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Comparison of pan-immune inflammation value, systemic inflammatory response index and systemic immune inflammation index in singleton and twin pregnancies: A retrospective cohort study

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Abstract

Aim: To evaluate Pan-immune inflammation value (PIV), Systemic inflammatory response index (SIRI) and Systemic immune inflammation index (SII) for the comparison of twin pregnancies with singleton pregnancies.

Materials and Methods: The cohort study was conducted retrospectively in the Ankara Etlik City Hospital Obstetrics and Perinatology Clinics between October 2022 and August 2024. Women with singleton pregnancies whose follow-up and delivery took place in the same tertiary center were included in the control group (Group I). Women with twin pregnancies who were followed up and delivered at the same tertiary center were included in the case group (Group II). The inflammation-based indices (PIV, SIRI and SII) of the two groups were compared with each other.

Results: 221 twin pregnancies were identified after screening according to the inclusion/exclusion criteria, the remaining 138 pregnancies were sorted chronologically by date of birth. The first 115 twin pregnancies in the ranking list that were eligible for the study according to the power analysis were included in group II. For each twin pregnancy that was eligible for Group II, the first singleton pregnancy in the rank order of files that met the inclusion criteria was selected for Group I as the control group. The groups differed significantly in hemoglobin and PIV values (p=0.045 vs. 0.007). There were no significant differences in demographic and inflammatory indices in mono- and di-chorionic pregnancies.

Conclusion: Low PLT and high LYM in twins lead to a statistically significant decrease in PIV, even if this is not statistically significant. We can say that this reflects the physiological inflammatory/immune response of pregnancy. However, our findings need to be supported by multicenter and prospective randomized controlled trials.

Introduction

The birth rate of twin pregnancies is increasing day by day, as the frequency of pregnancies using assisted reproductive techniques is rising [1]. Twin pregnancies are known to result in adverse fetal outcomes such as preterm birth, increased infant mortality due to prematurity and low birth weight, specific complications of twin pregnancies (twin-to-twin transfusion, twin anemia-polycythemia sequence, etc.), stillbirths and higher congenital anomalies, as well as unfavorable maternal outcomes such as gestational diabetes mellitus, hypertension, preeclampsia, maternal depression and maternal mortality [2-5]. One of the main causes of these various complications is the altered adaptation during a twin pregnancy [6]. Inflammatory and immune changes during gestational adaptation in twin pregnancies have previously been characterized by systemic inflammatory markers such as neutrophil (NEUT)-to-lymphocyte (LYM) ratio (NLR), platelet (PLT)-to-LYM ratio (PLR) and peripheral T helper type 1-2 [7,8].

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These inflammatory markers are gaining popularity in medicine day by day, notably in the field of obstetrics [9].

The new inflammation indices, the pan-immune inflammation value (PIV), the systemic inflammatory response index (SIRI) and the systemic immune inflammation index (SII) are more stable than NLR, PLR and the monocyte (MONO)-to-LYM ratio (MLR) and accurately indicate the inflammatory state of cancer patients [10-12].

Nowadays, these inflammatory indices are used in obstetrics and gynecology to predict the negative consequences of pregnancy or gynecological status [9,13,14]. Therefore, our main objective is to evaluate PIV, SIRI and SII for the comparison of twin pregnancies with singleton pregnancies.

Materials and Methods

This cohort study was conducted retrospectively in the Ankara Etlik City Hospital Obstetrics and Perinatology Clinics between October 2022 and August 2024. Approval was obtained from the Ethics Committee for Scientific Research for this study (May 22, 2024; No. AEŞH-BADEK-2024-468) and the principles of the Declaration of Helsinki were followed throughout the study.

Inclusion and exclusion criteria

The evaluation and management of twin pregnancies is based on the American College of Obstetricians and Gynecologists consensus on obstetric care [15].

Healthy singleton and twin pregnancies with spontaneous labor (from 37 weeks and 0 days) were included in the study.

Pregnant women with one or more of the following conditions or risk factors were excluded from the study: monoamniotic twin pregnancies, preterm labor, fetal growth restriction, preterm premature rupture of membranes, late and post-term pregnancies, fetal malformations or fetal anomalies, suspected or diagnosed chorioamnionitis, pregnancies with assisted reproductive techniques, concomitant maternal conditions, infectious or inflammatory conditions (in particular an infection such as an upper or lower respiratory tract infection, a urinary tract infection, an inflammatory pelvic disease, a coronavirus or influenza infection, as well as inflammatory processes such as an autoimmune disease and/or a chronic inflammatory disease); conditions that can impair the immune system (e.g. taking antibiotics, the use of antioxidants, corticosteroids or anti-inflammatory drugs, smoke cigarettes, cancer presence or cancer history, kidney and/or liver disease) and presence of cardiovascular problems (hyperlipidemia, coronary heart disease and hypertension).

Data analysis

The power analysis of the study was calculated with the manual program G*Power 3.1 [16]. The a priori power analysis showed that a sample size of 115 cases (twin pregnancies) and 115 controls (singleton pregnancies) would be sufficient to detect a significant interaction effect at step 3 with a power of 85% and an alpha of 0.05 [17].

The data for both groups were taken from patient files or hospital records. Demographic data (age, body mass index [BMI], gravidity, parity and abortion), week of gestation at the time of blood sampling and complete blood count (CBC) results were recorded. In our hospital, height and weight are measured in a standardized manner at the patient's first visit to the nurse's office in the first trimester and recorded in the patient's medical record to calculate BMI. This data was taken from the patient's records and included in the study.

Study design

Women with singleton pregnancies whose follow-up and delivery took place in the same tertiary center were included in the control group (Group I). Women with twin pregnancies who were followed up and delivered at the same tertiary center were included in the case group (Group II). Selection of the control group: For each twin pregnancy that met the inclusion criteria for group II, the first singleton pregnancy that met the inclusion criteria in the order of enrollment was selected as the control group. Group II, which included the twin pregnancies, was divided into two subgroups, the mono- and di- chorionic pregnancies, and the possible influence of chorionicity on the inflammatory indices was also investigated.

In our hospital, preoperative tests are carried out at 33 to 37 weeks of gestation before elective cesarean sections and spontaneous vaginal deliveries at term. The PIV (NEUT × MONO × PLT / LYM formula), the SIRI (NEUT × MONO / LYM formula) and the SII (NEUT × PLT / LYM formula) were calculated from the routine CBC tests of both groups at the preoperative testing time point [9,13,14]. These inflammation-based indices of the two groups were compared with each other.

Laboratory analysis of biological samples

CBC test parameters were analyzed using the Beckman Coulter® DxH 900 Workcell Automated Hematology Solution System (registered trademarks of Beckman Coulter, Inc. U.S.).

Statistical analysis

The data analysis was performed with Jamovi, an open statistical software for desktop and cloud. A significance level of p-value less than 0.05 was considered statistically significant for all statistical analyzes.

The variables were analyzed using analytical (Kolmogrov-Simirnov/Shapiro-Wilk test) and visual (probability plots, histograms) methods to determine whether they were normally distributed or not. The homogeneity of variance was assessed using the Levene test. The t-test for independent samples was used to compare normally distributed continuous variables between groups. Mann-Whitney U tests were used to compare non-normally distributed numerical data between groups. Results were expressed as mean ± standard deviation or median and interquartiles (Q1-Q3).

Results

After collecting the data, 221 twin pregnancies were identified that were admitted to our referral hospital. After screening according to the criteria described in the

Table 1. Comparison of demographic features, clinical characteristics and laboratory test results between the groups.

	Group I	Group II	p
Age (years)[a]	29.6 (± 6.03)	30.5 (± 6.07)	0.307*
BMI (kg/m^2)[b]	30 (28 - 32)	30 (26 - 33)	0.595†
Gravidity[b]	2 (1 - 4)	2 (1 - 3)	0.474†
Parity[b]	1 (0 - 2)	1 (0 - 2)	0.576†
Abortus[b]	0 (0 - 1)	0 (0 - 1)	0.268†
WGBS[b]	35 (34 - 36)	35 (34 - 36)	0.628†
HGB (g/dL)[a]	11.6 (± 1.40)	11.3 (± 1.41)	**0.045***
WBC (× 10^9/L)[b]	11550 (9660 - 13630)	11870 (9500 - 13720)	0.971†
LYM (x10^3/µL)[b]	1600 (1220 - 2030)	1640 (1180 - 2050)	0.961†
MONO (x10^3/µL)[b]	570 (440 - 760)	560 (340 - 690)	0.091†
NEUT (x10^3/µL)[b]	7600 (7160 - 8320)	7770 (6800 - 8400)	0.859†
PLT (x10^3/µL)[b]	244 (204 - 285)	215 (182 - 281)	0.076†
SIRI[b]	2498 (1918 - 3652)	2288 (1675 - 3380)	0.074†
SII[b]	1152 (753 - 1690)	1002 (698 - 1636)	0.135†
PIV[b]	626840 (434592 - 875520)	496585 (290830 - 770855)	**0.007**†

Abbreviations: BMI: body mass index; WGBS: week of gestation of blood sampling; HGB: hemoglobin; WBC: white blood cell; LYM: lymphocyte; MONO: monocyte; NEUT: neutrophil; PLT: platelet; SIRI: systemic inflammatory response index; SII: systemic immune inflammation index; PIV: pan-immune inflammation value. [a]Parametric data were expressed with mean and standard deviation; [b]Non-parametric data were expressed with median and interquartiles (Q1 – Q3). A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold. †Mann Whitney U test * t-test.

Table 2. Comparison of demographic features, clinical characteristics and laboratory test results between the subgroups of twin pregnancies.

	Group A (di-chorionic) n=97	Grıoup B (mono-chorionic) n=18	p
Age (years)[a]	30.7 (± 5.88)	28.9 (± 0.2)	0.253*
BMI (kg/m^2)[b]	29 (27 - 33)	31 (26 - 35)	0.935†
Gravidity[b]	2 (2 - 4)	2 (1 - 3)	0.170†
Parity[b]	1 (0 - 2)	1 (0 - 1)	0.172†
Abortus[b]	0 (0 - 1)	0 (0 - 0)	0.525†
WGBS[b]	35 (33 - 36)	35 (34 - 37)	0.477†
HGB (g/dL)[a]	11.2 (± 1.41)	11.3 (± 1.39)	0.779*
WBC (× 10^9/L)[b]	11800 (9380 - 13855)	12065 (10735 - 13718)	0.444†
LYM (x10^3/µL)[b]	1650 (1235 - 2045)	1535 (1058 - 2303)	0.680†
MONO (x10^3/µL)[b]	560 (325 - 680)	570 (415 - 715)	0.505†
NEUT (x10^3/µL)[b]	7710 (6770 - 8390)	7885 (7008 - 8910)	0.253†
PLT (x10^3/µL)[b]	214 (172 - 281)	226 (192 - 302)	0.426†
SIRI[b]	2272 (1693 - 3114)	2941 (1518 - 4101)	0.239†
SII[b]	999 (695 - 1626)	1111 (695 - 1965)	0.460†
PIV[b]	493727 (293332 - 743624)	676964 (289622 - 1046006)	0.248†

Abbreviations: n: number; BMI: body mass index; WGBS: week of gestation of blood sampling; HGB: hemoglobin; WBC: white blood cell; LYM: lymphocyte; MONO: monocyte; NEUT: neutrophil; PLT: platelet; SIRI: systemic inflammatory response index; SII: systemic immune inflammation index; PIV: pan-immune inflammation value. [a] Parametric data were expressed with mean and standard deviation; [b] Non-parametric data were expressed with median and interquartiles (Q1 – Q3). A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold. †Mann Whitney U test * t-test.

inclusion-exclusion criteria sub-section, the remaining 138 pregnancies were sorted chronologically by date of delivery. The first 115 twin pregnancies in the ranking list that were eligible for the study after power analysis were included in Group II. For each twin pregnancy that was eligible for Group II, the first singleton pregnancy in the rank order of files that met the criteria previously mentioned in the inclusion-exclusion criteria sub-section was selected for Group I as the control group (Figure 1).

The demographic and laboratory data of the twin and singleton pregnancies are shown in Table 1. The groups differed significantly in hemoglobin and PIV values (p=0.045 vs. 0.007). Table 2 shows the demographic and laboratory data of the twin pregnancy subgroups. There were no significant differences in mono- and di- chorionic pregnancies.

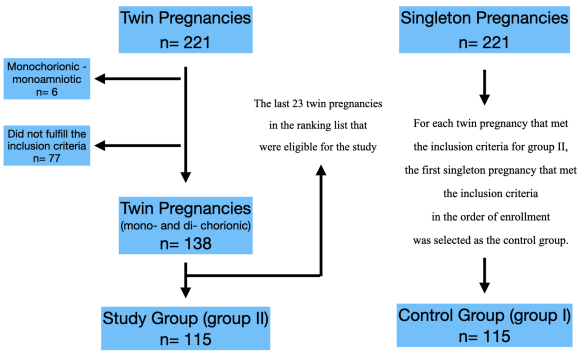

Figure 1. The flowchart of the participants.

Discussion

Inflammatory indices are becoming more and more important parameters in obstetrics and perinatology every day, with further research into the prediction of maternal and fetal diseases. However, the differences between twin and singleton pregnancies may prevent some standardization in the investigation of fetal and maternal diseases. Our aim was to assess this standardization in inflammatory indices. As we know, this is the first study to provide information on all the new indices (PIV, SIRI and SII) for comparing twin and singleton pregnancies. In the present study, PIV is significantly higher in singleton pregnancies than in twin pregnancies, but there is no significant difference between mono- and di- chorionic twin pregnancies.

In a normal and healthy pregnancy, the maternal immune system physiologically adapts to the process that is important for the successful union of mother and fetus [18]. During this process, cytotoxic adaptive immune responses decrease while regulatory adaptive immunity increases [19,20]. The studies have shown that the number of fetuses correlates significantly with trophoblast activity [21]. It has been reported that twin pregnancies produce more trophoblasts in the first trimester than singleton pregnancies [21,22]. For this reason, there are a growing number of studies investigating obstetric complications and aiming to predict maternal/fetal conditions associated with altered immunity and inflammation. Turgut et al. [21] aimed to evaluate the comparison of SII between twin and singleton pregnancies. They found a significantly higher PLR value in twin pregnancies and there was no statistical difference between NLR and SII values compared to singleton pregnancies [21]. In another study by Sabre et al [7], NLR and PLR values were examined in the first trimester. They found that NLR was significantly higher in twin pregnancies, but there was no significant difference in PLR values between twin and singleton pregnancies [7].

Inflammation-based indices such as NLR and PLR, which have been investigated previously, show contradictory results between different studies [7,21]. In present study, where indices such as PIV, SIRI and SII, which seem to be more stable and meaningful than NLR, PLR or MLR [9-12], were used together, no statistical difference was found between twins and singleton pregnancies, except for PIV.

Recommendations to the physicians

The CBC is one of the tests routinely ordered in pregnant women, and the PIV, SIRI and SII values can be easily calculated from this simple test. In our study, although the PIV score was statistically lower in twin pregnancies, there was no statistical difference between twin and singleton pregnancies and between mono- and di-chorionic twin pregnancies in terms of SIRI and SII scores. Therefore, we believe that studies comparing twin and singleton pregnancies on the basis of these inflammation-based indices in terms of maternal-fetal outcomes, predictions and complications could be informative.

Limitations

All participants in this study were selected according to certain standardized protocols and the number of participants required for the study was determined by a power analysis. The fact that PIV, SIRI and SII were used for the first time to compare twin and singleton pregnancies increases the strength of the study. All pregnant women were cared for and delivered in the same clinics according to standardized protocols. However, the limitations of this study are the relatively small number of cases (power 85%), the retrospective design and the experience at a single center.

Conclusion

In conclusion, low PLT and high LYM in twin pregnancies, although not statistically significant, lead to a statistically significant decrease in PIV when these values are calculated formulaically. We can say that this reflects the physiologic inflammatory/immune response of pregnancy. However, our findings need to be supported by multicenter and prospective randomized controlled trial studies.

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Competing interests

No competing interests.

Funding statement

None.

Ethical approval

Approval for this study was granted by the Scientific Research Ethics Committee of Ankara Etlik City Hospital (May 22, 2024; No. AEŞH-BADEK-2024-468). In view of the retrospective nature of the study, the ethics committee waived the required patient consent. All patient data was anonymized or treated confidentially.

Authors' contributions

Conceptualization FBF and SO; methodology FBF, SO and SS; software ST; validation SO, SS and ST; formal analysis SS and STS; investigation FBF and MLD;

resources REP; data curation ST and REP; writing—original draft preparation FBF; writing—review and editing FBF, SS and KYY; visualization SS, MLD and KYY; supervision KYY; project administration FBF and KYY. All authors have read and agreed to the last version of the manuscript.

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