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Research Article

The Systemic Immune-Inflammation Index and its Connection with Maternal Age in Naturally Conceived Pregnancies: A Single-Center Cohort Study

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Abstract

Aim: Maternal age is associated with perinatal outcomes, which include preeclampsia, low birth weight, preterm birth, neonatal mortality, increased cesarean rates, and maternal mortality. This study aimed to investigate the effects of maternal age on hematological parameters and systemic immune-inflammatory indices in pregnant women.

Material and Methods: A retrospective analysis of 400 pregnant women was conducted, divided into four age groups. Hematological parameters, systemic immune-inflammatory indices, and clinical outcomes were compared across these groups.

Results: The mean neutrophil count and monocyte count increased with maternal age, significantly highest in the 40-49 age group ($p<0.001$, $p=0.003$). Age-associated inflammation was reflected by increased NLR, MLR, PLR, and SII in the advanced age groups ($p<0.001$). Positive correlations were found between age, BMI ($r=0.301$, $p<0.001$), and MLR ($r=0.122$, $p=0.015$). The prevalence of chronic diseases, drug usage, and complications such as preeclampsia and gestational diabetes also significantly increased with age ($p<0.001$).

Conclusion: This analysis reveals age-related alterations in immune-inflammatory indices and clinical outcomes in pregnancy and provides insights for better management and monitoring of different age groups during pregnancy, particularly those at advanced maternal age.

Keywords: Maternal age, systemic immune-inflammatory indices, pregnancy outcomes

INTRODUCTION

Maternal age is associated with perinatal outcomes, which include preeclampsia, low birth weight, preterm birth, neonatal mortality, increased cesarean rates, and maternal mortality (1). Adolescent pregnancy, defined as ages 10-19, accounts for 11% of all births globally, with over 90% occurring in developing countries (2). The pregnancies are associated with adverse obstetric results and maternal neonatal mortality (3). Advanced maternal age pregnancies aged 35 and over and very advanced maternal age pregnancies are terms used by the International Federation of Gynecology and Obstetrics (4). The trend towards fertility at older ages has been popularized in the last decade due to increasing marriage age, second marriages, more significant opportunities for education and career development, improving family planning methods, and advances in assisted reproductive techniques (5).

The systemic inflammatory process can inform physicians about pregnancy-related disorders (6). Parameters from blood counts such as neutrophil-lymphocyte, platelet counts, and ratios can predict the systemic inflammatory process (7). The ratio of neutrophil to lymphocyte (NLR), monocyte to lymphocyte (MLR), platelet to lymphocyte (PLR), and the Systemic Immune-Inflammation index (SII) were evaluated in diseases where inflammation is thought to be involved in the pathogenesis, such as preeclampsia, gestational diabetes mellitus, low birth weight, and their relationship with inflammation was investigated (8). The SII, calculated using platelet, neutrophil, and lymphocyte counts together, is a more important indicator of inflammation and immune response than the neutrophil to lymphocyte and platelet to

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lymphocyte ratios (9,10). Examining the interplay between age groups and the Systemic Immune-Inflammation Index (SII) could potentially illuminate predictive insights for clinicians regarding post-pregnancy complications, underscoring the further exploration in this area.

The current research aims to analyze the differences observed in the first trimester of adolescent, adult, and advanced-maternal age pregnant by calculating and comparing the NLR, MLR, PLR, and SII in naturally conceived pregnancies.

MATERIAL AND METHOD

Study Design and Participants

This retrospective single-center cohort evaluated the first-trimester blood count parameters of naturally conceived pregnancies. Out of 532 potential participants, the final sample size was reduced to 400 pregnant women for various reasons, including exclusion criteria, non-compliance, and loss of follow-up. These 400 pregnant women were divided into four groups based on age: adolescent (15-19 years, n=81), adult (20-34 years, n=172), advanced maternal age (35-39 years, n=106), and very advanced maternal age (40-49 years, n=41).

Ethical Statement

The study was initiated with the approval of the Ankara Etlik City Hospital Clinical Researches Ethics Committee (Date: 14/06/2023, Decision No: AEŞH-EK1-2023-247). Every method carried out in the research adhered strictly to the ethical guidelines set by our institutions and national research committee and those established in the 1964-Helsinki Declaration and its subsequent updates or ethical norms.

Data Collection

The cornerstone of this research was a meticulous gathering of data, primarily sourced from hospital records, ensuring accuracy and consistency. To begin with, we extracted demographic details that would provide a holistic understanding of the participant's profile. The maternal age served as a baseline, indicating the pregnant woman's age during her first trimester. Another fundamental parameter was gravida, which revealed the number of times a woman had been pregnant, regardless of the pregnancy's progression or outcome. Complementing this, parity was used to identify the number of pregnancies a woman had carried past the pivotal gestational age of 24 weeks, irrespective of whether they culminated in live births or other outcomes. Recognizing the significance of conception methods in modern times, we documented the mode of fertilization. This allowed us to differentiate between pregnancies resulting from natural processes and those conceived through assisted reproductive technologies. Another vital metric was the Body Mass Index (BMI), which furnished insights into the nutritional and health status of the participants.

As smoking and underlying health conditions can significantly influence pregnancy outcomes, data on smoking status and the presence of other diseases were meticulously logged. Medications, especially during pregnancy, can bear considerable implications. Hence, a comprehensive list of medication use was drawn for each participant. Recognizing the potential challenges some pregnancies face, specific data on complications like gestational diabetes mellitus and hypertensive disorders of pregnancy were diligently recorded. Outcomes of pregnancies, particularly preterm birth, birth weight, and the newborn's health reflected in the APGAR score, were essential components of our data set. We derived specific indices from the first-trimester complete blood count parameters to delve into the hematological aspect. This involved calculating the NLR, MLR, PLR, and SII. For precision, the SII was determined using the formula: Platelet count multiplied by Neutrophil count, divided by Lymphocyte count.

Patients Selection Criteria

Inclusion Criteria: The study prioritized including pregnant women within specified age brackets. The adolescent group consisted of those aged 15-19 years; the adult group, 20-34 years; the advanced maternal age group, 35-39 years; and the advanced maternal age group, 40-49 years. Only participants experiencing a single pregnancy were considered. Furthermore, an essential criterion was the availability of comprehensive medical records necessary for the study. A clear history devoid of recurrent miscarriages and hematological disorders was also pivotal for inclusion.

Exclusion Criteria: Several factors led to the exclusion of potential participants. Pregnant women diagnosed with an active infection were omitted from the study. Similarly, if a participant had an autoimmune disease or a history of any malignancy, they were excluded. The study also refrained from including those on a current or recent steroid regimen. Pregnancies involving multiple births, such as twins or triplets, were not considered. Women undergoing fertility treatments or had a history of severe anemia or other blood-related conditions were also left out. Lastly, the study ensured that pregnant women with any known genetic disorders that might influence them were excluded.

Data Analysis

Using the SPSS software, our first step in the analytical journey was using descriptive statistics. It represented continuous variables as mean values accompanied by their standard deviations, while categorical variables found representation through frequency counts. Once this foundational analysis was established, we progressed to inferential statistics to draw comparisons across the diverse groups. The Chi-square test became our primary tool for categorical variables, allowing us to discern the proportions scattered across the groups. When the Chi-square test faltered due to inadequately populated cells, we used Fisher's exact test as a reliable alternative. On the front of continuous variables, we employed the Analysis of Variance (ANOVA) – but this was contingent on data

behaving in a normally distributed fashion. When this assumption didn't hold, we opted for the Kruskal-Wallis test, a non-parametric counterpart. Following instances where either ANOVA or Kruskal-Wallis yielded significant findings, we conducted post-hoc analyses to pinpoint the groups with pronounced differences. Our statistical litmus for significance was a p-value under 0.05.

RESULTS

In this study, we compared a variety of parameters across four distinct age groups: 15-19 (n=81), 20-34 (n=172), 35-39 (n=106), and ≥40 (n=41) years, as seen in Table 1. The mean age for the respective groups was 18.1±1, 26.4±3.3, 36.5±1.3, and 42.2±2 years (p<0.001). A similar pattern of differences (p<0.001) was observed for BMI, with mean values of 27.1±4.3 kg/m², 29.1±4.8 kg/m², 31.4±4.5 kg/m², and 30.3±5 kg/m² respectively. Although Delta Hemoglobin levels were relatively consistent across groups (p=0.442), the average delivery week differed (p=0.032) with values of 38±3.1, 38±2.3, 38±3.2, and 37±3.3 weeks in respective groups. The mean birth weights were 2808±603, 3058±549, 3035±608, and 2838±705 g, which showed a significant variation (p=0.005).

Regarding health conditions and lifestyle factors, the prevalence of chronic diseases and drug usage increased with age (p=0.027 and 0.041, respectively). The occurrences of preeclampsia and gestational diabetes mellitus also escalated in older age groups (p<0.001), as did the rate of cesarean section deliveries (p=0.026). Conversely, no differences were observed across the age groups for cigarette usage (p=0.872), preterm birth rate (p=0.112), the incidence of intrauterine growth restriction (p=0.077), and the proportion of male babies (p=0.984).

There was a variation in the mean neutrophil counts for the respective groups, which were 7583±1911, 6407±1834, 6686±1828, and 7289±1939 cells/μL (p<0.001). Similarly, as seen in Table 2, monocyte counts varied across the groups with respective counts of 680±192, 621±182, 577±139, and 690±266 cells/μL (p<0.001). In contrast, lymphocyte and platelet counts did not differ between the groups, with lymphocyte at 1909±694, 2101±640, 2043±587, and 2062±871 cells/μL (p=0.187) and platelet counts at 280±58, 276±58, 265±58, and 282±60 cells/μL (p=0.216). The NLR and MLR varied across the groups p<0.001). NLR values for the respective groups were 4.6±2.3, 3.3±2, 3.6±1.6, and 4.1±2.6, and MLR values were 2.9±1.1, 3.6±1.3, 3.6±1.1, and 3.2±1.2. The PLR showed a difference (p=0.015) with respective ratios of 167.4±77.7, 142.9±60.4, 141.2±57.3, and 161.8±97.1. The SII also showed variation with values of 1299.2±733, 911.3±470.9, 947.5±514.2, and 1203±1025.2 respectively (p<0.001). Significant differences were observed in neutrophil and monocyte counts and in the NLR, MLR, PLR, and SII across the different age groups. In contrast, lymphocyte and platelet counts remained consistent.

Our correlation analysis yielded significant associations between age, BMI, NLR, MLR, PLR, and SII variables. Age was positively correlated with BMI (r=0.301, p<0.001), suggesting that an increase in age is associated with a higher BMI. The age factor positively correlated with MLR (r=0.122, p=0.015). Age was not significantly correlated with NLR, PLR, or SII. Despite a slight positive correlation with age, BMI did not show correlations with any of the remaining variables. PLR and SII displayed a strong positive correlation (r=0.875, p<0.001).

Table 1. Comparative analysis of parameters across age groups

Variables	15-19 (n=81)	20-34 (n=172)	35-39 (n=106)	≥40 (n=41)	p value
Age, years	18.1±1	26.4±3.3	36.5±1.3	42.2±2	0.001
BMI, kg/m²	27.1±4.3	29.1±4.8	31.4±4.5	30.3±5	0.001
Delta HB, mg/dL	1.5±0.8	1.5±1	1.5±1.3	1.2±0.9	0.442
Delivery, week	38±3.1	38±2.3	38±3.2	37±3.3	0.032
Baby weight, g	2808±603	3058±549	3035±608	2838±705	0.005
Chronic disease, yes	2 (2.5%)	22 (12.8%)	16 (15.1%)	7 (17.1%)	0.027
Drug usage, yes	2 (2.5%)	22 (12.8%)	16 (15.1%)	5 (12.2%)	0.041
Cigarette usage, yes	15 (18.5%)	29 (16.9%)	21 (19.8%)	6 (14.6%)	0.872
Preeclampsia, yes	0 (0%)	2 (1.2%)	6 (5.7%)	8 (19.5%)	0.001
GDM, yes	0 (0%)	8 (4.7%)	14 (13.2%)	7 (17.1%)	0.001
Preterm birth, yes	19 (23.5%)	22 (12.8%)	19 (17.9%)	10 (24.4%)	0.112
IUGR, yes	24 (29.6%)	29 (16.9%)	19 (17.9%)	6 (14.6%)	0.077
Birth method, C/S	30 (37%)	83 (48.3%)	61 (57.5%)	24 (58.5%)	0.026
Baby gender, male	40 (49.4%)	84 (48.8%)	54 (50.9%)	22 (53.7%)	0.984

BMI: body mass index, HB: hemoglobin, GDM: gestational diabetes mellitus, IUGR: intrauterine growth restriction, C/S: cesarean section, Delta Hemoglobin: change in hemoglobin, the age groups are segmented as under 19, 20-34, 35-39, and above 40 years. The p-value less than 0.05 is considered significant. For continuous variables (like age, BMI, delta hemoglobin, delivery week, and baby weight), means and standard deviations were calculated for each group using Analysis of Variance (ANOVA). For categorical variables, the numbers and percentages of individuals for each category within the groups were computed using a chi-square or Fisher's exact, depending on the data characteristics

Table 2. Comparative analysis of hematological parameters and indices across age groups

Variables	15-19 (n=81)	20-34 (n=172)	35-39 (n=106)	≥40 (n=41)	p value
Neutrophil, cells/μL	7583±1911	6407±1834	6686±1828	7289±1939	0.001
Lymphocyte, cells/μL	1909±694	2101±640	2043±587	2062±871	0.187
Monocyte, cells/μL	680±192	621±182	577±139	690±266	0.001
Platelet, cells/μL	280±58	276±58	265±58	282±60	0.216
NLR, ratio	4.6±2.3	3.3±2.0	3.6±1.6	4.1±2.6	0.001
MLR, ratio	2.9±1.1	3.6±1.3	3.6±1.1	3.2±1.2	0.001
PLR, ratio	167.4±77.7	142.9±60.4	141.2±57.3	161.8±97.1	0.015
SII, ratio	1299.2±733	911.3±470.9	947.5±514.2	1203±1025.2	0.001

NLR: neutrophil to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, PLR: platelet to lymphocyte ratio, SII: systemic immune-inflammation index, The p-value is derived from a statistical test (ANOVA) comparing the means of the age groups. A p-value less than 0.05 indicates the difference

DISCUSSION

The present study analyzed the comparative results of hematological parameters and indices across four age groups. We found several notable trends and correlations in the data, underpinning the intricate dynamics between age, BMI, and systemic immune-inflammatory markers. This study not only expands our knowledge of the relationship between age and systemic inflammation for pregnant but also invites further exploration into the practical implications of this relationship in clinical and public health settings.

Considering the increasing trend of advanced maternal-age pregnancies worldwide, our findings significantly affect public health (11). Recognizing the changes in systemic inflammation with aging, as indicated by SII (12-14), could guide the development of preventive measures and health promotion strategies for older pregnant women. Several studies have suggested that a high SII is linked to unfavorable outcomes in numerous medical conditions, including preeclampsia and gestational diabetes (15,16). Our findings support the hypothesis that age-related variations in SII might influence the risk of these complications in pregnant women. This result aligns with the growing body of evidence suggesting that aging is associated with chronic, low-grade inflammation, a phenomenon termed "inflammaging" for pregnant (17). The aging process, characterized by immunosenescence, is linked with altered immune cell functions and inflammatory markers imbalances, which could explain the noted variations in SII (18). Given the potential clinical utility of SII as an inflammatory marker in various conditions, its relationship with age merits further investigation (19,20). Our study has linked higher SII values with adverse outcomes in different medical conditions, including preeclampsia and gestational diabetes mellitus. Hence, our findings shed light on the influence of age-related changes in SII and how they might impact the risk of these complications in pregnant women. The significant difference we observed in the SII across different age groups suggests a need for age-specific SII cut-offs to enhance the predictive accuracy for pregnancy complications. These key insights contribute towards a more profound understanding of how immune system changes associated with aging might impact pregnancy outcomes, potentially influencing management strategies during pregnancy.

Notably, age positively correlated with BMI, reflecting the well-documented trend of increasing BMI with advancing age (21). This result further supports the broad consensus that aging is associated with changes in body composition, including an increase in adipose tissue (22,23). Although age also demonstrated a positive correlation with MLR, its lack of significant correlations with other systemic immune-inflammatory indices suggests that additional factors, possibly genetic, environmental, or lifestyle-related, might influence these indices. Our findings did, however, expose a disparity between different age groups regarding the prevalence of certain health conditions and lifestyle factors. An increase in the rate of chronic diseases, drug usage, and conditions like preeclampsia and gestational diabetes mellitus in older age groups underscores the influence of aging on health status. These findings align with the well-established understanding that aging is a significant risk factor for numerous chronic diseases and health conditions.

While our study unveils significant insights, it is imperative to recognize its inherent limitations. Foremost among these is our study's cross-sectional retrospective design. Such a design inherently challenges drawing definitive causal links between observed associations. Additionally, selection bias could have been introduced because our sample was derived from a single center. This could impact the generalizability of our findings to a broader population. Instruments used might have varied in calibration, or the personnel recording the data might have interpreted values differently. Given these limitations and potential biases, we must approach our findings with a degree of caution. We emphasize the need for future longitudinal studies.

CONCLUSION

In conclusion, our study presents significant insights into the relationship between age, hematological parameters, and systemic immune-inflammatory indices, especially

the SII. These findings reinforce our understanding of the role of systemic inflammation in aging but also highlight the potential clinical utility of markers like SII in assessing inflammatory status across different age groups. Future research could investigate whether age-specific SII cut-offs might improve the predictive accuracy for these pregnancy-related complications.

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Conflict of Interest: *The authors declare that they have no competing interest.*

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