oxide synthase and cyclooxygenase [19], [20] is the lead process in "cerebrovascular inflammation." Cyclooxygenase is upregulated during cerebral ischemia which results in the generation of prostanoids, such as PGE2, and are considered to be harmful to stroke outcomes [21]. After cerebral ischemic injury [22] expression of iNOS is increased and its peak is shown in 24–48 h. No production is thought to have either beneficial or detrimental effects following ischemia, quantities are produced and the stage of "evolution of cerebral injury" [22], [23] depends on the cellular compartment.

Estrogen has constructive influences on paradigms of cardiovascular damage [10] according to experimental animal studies. While effects of progestogens "cerebrovascular inflammation" are still unknown. To answer this question, rat models were used in the *in vivo* progestogen treatment, which is just a reflection of known clinical blood levels [24], [25]. During the process, the unpredicted unfavorable effects of combined HRT on stroke were seen [26], and researchers hypnotized that progestogens, progesterone, or MPA, undo the influences of estrogen on inflammation. They also hypnotized the normal alteration in "endogenous estrogen" and progesterone and that caused alteration in cerebrovascular inflammation throughout the estrous cycle.

To begin, a lot of controversies exist about using progesterone in systematic inflammation. To check the different effects of "estradiol and progesterone" on the "inflammatory and apoptotic responses" in rat models using commercially available estrogen-progesterone combination products, the present study was created.

Materials and Methods

A total of 50 healthy female "Wistar albino rats" (age 10–12 weeks; weight 200–260 g) were collected from the "animal house of Medical Research Institute in University of Mosul," the period of the study ranges from January 1, 2020, to December 1, 2020. Animals were endorsed in the "animal house of Mosul University" and were avowed under meticulous settings of temperature (24 ± 2°C), "light-dark periods" of 12 h, and free access to water and commercial diet [27], [28]. The "international guiding principles" for biomedical research involving animals were adopted. The animals were administered a 4-week adaptation period after they were located in their new environment. The animals were divided into five groups, ten rats each: Control group, Microgynon® group, Depo-Provera group, Marvelon group, Yasmin® group. The dose administration is listed in Table 1.

Blood samples were withdrawn from all groups initially at baseline, after 4 weeks of therapy, and after 8 weeks of therapy. The serum was collected and stored frozen at –20 until ready for further analysis. The collected samples were then subjected to measurement of tested parameters using sandwich ELISA techniques based on kits supplied by Elabscience (USA). The assay procedure started with the addition of diluted standard and sample to a precoated 96-well plate with a rat capture antibody specific to the tested parameter (whose catalogue numbers are CRP [E-EL-R0506], IL1B [E-EL-R0012], IL6 [E-EL-R0015], TNF-a [E-EL-R2856], and D-dimer [E-EL-R0317]). After an incubation period of 2 h, the content of the plate was removed and washed with previously prepared washing buffer provided by the supplier; then, a 100 ml of biotinylated detection antibody was added to each well and incubated for further an hour before the addition of horseradish peroxidase to initiate enzymatic reaction producing blue-colored solution with the detection antibody, an action which has been terminated by addition of stop solution turning the solution to yellow color which has been quantified at an optical density of 450 nm.

Results

Following biochemical analysis of serum samples; data were collected and statistically analysed. The results of samples were statistically analyzed and a comparison was conducted between Microgynon, Depo-Provera, Marvelon, and Yasmin group compared to the control group (Figure 1).

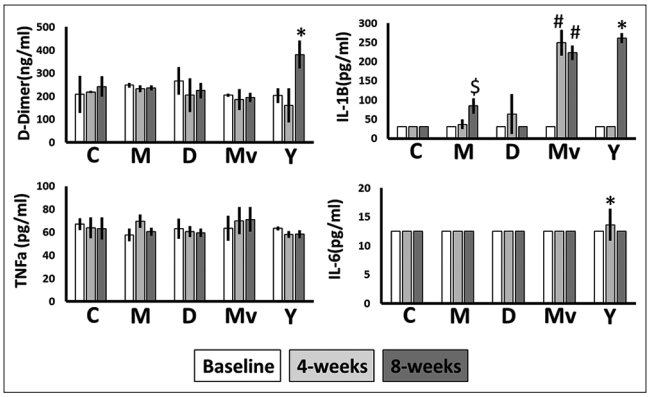

*Figure 1: Hormonal upset in rats treated by commercially available contraceptive medicines; Microgynon (M), Depo-Provera (D), Marvelon (Mv), and Yasmin (Y). Data expressed as mean ± SD. *p < 0.05 Yasmin compared to baseline, #p < 0.05 Marvelon compared to baseline, and $p < 0.05 Microgynon compared to baseline*

Regarding CRP and D-dimer, as a as a predictor of infectious and metabolic diseases; a non-consistent outcome was reported since all studied groups show the same level of CRP (0.16 ng/ml) which is considered a normal level, while, regarding D-dimer levels (ng/ml), non-significant differences exist between all studied groups (levels are approximate to 200 ng/ml) except for the Yasmin group at 8-week time point, where the level shows significant ($p < 0.05$) elevation to reach

Table 1: Specification of used drugs

Trade name	Composition		Manufacturer (origin)	Administration and dosing schedules
	Progestin	Estrogen		
Microgynon pills	Levonorgestrel (0.15 mg/kg)	Ethinylestradiol (0.03 mg/kg)	Bayer (Germany)	Orally for 4 days; 1 day break for 8 weeks
Depo-Provera injection	Medroxyprogesterone (3.5 mg/rat)		Pfizer (USA)	I.M.; once weekly for 8 weeks
Marvelon pills	Desogestrel (0.15 mg/kg)	Ethinylestradiol (0.03 mg/kg)	MSD (USA)	Orally for 4 days; 1 day break for 8 weeks
Yasmin pills	Drospirenone (0.5 mg/kg)	Ethinylestradiol (0.03 mg/kg)	Bayer (Germany)	Orally for 4 days; 1 day break for 8 weeks)

380.6 ± 19 compared to control or other groups at same time points.

Regarding IL-1B levels (pg/ml), non-significant differences exist between baseline and week-4 timepoints in all studied groups (levels are approximate 200ng/ml) except for Marvelon which showed significant differences at week-4. However, at week-8 timepoints, all studied groups show significantly higher IL-1B levels compared to baseline except for Depo-Provera which showed non-significant differences with baseline levels.

Regarding TNFa levels (pg/ml), non-significant differences exist between baseline and week-4 or week-8 timepoints in all studied groups (levels are approximate 60pg/ml) except for Marvelon which showed slight non-significant elevation differences at week-4 and week-8 timepoints compared with baseline levels.

Regarding IL-6 levels (pg/ml), non-significant differences exist between baseline and week-4 or week-8 timepoints in all studied groups (levels are approximate to 12.5 pg/ml) except for Yasmin which showed significant differences at week-4 compared to baseline which soon returned to baseline at week-8.

Discussion

The present study confirmed that hormonal replacement therapy carries a proinflammatory risk. The study findings support this statement as confirmed by measured proinflammatory markers. However, there have been discrepancies in the outcomes when these commercial products are compared to each other. Compared to 4 weeks, the proinflammatory defection was more obvious at 8-weeks, if any. Yasmin pills have shown the most deleterious defect compared to Microgynon, Marvelon, and Depo-Provera. Yasmin induced significantly higher D-dimer and IL-6. Surprisingly, Yasmin-induced IL-6 elevation was acute since the elevation was obvious in 4 weeks, and the level reduced to baseline after 8 weeks. This effect interestingly might confirm that tolerance to Yasmin-IL-6 proinflammatory effects might be produced. Yasmin induced significantly higher proinflammatory status, indicated by higher IL-6 at week 4 and elevated IL-1B, and D-dimer at week-8. The second deleterious agent was Marvelon; which was associated with increased IL1B whether during the first 4-week or in 8-week time points.

Obvious changes were seen after the treatment which continued for 4 weeks [29] and before that, two large “observational studies” [30], [31] and two clinical trials [29], [32] “significant elevations” in CRP in women who are taking replacement therapy (48–260% higher than in non-users). CRP hepatic formation is chiefly conducted for the promotion of inflammation cytokine IL-6 [1]. Elevated levels of CRP are possibly linked with cardiovascular events in healthy subjects [33], [34], [35], [36], [37] and also in the subjects with established vascular disease [34], [35], [38], [39].

HRT was considered an increase in CRP caused by “systematic inflammation,” but it was the cause of direct hepatic passing of oral estrogen [38]. In evidential form, they showed that plasma IL-6 levels were quite similar in the estrogen users and in the non-user women who were CHD free or in the individuals whose CHD eventually developed [40]. The plasma levels of CRP and IL-6 in obese women are increased by HRT, and it was a random study illustrated by Herrington *et al.* [41]. Along with it, Brooks-Asplund *et al.* [2] reported that “mononuclear cell-derived tumor necrosis factor-a and IL-6” secretion is increased by HRT.

Reduction of “TNF-α expression by progesterone” in a rat model of brain injury was reported by Jiang *et al.* [42], where conflicted data with the findings of researchers were also observed. At the same time, Roof *et al.* [43] revealed that the “membrane-stabilizing effect” can also reduce oxidative stress by progesterone. Estradiol reduces the “TNF-α expression” in female rats managed with “a combination of progesterone and estradiol” [44] and estradiol also protects the CNS against neurotoxic stimuli. However, this finding contradicts the finding of our research, which highlighted the anti-inflammatory role of estradiol [45], possibly through immune cell-intrinsic estrogen receptors (EPα and EPβ) as indicated by estrogen receptors expressed by microglial cells [46].

Conclusion

The outcome confirmed that sex hormone medicines has jeopardized the proinflammatory marker, showing variation between the outcome when different brands were used. Yasmin has the utmost deleterious outcome compared to others while Depo-Provera was the safest product. A clinical trial is advised to be conducted to translate these effects into a human using different brands of commercially available treatment options.

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