

# Perinatal and neonatal outcomes of adolescent pregnancies over a 10-year period

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## ABSTRACT

**Objectives:** Poor overall neonatal outcomes, small neonatal head circumference, neonatal hypoglycemia, need for Neonatal Intensive Care Unit and late-onset neonatal sepsis are more common in adolescents. The aim of this study is to draw attention to the outcomes of adolescent pregnancies.

**Material and methods:** This retrospective study was conducted in adolescent singleton pregnancies with maternal age < 15 years (n = 20, Group 1), 16–19 years (n = 1929, Group 2), and 20 years (n = 866, Group 3). Age, gravidity, parity, and body mass index (BMI) measurements of mothers; mode of delivery, maternal and neonatal outcomes were evaluated and compared.

**Results:** The rate of preterm birth, postpartum hemorrhage, asymmetrical intra-uterine growth restriction (IUGR, as 3% percentile), macrosomia, and height of newborn of Group 3 was significantly higher. The rate of asymmetrical IUGR (as 10% percentile) was significantly lower in Group 3. The rate of severe preeclampsia and cesarean section was significantly higher in Group 3. The rate of Small for Gestational Age newborn, neonatal hypoglycemia, and late-onset neonatal sepsis was significantly higher in Group 1.

**Conclusions:** Neonatal problems with poor obstetric outcomes are common in adolescent pregnant women, so that a family planning and baby care social trainings are important in achieving good long-term maternal and neonatal outcomes.

**Key words:** adolescent; teenagers; pregnancy; maternal outcome; neonatal outcome; primary care

Ginekologia Polska 2023; 94, 6: 500–506

## INTRODUCTION

The World Health Organization (WHO) describes adolescence as a period of transition from childhood to adulthood at ages between 10 and 19 [1]. Sexual activity in adolescence leads to increased frequency of sexually transmitted diseases (STDs) and immediate undesirable consequences, such as pregnancy [2]. An estimated 21 million girls between the ages of 15–19 become pregnant each year in developing regions, and about 12 million of them give birth [1]. The adolescent birth rate is 21/1000 in 2020 among girls aged 15–19 [3]. Unfortunately, the prevalence of adolescent preg-

nancy is rising, especially in developing countries leading to a great public health problem [4]. Adolescent pregnancy is related to such conditions, as maternal low education level, single living arrangement, high parity, prosperity dependency, elevated suicide risk, poverty, inadequate family support and elevated sexually transmitted disease risk. Moreover, being a child of a teenage mother brings the risk of exposure to similar poor social and economic conditions [5–8]. The teenage years is a high risky period for poor obstetric and neonatal outcomes due to biological immaturity, physical, mental and social unpreparedness of adolescents

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Received: 18.04.2022 Accepted: 1.08.2022 Early publication date: 26.09.2022

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for pregnancy [9]. Giving birth in adolescence is related to such maternal and fetal complications that preterm delivery, low birth weight, preterm premature rupture of membranes, maternal anemia, urinary tract infections, miscarriages, hypertensive disorders, postpartum bleeding, fetal asphyxia, fetal death, and delivery trauma [10].

Eighty percent are unwanted adolescent pregnancies and the highest percentage of birth belongs to the group in poor socioeconomic condition [11]. Although most adolescents have easy access to primary health care, there is no study showing that adolescents use primary health care services in terms of contraception or pregnancy process and outcomes [12]. If social healthcare is much more careful and focused in the follow-up of adolescent pregnancies [13, 14], more satisfactory maternal and fetal results can be obtained. The more reasonable strategy to protect adolescents from pregnancy and related complications is to inform them about sexual health and contraceptive use [1]. However, literature data showed that there is no significant relationship between neonatal negative outcomes and young maternal age, even if few studies have been performed on adolescent pregnancy in Turkey [15, 16].

### Objectives

In this investigation, authors evaluated 10-year data of adolescent and young adult pregnancies, comparing obstetric, perinatal and neonatal outcomes of these pregnancies.

### MATERIAL AND METHODS

This retrospective cohort study was performed at Samsun Training and Research Hospital, a tertiary center, during 2010 and 2020 years, including pregnant women between 14 and 20 years of age, with a singleton birth of, at least, 20 gestational weeks or a minimum of 400 gr of neonatal weight. The data of participants was obtained from Samsun Educational and Research Hospital database records. Since all singleton pregnancies in the obtained data were included in the study, power analysis was not performed. The Human Research Ethics Committee of the University of Health Sciences approved the research protocol (process KAEK 2020/11/11 dated 2020), and GOKA numbered 2020/15/10 was obtained for conducting the research. This study was performed within the guidelines of the Helsinki Declaration. Since the study setup was retrospective file review, patient consent was not obtained.

World Health Organization defines adolescence as the transition period from childhood to adulthood between the ages of 10 and 19 [1]. The study group consisted of pregnant women divided into two categories: early adolescents are younger than 15 years of age (Group 1), and late adolescents, aged between 15 and 19 years (Group 2). Early adolescents (Group 1) were selected and evaluated separately, because

this group has been shown to increase the risk of adverse pregnancy outcomes [17–19]. However, the number of people giving birth in this age group is low. For this reason, the number of participants in this group was limited. The control group includes the mothers aged 20 years old (Group 3). Maternal age was defined as the completed age [in years] of the mother at the time of delivery. Exclusion criteria were pregnant women: having multiple pregnancies, suffering any major chronic disease such as renal and cardiopulmonary disorders, including hypertension, thyroid disorders, pregestational diabetes mellitus, any systemic autoimmune disease and obtained incomplete data. Collected parameters for data analysis were age, gravidity, parity, nationality, body mass index (BMI), and mode of delivery (cesarean section or vaginal birth) of mothers; birth weight, head circumference, height measurements, and Apgar scores at 1 and 5 minutes, of newborns. Preterm birth was defined as less than 37 completed weeks of gestation [20]. These examined findings were defined as the following: systolic blood pressure > 160 mmHg and/or diastolic pressure > 110 mmHg 2 times at least 4 hours apart while the patient is at bed rest, preeclampsia; 24-hour urine > 5 g or urine dip 3+ protein, proteinuria; serum aspartate amino transferase > 64 U/L or serum alanine amino transferase > 80 U/L, liver dysfunction; platelet count < 100,000, thrombocytopenia; urine output < 500 mL in 24 hours, oliguria; creatinine > 1.1 mg/dL, renal dysfunction; convulsions and/or auditory or visual symptoms without a history of epilepsy, cerebral impairment [21]. A gestation period greater than 14 days after estimated delivery or 42 weeks (294 days) was defined as post-term pregnancy [22, 23]. Two or more of the four criteria; "fasting blood glucose > 95 mg/dL; following 100 mg glucose intake in oral glucose tolerance test; > 180 mg/dL after 60 minutes, > 155 mg/dL after 120 minutes, > 140 mg/dL after 180 minutes" was diagnosed with gestational diabetes mellitus [24]. Unexplained pruritus, abnormal liver function tests and/or bile acids above 10 µmol/L and resolution after birth; was diagnosed with gestational cholestasis [25]. Postpartum hemorrhage (PPH) > 500mL mild; > 1000 mL was named severe. It was also defined as finding excessive postpartum hemorrhage, independent of the amount of bleeding, in patients with tears, loss of tissue tone, or thrombin problems, according to the physician's clinical decision [26]. Birth weight below 10<sup>th</sup> percentile, small for gestational age (SGA); Live birth resulting in death within the first 28 days has been defined as neonatal death [27].

### Statistical analysis

IBM SPSS for Windows version 23 (USA) was used for statistical analyses. Data were evaluated with descriptive statistical methods. The normality of numeric variables was tested with the Shapiro-Wilk test. Kruskal-Wallis ANOVA test with

**Table 1. Maternal characteristics of the study population**

Variables	Early adolescents (n = 20, Group 1)	Late adolescents (n = 1929, Group 2)	Young adults aged 20 years (n = 866, Group 3)
Age [y]	14 (14–14) <sup>a</sup>	18 (17–19) <sup>b</sup>	20 (20–20) <sup>c</sup>
Gravidity	1 (1–2) <sup>b</sup>	1 (1–1) <sup>a</sup>	1 (1–2) <sup>b</sup>
Parity	0 (0–1) <sup>a</sup>	0 (0–0) <sup>a</sup>	0 (0–1) <sup>a</sup>
Nationality (%)			
Native	10 (50%)	1685 (87.4%)	746 (86.1%)
Immigrant	10 (50%) <sup>a</sup>	244 (12.6%) <sup>b</sup>	120 (13.9%) <sup>b</sup>
Body mass index [kg/m <sup>2</sup> ]	20.1 (18.9–20.7) <sup>a</sup>	24.7 (22.2–28.2) <sup>b</sup>	27.7 (23.1–33.6) <sup>c</sup>

Data are expressed as median with interquartile range or number with percentage as analyzed with Kruskal-Wallis ANOVA or chi-square tests as appropriate. Significances of chi-square tests were presented with p values adjusted with the Bonferroni method. P values less than 0.05 are accepted as significant and presented as superscript letters. When the values are not different, they are marked with the same letter; a, b, c; according to Bonferroni correction, there is no statistical difference between data with the same superscript letters

**Table 2. Baseline maternal outcomes**

Variables	Early adolescents (n = 20, Group 1)	Late adolescents (n = 1929, Group 2)	Young adults aged 20 years (n = 866, Group 3)
Preterm birth (%)	1 (5%) <sup>a</sup>	170 (8.8%) <sup>a</sup>	102 (11.8%) <sup>b</sup>
Postterm pregnancy (%)	0 (0%) <sup>a</sup>	220 (11.4%) <sup>a</sup>	91 (10.5%) <sup>a</sup>
Severe preeclampsia (%)	0 (0%) <sup>a</sup>	91 (4.7%) <sup>b</sup>	20 (2.3%) <sup>a</sup>
Gestational diabetes mellitus (%)	2 (10%) <sup>a</sup>	212 (11%) <sup>a</sup>	78 (9%) <sup>a</sup>
Cholestasis of pregnancy (%)	0 (0%) <sup>a</sup>	28 (1.5%) <sup>a</sup>	7 (0.8%) <sup>a</sup>
Asymmetrical intrauterine growth restriction (%)			
% 10 percentile	2 (10%) <sup>a</sup>	124 (6.4%) <sup>a</sup>	24 (2.8%) <sup>b</sup>
% 3 percentile	0 (0%) <sup>a</sup>	5 (0.3%) <sup>a</sup>	16 (1.8%) <sup>b</sup>
Placental abruption (%)	0 (0%) <sup>a</sup>	57 (3%) <sup>a</sup>	29 (3.3%) <sup>a</sup>
Placenta previa (%)	0 (0%) <sup>a</sup>	21 (1.1%) <sup>a</sup>	4 (0.5%) <sup>a</sup>
Postpartum hemorrhage (%)			
Mild-moderate	0 (0%) <sup>a</sup>	132 (6.8%) <sup>b</sup>	60 (6.9%) <sup>b</sup>
Severe	0 (0%) <sup>a</sup>	91 (4.7%) <sup>b</sup>	20 (2.3%) <sup>b</sup>

Data are expressed as a number with percentage as analyzed with chi-square tests as appropriate. Significances of chi-square tests were presented with p values adjusted with the Bonferroni method. P values less than 0.05 are accepted as significant and presented as superscript letters. When the values are not different, they are marked with the same letter; SGA — small for gestational age; a, b, c; according to Bonferroni correction, there is no statistical difference between data with the same superscript letters

Mann-Whitney test as post hoc test and chi-square test were used as appropriate and significances were evaluated with adjusted p used for comparison of qualitative data. A p-value of <0.05 was accepted as statistically significant.

## RESULTS

Sixty-eight pregnant women with incomplete records and information regarding adverse pregnancy outcomes, three pregnant women with multiple pregnancy and five pregnant women with thyroid disorders were not included in the study. The study was conducted on 2815 mothers, categorized as early adolescents (n = 20, 0.7%), late adolescents (n = 1929, 68.5%), and 20-year-old young adults (n = 866, 30.8%) (Tab. 1). All pregnant women in early adolescence were 14 years old, coming from substantial immigrants and the majority of late adolescents were 18 years old. There was no significant difference between the three groups in terms of gravity numbers and parity, but the mean BMI of the groups

were significantly different. The main characteristics of three groups were shown in Table 2. The rate of preterm birth was significantly higher in Group 3 compared to the other groups. The rate of severe preeclampsia in late adolescents was significantly higher than the other groups. Group 1 and Group 3 resulted similar in the rate of severe preeclampsia. The rate of asymmetric intra-uterine growth restriction (IUGR), categorized as the 10% percentile in Group 3, was significantly lower than the other groups. The rate of asymmetric IUGR, categorized as the 3% percentile, was significantly higher in Group 3 compared to the other groups. Severe PPH was significantly higher in Group 2 and Group 3 than in early adolescents. Post-term pregnancy, gestational diabetes mellitus, gestational cholestasis, ablatio placentae and placentae previa rates were similar among the three groups. Perinatal and neonatal characteristics of three groups are presented in Table 3, with no significant difference in terms of gestational age at delivery. Cesar-

**Table 3. Perinatal and neonatal characteristics**

Variables	Early adolescents (n = 20, Group 1)	Late adolescents (n = 1929, Group 2)	Young adults aged 20 years (n = 866, Group 3)
Gestational age at birth [w]	38 (37–40) <sup>a</sup>	39 (37–40) <sup>a</sup>	38 (37–40) <sup>a</sup>
Mode of delivery (%)			
Vaginal	20 (100%)	1186 (61.5%)	705 (81.4%)
Primary cesarean section	0 (0%) <sup>a</sup>	743 (38.5%) <sup>b</sup>	161 (18.6%) <sup>a</sup>
Birth weight [g]	2675 (2412–3247) <sup>a</sup>	3100 (2580–3500) <sup>a</sup>	3385 (2680–3682) <sup>b</sup>
SGA newborn (%)	10 (50%) <sup>a</sup>	271 (14%) <sup>b</sup>	101 (11.7%) <sup>b</sup>
Macrosomia (%)	1 (5%) <sup>a</sup>	118 (6.1%) <sup>a</sup>	80 (9.2%) <sup>b</sup>
Head circumference of a newborn [cm]	35 (34–36) <sup>a</sup>	36 (35–37) <sup>b</sup>	37 (36–37) <sup>b</sup>
Height of newborn (cm)	47 (46–48) <sup>a</sup>	48 (46–51) <sup>a</sup>	50 (48–53) <sup>b</sup>
Apgar score at 1 min	9.5 (8–10) <sup>a</sup>	9 (8–10) <sup>a</sup>	9 (8–10) <sup>a</sup>
Apgar score at 5 min	10 (9–10) <sup>a</sup>	10 (9–10) <sup>a</sup>	9 (9–9) <sup>a</sup>
Meconium at birth (%)	0 (0%) <sup>a</sup>	291 (15.1%) <sup>a</sup>	131 (15.1%) <sup>a</sup>
Meconium aspiration syndrome (%)	0 (0%) <sup>a</sup>	66 (3.4%) <sup>a</sup>	40 (4.6%) <sup>a</sup>
Need for neonatal transfusion (%)	0 (0%) <sup>a</sup>	83 (4.3%) <sup>a</sup>	45 (5.2%) <sup>a</sup>
Neonatal hypocalcemia (%)	3 (15%) <sup>a</sup>	107 (5.5%) <sup>a</sup>	40 (4.6%) <sup>a</sup>
Neonatal hyponatremia (%)	0 (0%) <sup>a</sup>	71 (3.7%) <sup>a</sup>	42 (4.8%) <sup>a</sup>
Neonatal transient tachypnea (%)	3 (15%) <sup>a</sup>	213 (11.0%) <sup>a</sup>	81 (9.4%) <sup>a</sup>
Respiratory distress syndrome (%)	0(0%) <sup>a</sup>	99 (5.1%) <sup>a</sup>	50 (5.8%) <sup>a</sup>
Neonatal hypoglycemia (%)	7 (35%) <sup>a</sup>	255 (13.2%) <sup>b</sup>	61 (7%) <sup>c</sup>
Neonatal hyperbilirubinemia (%)	4 (20%) <sup>a</sup>	298 (15.4%) <sup>a</sup>	144 (16.6%) <sup>a</sup>
Cardiac malformation (%)	0 (0%) <sup>a</sup>	70 (3.6%) <sup>a</sup>	42 (4.8%) <sup>a</sup>
Congenital malformation (%)	0(0%) <sup>a</sup>	98 (5.1%) <sup>a</sup>	45 (5.2%) <sup>a</sup>
Neonatal sepsis (%)			
No sepsis	18 (90%) <sup>a</sup>	1792 (92.9%) <sup>a</sup>	792 (91.5%) <sup>a</sup>
Early-onset	0 (0%) <sup>a</sup>	97 (5%) <sup>a</sup>	52 (6%) <sup>a</sup>
Late-onset	2 (10%) <sup>a</sup>	40 (2.1%) <sup>b</sup>	22 (2.5%) <sup>b</sup>
Need for NICU admission (%)	6 (30%) <sup>a</sup>	215 (11.1%) <sup>b</sup>	81 (9.4%) <sup>b</sup>
Need for intubation (%)	0 (0%) <sup>a</sup>	97 (5.0%) <sup>a</sup>	40 (4.6%) <sup>a</sup>
Need for mechanic ventilation (%)	0 (0%) <sup>a</sup>	99 (5.1%) <sup>a</sup>	40 (4.6%) <sup>a</sup>
Neonatal death (%)	0 (0%) <sup>a</sup>	15 (0.8%) <sup>a</sup>	0 (0%) <sup>a</sup>
Cerebral palsy (%)	1 (5%) <sup>a</sup>	24 (1.2%) <sup>a</sup>	12 (1.4%) <sup>a</sup>

Data are expressed as median with interquartile range or number with percentage as analyzed with Kruskal-Wallis ANOVA or chi-square tests as appropriate. Significances of chi-square tests were presented with p values adjusted with the Bonferroni method. P values less than 0.05 are accepted as significant and presented as superscript letters. When the values are not different, they are marked with the same letter; NICU — neonatal intensive care unit; a, b, c; according to Bonferroni correction, there is no statistical difference between data with the same superscript letters

ean section (CS) rate in Group 2 was significantly higher than Group 3. None of the mothers needed CS surgery in Group 1. Birth weights of Group 2 were significantly higher than other groups and Group 1 and Group 3 were similar in terms of birth weight. The rate of SGA newborns in Group 1 was significantly higher than the other groups, and the rate of SGA newborns in Group 2 and Group 3 was similar. Macrosomia rate in Group 2 was significantly higher than other groups ( $p < 0.05$ ) and Group 1 were similar in terms of macrosomia rate. Head circumference of the Group 1 newborn was significantly lower than the other groups, and Group 2 and 3 were similar. Neonatal heights of Group 2 were significantly higher than other groups, but Group 1 was

similar to other groups in terms of newborn heights. Neonatal hypoglycemia rate was higher in Group 1 than other groups. Neonatal hypoglycemia rate was higher in Group 2 compared to Group 3. There was no early-onset neonatal sepsis in the study groups. However, the rate of late-onset neonatal sepsis in Group 1 was higher than other groups, while the 1<sup>st</sup> and 5<sup>th</sup> minute Apgar scores, rates of meconium presence at birth, meconium aspiration syndrome, neonatal transfusion need, neonatal hypocalcemia, neonatal hyponatremia, neonatal transient tachypnea, respiratory distress syndrome, neonatal hyperbilirubinemia, cardiac malformation, congenital malformation, need intubation, mechanical ventilation in terms of need, neonatal death

and cerebral palsy, were no statistically different between the groups.

## DISCUSSION

According to the study outcomes, early adolescents had significantly higher rates of poor neonatal outcomes related to SGA newborn, small neonatal head circumference, neonatal hypoglycemia, and need for neonatal intensive care unit (NICU) and late-onset neonatal sepsis. On the contrary, preterm birth, macrosomia and asymmetrical IUGR, categorized as 3% percentile rates of young adults were higher than adolescents, while poor obstetric outcomes, such as severe preeclampsia and high CS rate, were significantly prevalent in late adolescents. A noteworthy point is that half of the early adolescents are immigrants. Evaluating *ad hoc* literature, a prospective study of Althabe et al. [28] consisting of 269,273 women from six different African countries revealed that both early and late adolescents had no increased risk of poor maternal outcomes, and risks of low birth weight and preterm birth were higher than adults. Regarding maternal outcomes, the results of Althabe et al. [28] study have some discordant findings with the current study. In addition, study data revealed that poor neonatal outcomes such as SGA infant and small infant head circumference were significantly more common in early adolescents and IUGR, categorized as 10% percentile in all adolescents, rather than preterm birth. Concerning this aspect, outcomes of literature studies show a partial agreement with one another. The reason for this difference, might be consisting of a distinct ethnic population. There are several literature studies revealing that adolescent pregnancies increased incidence of SGA infants similar to our results [19, 29], even if some authors reported reverse outcomes [30, 31]. It was suggested that the growing teenage pregnant may compete with the growing fetus for required nutrients, leading to subsequent small fetus and growth retardation [32]. Decreasing BMI levels regarding age in our results might be interpreted as contributing the growth retardation. The CS delivery rate was the highest in late adolescents and there was no CS delivery among early adolescents, although vaginal delivery was the main route in each group, considering our outcomes. Different comments are reported in literature concerning this issue. According to the consequences of a large population-based cohort study conducted by Marvin-Dowle et al. [33], adolescents had a significantly lower risk of CS. However, in this study, groups were not further divided as early and late adolescents [33]. Furthermore, a large sample-sized, multi-country study by Ganchimeg indicated that CS rates of younger adolescents ( $\leq 15$  years) were higher than that of adults and other adolescents unlike our study results [34]. However, the CS rate of teenagers was found to be higher than that of adults according to the results yielded from the study by

Ezegwui et al. [35], similarly with our outcomes. In addition, in another study, the CS prevalence of teenage mothers was found to be higher especially due to cephalopelvic disproportion [36]. Inadequate growth of pelvic bones and delivery canal in teenagers has been suggested as the main reason for obstructed labor leading to CS indication [30]. There are many reports in literature on preeclampsia risk in adolescents. Severe preeclampsia was significantly the most prevalent among late adolescents concerning our study results. Similarly, the outcomes of a large sample-sized retrospective cohort study presented that preeclampsia risk was significantly higher in adolescent mothers [37]. On the contrary, an Arabian study revealed that preeclampsia was more common in adult mothers than adolescents. Apart from both studies, a population-based large study by Conde-Agudelo [19] pointed that there was no significant difference between adult and teenage pregnancies concerning preeclampsia. Uterine immaturity of teenage pregnant leading to impaired deep uterine vascularization during placentation and atherosclerosis of uteroplacental arteries is a possible mechanism of adolescent preeclampsia also IUGR [38]. The Neonatal Intensive Care Unit (NICU) admission rate or fetuses of adolescent mothers was significantly higher than adults in our study. Correspondingly, Fleming et al. [37] and Bostancı Ergen et al. [16] reflected that the need for NICU was significant in newborns of adolescent mothers. However, Badawie et al. [4] reported no significant difference between newborns of adult and teenage mothers concerning NICU admission. While our investigation reported that late neonatal sepsis was prevalent among infants of early adolescents, Mukhopadhyay et al. [39] declared that there was no difference between babies of adolescent and adult mothers concerning neonatal sepsis. A major limitation of our study was being conducted in a single tertiary care center. Although this feature could be also a strength, for having collected a good sample size and evaluated a cosmopolitan population, especially early adolescent pregnant, due to the region of the hospital. Nevertheless, the study might, on the contrary, not represent the existing situation of the national whole population setting. Since all sociodemographic characteristics and income distribution of the patients were not recorded, their relationship could not be examined, and a causal association between these characteristics and the pregnancy complications could not be well established.

## CONCLUSIONS

Poor neonatal outcomes for SGA newborns, small neonatal head circumference, neonatal hypoglycemia, NICU need, and late-onset neonatal sepsis were more common in pregnant adolescents. Poor obstetric outcomes such as severe preeclampsia and a high cesarean rate were sig-

nificantly common in late adolescents. Literature different results might be due to various study populations and sample sizes. Anyway, adolescent pregnancy is substantially “at risk” for maternal and neonatal outcomes and is not an uncommon public health problem. Considering the easy accessibility of primary healthcare services in developed countries, providing sexual and social information such as contraception methods, they may be useful in reducing these adolescent pregnancies and related complications. Anyway, more prospective and larger sample size studies, also in undeveloped countries, establishing causal links between maternal age and related pregnancy outcomes, may broaden knowledge on this sensitive social and health issue.

### Ethical approval

The Human Research Ethics Committee of the University of Health Sciences approved the research protocol (process KAEK 2020/11/11 dated 2020), and GOKA numbered 2020/15/10 was obtained for conducting the research. This study was performed within the guidelines of the Helsinki Declaration.

### Acknowledgements

Main idea of the study: BY, HG, NY, CSC, SC. Design: BY, HG, SC, AT. Data collection: BY, CSC, SC. Analysis and interpretation of data: BY, HG, NY. Article drafting: BY, HG, NY, AT. Review of the final version of the article: BY, HG, NY, CSC, SC, AT.

### Conflict of interest

All authors declare no conflict of interest.

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