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RESEARCH PAPER

Immunological Status of Pregnant Women in Different Trimesters

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A B S T R A C T:

During pregnancy, disease activity usually improves, but only to a lesser extent than previously thought. Pregnancy outcomes are also hampered, particularly in women with high disease activity. Early pregnancy causes an increase in oxidative stress due to the placenta's high metabolic rate, which causes an increase in ROS production. Placental progesterone also increases blood lipids and malondialdehyde levels (MDA). The lipid peroxidation (LPO) process begins when ROS interact with polyunsaturated fatty acids in membranes or lipoproteins. This investigation is done to evaluate the immunological status of pregnant women in different trimesters during pregnancy. After performing inclusion and exclusion criteria, this study included 40 pregnant women and 40 healthy women who had married but were not pregnant as a control group. The serum was obtained from pregnant women in three different trimesters and from control group. Interferon γ (IFN-γ), Immunoglobulin-G (IgG) IgA, Rheumatoid factor (RF) and Malondialdehyde (MDA) were measured. The results demonstrate a statistically significant reduction in IFN-γ with respect to the 2nd and 3rd trimesters in comparison to the control group, with no significant change between the control and 1st trimester and a statistical decrease in the 3rd trimester when compared to the 1st trimester. Regarding the total IgG, the result showed a significant decline in the level of IgG in the 1st trimester in comparison to the control group. At the same time, there is a significant elevation in the level of IgG in the 3rd trimester compared to the 2nd trimester. However, there is a significant increase of IgA in the 2nd trimester in comparison to the control group. Meanwhile, its level decreases in the 3rd trimester in comparison to 1st and 2nd trimesters. RF increased significantly in the 1st and 2nd trimesters in comparison to the control group, but statistically, there is a significant decrease in 3rd trimester compared to the 1st and 2nd trimesters. Finally, the level of MDA increases in all trimesters compared to the control group.

KEYWORDS: IFN- γ, IgG, IgA, Rheumatoid factor, Malondialdehyde.
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1. INTRODUCTION:

Pregnancy causes considerable alterations to the immune system to defend the mother and the embryo against disease while preventing detrimental immune reactions to the allogeneic fetus. Despite the few evidence suggesting that a woman's immunity is generally suppressed in pregnancy, higher risks of getting particular illnesses indicate to significant qualitative immunological changes (Amino et al., 1978; Kourtis et al., 2014).

Understanding how particular immunological, physiological, endocrinological, and aspects increase the chance of infection requires significant thought because of the intricacy and special situations that surround a typical pregnancy. For instance, due to changes in the circulatory system and decreased functional residual lung capacity as a result of elevated abdominal pressure during pregnancy, urinary tract infections may be more frequent and pneumonia may be more severe (Schnarr & Smaill, 2008; Sheffield & Cunningham, 2009).

The broad family of glycoproteins known as cytokines includes the interferons (also known as IFNs). As the first line of defense against

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infections and some tumours, host cells release these substances. IFNs have a major impact on cell differentiation and proliferation and are essential for the immune system to function properly. The higher IFN levels have been linked to miscarriage. particularly IFN-γ. Nevertheless, because it contributes to preserving the decidual layer and uterine vasculature remodeling, this cytokine is essential for successful murine pregnancies (Micallef *et al.*, 2014).

Negative role: Human trophoblast cells are harmed by IFN-γ *in vitro* (Yui *et al.*, 1994) and inhibit trophoblast cell growth (Berkowitz *et al.*, 1988). The capacity of IFN to suppress renin secretion causes a reduction in angiotensin through the renin-angiotensin system. Angiotensin II stimulates the formation of the blood vessel, so if IFN-γ starts releasing is dramatically increased, angiogenesis and vessel maturation of the uteroplacental unit may be harmed (Jikihara *et al.*, 1996).

Positive role: According to investigations, this cytokine is essential for human pregnancies. During pregnancy, IFNGR1 and R2 are both expressed by trophoblast cells (Banerjee *et al.*, 2005). Similar to mouse NK cells, human uterine NK cell secretes IFN-γ (Banerjee *et al.*, 2005). IFN-γ, as well as being partly has role in generating a polarized environment in the endometrial, increases major histocompatibility complex (MHC I and II) expression in endometrium. (Tabibzadeh, 1994). Cells of trophoblast have no polymorphic MHC II genes, unlike endometrium. It is thought that this will diminish rejection reactions to the developing embryo. (Hunt, 2006).

The production of antibodies (Abs), specifically IgG, is necessary for transplacental transfer to the baby during pregnancy, giving the newborn resistant to infection for the beginning few months of life. Different immunological issues with links to autoimmune Ab production and Ab functions must continue receiving treatment while pregnant (Malek, 2013).

Maternal and fetal infections are among the major causes of mortality and morbidity in pregnancy. Since the fetus' immune systems are still developing, immunological resistance is given during pregnancy and is reliant on the maternal- to fetal placental supply of maternal Abs, which are transported and inter to the fetal blood via mother's blood. During the second half of pregnancy, only IgG with exponential profiles can transmit Abs to the fetal tissue(Malek *et al.*, 1996; Malek *et al.*, 1994). Although IgA accounts for just 10 to 15% of total Ab in blood, it is the most prominent Ab type in bodies fluids like breast milk, saliva, tears, and mucus of the urogenital, respiratory tract and intestinal tracts. The secretory IgA is found in secretions as a dimer that bind together by J-chain and have a secretory piece. The secretory piece comes from the receptor that transports dimer IgA through cell membranes (Punt *et al.*, 2022).

Rheumatoid arthritis (RA), an autoimmune disease, is exceedingly complex. It is assumed to begin with a Th1-type reaction, which induces immune cells to damage the joint(Müller-Ladner *et al.*, 2007). RA is frequent in women of age of childbearing. Women with RA have decreased fertility as a result of taking specific drugs and having the disease. Even while RA frequently gets better when a woman is pregnant, during the 3rd trimester, the disease is still active in more than half of the patients. Pregnancy rates are somewhat less favorable, notably in women with severe disease (Smeele & Dolhain, 2019).

When the oxidative-reductive state of cells is out of balance, oxidative stress, a complicated pathophysiological mechanism, results, which can lead to a number of clinical diseases (Bogavac *et al.*, 2012). Apoptosis and necrosis are two further outcomes of lipid peroxidation, which begins with the oxidation process of structural lipids in cell membranes or cellular components. Free radicals initiate this process, which results in secondary free radical generation. These free radicals then participate in a cascade of chain reactions with other compounds to increase the oxidative damage (Đukić *et al.*, 2008).

The current work attempted to explore the change in immunity of pregnant women in different trimesters, which is represented by IFN-γ, total IgG, IgA, RF, and MDA.

2.MATERIALS AND METHODS

2.1. MATERIALS

2.1.1 Patient and sample collection:

The study sample was collected from maternity teaching hospital in Erbil. The Human Ethics Committee of Salahaddin University-College of Science gave its approval to the current investigation (No. 4S/70; Date,15/5/2021; Erbil, Iraq) and it was done in accordance with the principles of Declaration of Helsinki. Blood samples were obtained from forty healthy pregnant women aged between (18-28) years and forty healthy women who had married but were not pregnant aged between (20-28) years. This work was done between July 2021to June 2022

2.1.2 Blood sample collection

The blood was drawn from pregnant women in each trimester of the pregnancy into a 5 ml syringe tube, as well as from a control group. The blood was then placed to a non-heparinized gel tube and sent immediately to the lab where it was centrifuged at 5000 rpm for 10 min. Serum samples were collected and stored in Eppendorf tube at -80 ºC until the time of assay.

2.2 Determination of Interferon-γ, total IgG, IgA and Rheumatoid factor

The serum concentration of IFN-γ, total IgG, IgA and RF were measured using Human Interferon-γ (IFN-γ) Enzyme Linked Immunosorbent Assay (ELISA) Kit (cat. No. E-EL-H0108), Human IgG ELISA Kit (cat. No. E-EL-H0169) and Human IgA ELISA Kit (cat. No. E-EL-H0169) (Elabscience, Inc), and human RF ELISA Kit (cat. No. MBS1616420) (Mybiosource) respectively, using the principle of Sandwich-ELISA.

2.3 Determination of Malondialdehyde

The serum MDA levels were calculated using Kartha and Krishnamurthy's methodology. Using a spectrophotometer and a thiobarbituric acid (TBA) solution, MDA was quantified. briefly, 150 µl of serum received 1 ml of 17.5% trichloroacetic acid (TCA) and 1 ml of 0.66% TBA, were thoroughly mixed using a vortex, heated in water bath for 15 min. in boiling water, cooled at 25Cº. One ml of 70% TCA was added, after 20 min. of standing at room temperature, the mixture was centrifuged for 15 min. at 2000 rpm to separate the supernatant, then analyzed at 532 nm by spectrophotometer (D'souza *et al.*, 2012).

2.4. Statistical Analysis

The statistical analysis was performed using GraphPad Prism 8.0.1 software (GraphPad Software, Inc.). D'Agostino & Pearson test, and Shapiro-Wilk test were applied to determine normality and lognormality. Because the data did not pass the normality test, statistical differences were determined using the Kruskal-Walli test. The data was expressed as median and interquartile range, and the level of significance was set at $P<0.05$.

3.RESULTS AND DISCUSSION

3.1. Serum interferon- γ (IFN-γ)

The level of IFN-γ in 1st, 2nd, and 3rd trimesters were (median, 18.04, 14.24, and 10.64 respectively compared to control group median, 20.84). the results show significant decreasing in 2nd and 3rd trimesters comparing to control group, while there was no statistical change between control with 1st trimester, meanwhile there is a significant decreasing in the 3rd trimester in comparison to 1st trimester. (Table 1, Fig. 1).

Table1 Serum level of IFN- γ, total IgG, total IgA, RF and MDA in control and pregnant women in different trimesters. Median (interquartile range)

Groups	IFN-γ (pg/ml)	IgG (mg/dl)	IgA (mg/dl)	RF (IU/ml)	MDA (mmol/L)
Control	20.84 (17.44-71.04)	1252 (1011-1747)	231.50 (69.70-277.3)	42.70 (35.78-48.75)	2.86 (2.60-3.11)
1st trimester	18.04 (15.40-53.84)	897.50 (526.50 -1380)	242.60 (209.70-277.30)	74.90 (63.45-82.80)	3.78 (2.60-6.47)
2nd trimester	14.24 (11.44-17.84)	754.80 (300.10 - 1294)	277.30 (220.50-460.90)	54.89 (48.22-62.20)	3.95 (3.19-5.88)
3rd trimester	10.64 (8.24-15.04)	2944 (526.70 - 2944)	148.70 (111.70-177.50)	47.95 (40.62-53.65)	4.58 (3.02-5.21)

3.2. Serum Total IgG

The concentration of IgG in 1st, 2nd, and 3rd trimesters were (median, 897.50, 754.80, and 2944 respectively compared to control group median, 1252). There was significant decline in IgG concentration in 1st and 2nd trimesters

comparing to control group, meanwhile the IgG level ameliorates in 3rd trimesters with no significant change in comparison to control group. Although, the IgG level highly significantly elevated in 3rd trimester comparing to 2nd trimester (Table 1, Fig. 2).

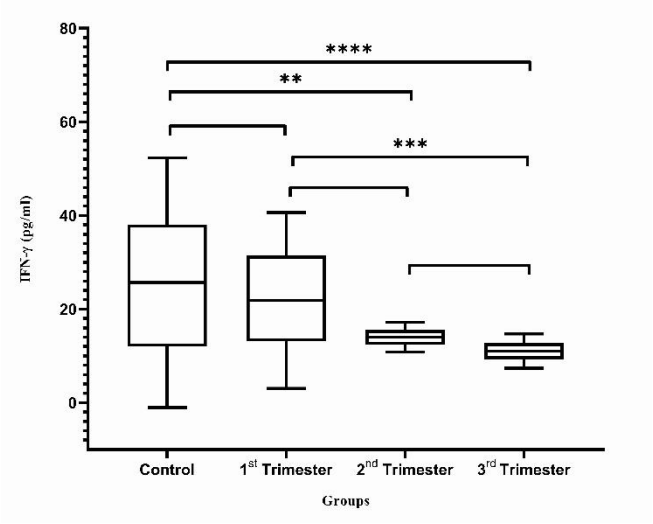

Figure 1 Serum level of IFN- γ in control and pregnant women in different trimesters.

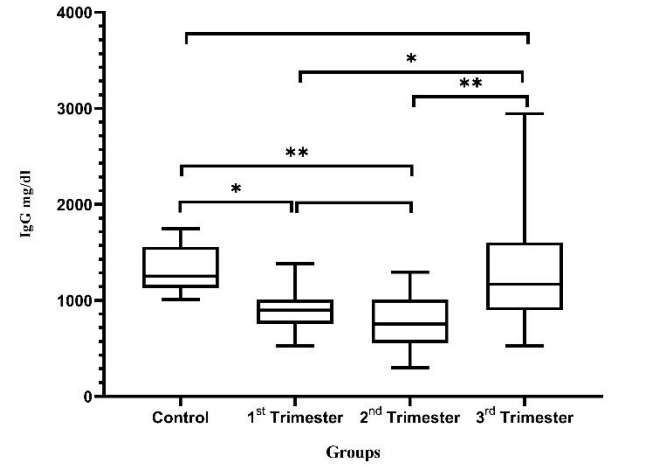

Figure 2 Serum level of Total IgG in control and pregnant women in different trimesters.

3.3. Serum Total IgA

The concentration of IgA in 1st, 2nd, and 3rd trimesters were (median, 242.60, 277.30, and 148.70 respectively compared to control group median, 231.50). Statistically there is only significant increase in 2nd trimester comparing to control group and its level were decreased significantly in 3rd trimester comparing to 1st and 2nd trimesters (Table 1, Fig. 3).

3.4. Serum Rheumatoid factor (RF)

The concentration of RF in 1st, 2nd, and 3rd trimesters were (median, 74.90, 54.89, and 47.95 respectively compared to control group median, 42.70). Depending on the result, the level of RF significantly increases in 1st and 2nd trimesters comparing to control group, while there is no significant change in 3rd trimester comparing to control group, and it seems that the level of RF significantly decreased in 3rd trimester in comparison to 1st and 2nd trimesters (Table 1, Fig. 4).

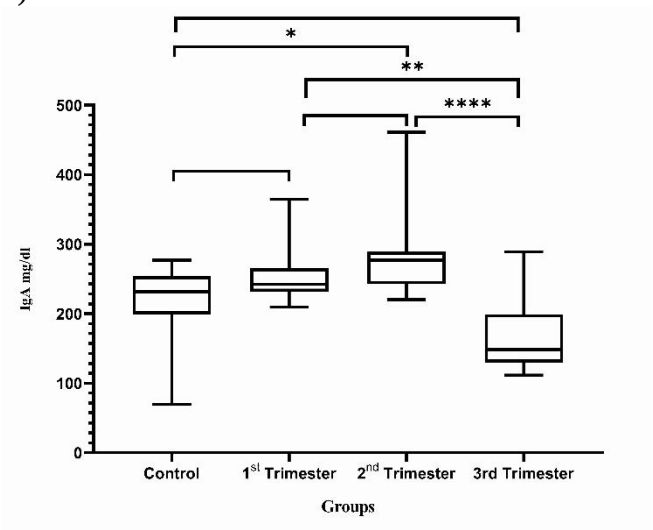

Figure 3 Serum level of Total IgA in control and pregnant women in different trimesters.

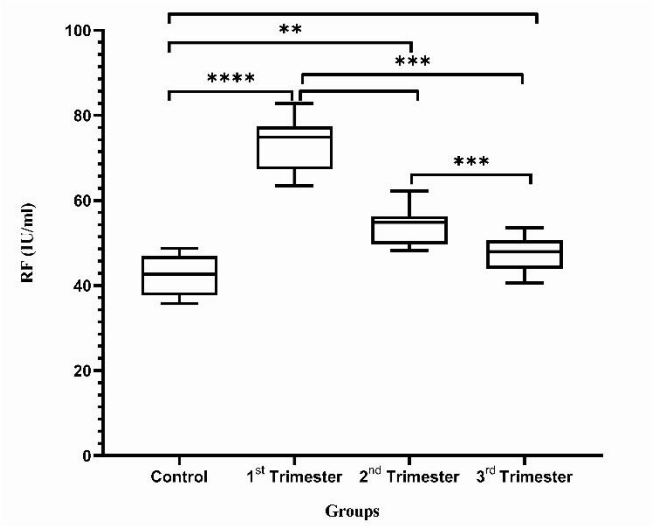

Figure 4 Serum level of Rheumatoid Factor in control and pregnant women in different trimesters.

3.5. Serum Malondialdehyde (MDA)

The concentration of MDA in 1st, 2nd, and 3rd trimesters were (median, 3.78, 3.95, and 4.58 respectively compared to control group median, 2.86). It is clear from the result that statistically

the level of MDA in all three trimesters comparing to control group significantly elevated (Table 1, Fig. 5).

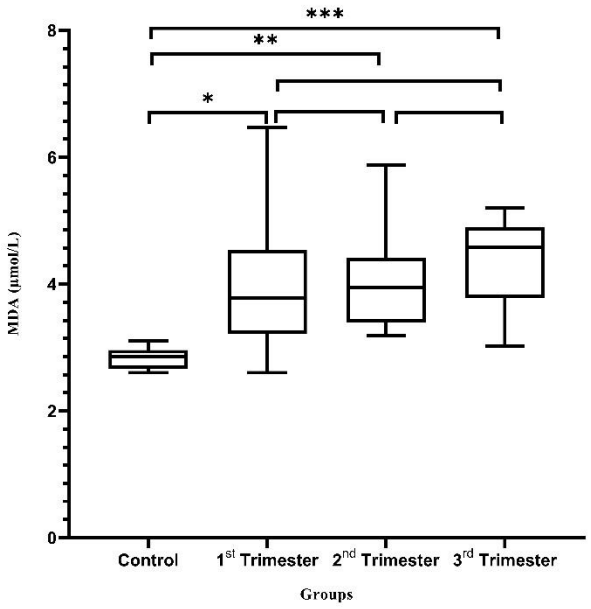

Figure 5 Serum level of MDA in control and pregnant women in different trimesters.

4.Discussion

During pregnancy, A combination of physiological and immunological alterations enhance both the risk and severity of several diseases. To comprehend how the mother's immunity maintains tolerance toward the fetus, it is important to characterize the mother's immune system during pregnancy. During pregnancy, the mother's immune system encounters major alterations so as to defend the mother and her baby against disease while preventing unwanted immune response to the allogeneic fetus. Although there is minimal proof that the mother's immunity system is weakened generally at pregnancy, significant qualitative immunological alterations are associated with rising disease risks (Abu-Raya *et al.*, 2020).

Lipopolysaccharide (LPS)-activating interleukin (IL-12) and tumour necrosis factor-α (TNF-α) production by macrophage was reduced in 3rd trimester women in comparison to non-pregnant controls.(Ziegler *et al.*, 2018), Furthermore, because IL-12 is important in increasing IFN-γ so level of IFN-γ in pregnant women decreased. (Tominaga *et al.*, 2000), Additionally, Borzychowski *et al.* reported that (NK) cells, a source of IFN-γ production, were lower in 3rdtrimester pregnant women compared to healthy controls. (Borzychowski *et al.*, 2005), and this supports the current study's finding that the IFN-γ was decreased in the 3rd trimester in comparison to the control.

Interferon-γ (IFN-γ) is a cytokine that is produced by T-helper 1 (Th1)(Bradley *et al.*, 1996), meanwhile hormones have role in influence the Th cells differentiation (Pazos *et al.*, 2012). Th1 responses are promoted by low levels of estrogen, however ,high estrogen concentration promote responses of Th2. (Kourtis *et al.*, 2014). During pregnancy, increasing progesterone decreases Th1 responses.(Piccinni *et al.*, 1995) and it has role in inducing cytokines of Th2 cells (IL-4 and IL-5) (Piccinni *et al.*, 2000) .

The most important maternal immunological response for protecting the child soon after birth is maternal Ig (D. Muzzio *et al.*, 2013). It has been demonstrated that in the 1st trimester of pregnancy, the majority of women are found to produce non-cytotoxic Ab produced by the mother's B cells that are directed against the paternal antigens, whereas the vast majority of women who have spontaneous abortions do not. This suggests that these Abs might be essential for a healthy pregnancy (Power *et al.*, 1983).

Studies conducted in the 1960s-1970s produced contradictory findings on the levels of Ab during pregnancy, some researchers indicate that total IgG levels stay steady during pregnancy (Best *et al.*, 1969; Mendenhall, 1970), whereas other researchers show that IgG levels decline in late gestation (Amino *et al.*, 1978; Larsson *et al.*, 2008; Lima *et al.*, 2019). But Amino *et al.*, demonstrated that the level of IgG and IgA considerably decreased in the first two trimesters compared to the non-pregnant group which is somewhat agree with the findings of this investigation. Pazos *et al.*, found in their study that there is a decreased in circulating of B cells during 3rd trimester (Pazos *et al.*, 2012), because of the effect of the increasing level of estrogens on lymphocyte formation (D. O. Muzzio *et al.*, 2014). This decrease in B cells is explained by cellular movement to tissues, such as the placental decidua, and shows that B cells are crucial for

sustaining tolerance at the mother and embryo interaction (Hussein *et al.*, 2009).

Total Ab levels may drop in pregnancy for a variety of reasons, including decreased cell-mediated immunity, protein loss in urine, hemodilution, IgG transfer from the mother to the fetus, or hormones, particularly steroids that affect protein synthesis (Pitcher-Wilmott *et al.*, 1980; Tandon *et al.*, 1984). The low Ig levels might be explained by hemodilution because of increasing of intravascular volume throughout pregnancy. While some evidence suggests that the levels of IgA do not significantly change during pregnancy (Larsson *et al.*, 2008; Lima *et al.*, 2019; Mendenhall, 1970), these results are compatible with the present study specifically in 1st and 3rd trimesters.

Pregnancy and inflammatory arthritis have long been a topic of discussion, with early data from the 19th century suggesting a positive response in RA. (Straub *et al.*, 2005). More specifically, study has revealed a threat of a postpartum flare while disease progression improves in up to 90% of pregnant RA patients. (Hazes *et al.*, 2011).

Vitamin D has been shown to modulate immune system cells, notably T lymphocytes. It was demonstrated that the production of IL-1, IL-6, and TNF-α in synovial tissue macrophages is inhibited by vitamin D (Cyprian *et al.*, 2019). Considering that pregnant women frequently lack vitamin D. Therefore, It has been suggested that a lack of vitamin D may increasing chance of developing RA (Grazio *et al.*, 2015; Kerr *et al.*, 2011), and this is compatible with results of the present study which shows increasing in RF in pregnant women in comparison to control group.

Pregnancy is a condition full of stress marked by increase in energetic and oxygen demands for fetal growth and development(Mutinati *et al.*, 2013). Because of the increased requirement for tissue oxygen during pregnancy, the level of oxidative stress rises, which can be characterized as a situation when the mechanisms of detoxification are imbalanced with the levels of reactive oxygen species (ROS). (Closa & Folch-Puy, 2004). Since MDA is a lipid peroxidation byproduct and is stable, it can be utilized as a reliable indicator of the level of tissue damage by free radical (Singh *et al.*, 2020). The result of the present study is in accordance with other studies who showed that the level of MDA increases in pregnant women in comparison to the control group (Patil *et al.*, 2007; Toescu *et al.*, 2002; Upadhyaya *et al.*, 2005).

Early pregnancy is characterized by anabolic processes and a rise in insulin sensitivity, whereas late pregnancy is characterized by catabolic processes and an increase in insulin resistance, which reduces the amount of unsaturated fatty acids and level of glucose that are available to the fetus. (Weissgerber & Wolfe, 2006). With a higher gestational age of pregnancy, increased free radicals of unsaturated fatty acids may lead to a more pronounced oxidative stress. (Karthikeyan & Rani, 2003).

Neutrophils are use glycolysis to produce energy and keep oxygen for the generation of ROS by the mitochondria. Hexose monophosphate shunt metabolism of glucose creates NADPH for the oxidative burst in order to meet their metabolic needs. The fact that certain metabolic enzymes are transported retrogradely to centrosomes in the neutrophils of pregnant women suggests that metabolic upregulation is actively prevented: Although glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase are still active in pregnant neutrophils, and the activity is limited to the cytoplasm, which lowers the metabolic production (Kindzelskii *et al.*, 2002; Kindzelskii *et al.*, 2004). This could help to explain why pregnant women's *in vitro* activated neutrophils exhibit reduced respiratory burst activity (Crocker *et al.*, 2000; Kindzelskii *et al.*, 2004; Naccasha *et al.*, 2001). Generally, these investigations which done *in vitro* show that neutrophil activity increases at resting stage, but its activity decreases after pregnancy.

Apparently conflicting observations of neutrophil activity during pregnancy may be explained by the difference between resting and active neutrophils. The increasing of neutrophil activation in pregnancy may be explained by a more efficient cell membrane surface localization

of myeloperoxidase after stimulation. Without the requirement for re-stimulation, Constancy of cell surface expressing in pregnancy may result in formation of ROS(Kindzelskii *et al.*, 2006)

5.CONCLUSIONS

The results of the present investigation demonstrated that, when IFN-γ and IgG levels decrease, the immune response during pregnancy shifted toward an anti-inflammatory response. RA risk increased in the 1st and 2nd trimesters. Free radical levels increased, though, and these might make pregnant women more susceptible to certain inflammatory conditions.

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