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Impact of Depressive Symptoms during the Second Trimester of Pregnancy on Maternal and Fetal Heart Rate Variability

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Objective: This study explores how maternal depressive symptoms during the second trimester, a critical phase for autonomic nervous system (ANS) development, affect maternal and fetal heart rate variability (HRV) in the third trimester, with implications for infant development.
Methods: We examined the effects of second trimester maternal depression on subsequent maternal and fetal HRV. A cohort of women in early or late second trimester completed depression assessments using the Edinburgh Postnatal Depression Scale (EPDS) and underwent HRV evaluations in the third trimester.
Results: Among 118 participants, 97 completed the EPDS at 14−20 weeks, with 12 showing depressive symptoms. At 21−28 weeks, 111 participants were assessed, and 24 were identified as possibly depressive. Depressive symptoms were linked to increased maternal pNN50% (percentage of successive NN intervals differing by more than 50 ms) and decreased detrended fluctuation analysis alpha, indicating hemodynamic shifts. Their fetuses showed reduced root mean square of successive differences, standard deviation of successive differences, and short-term and long-term variability indices, suggesting weakened parasympathetic activity.
Conclusion: Prenatal depression influences maternal physiological adaptation and fetal ANS development, highlighting HRV as a potential biomarker for predicting neurodevelopment. Early identification and treatment of mid-pregnancy depressive symptoms may help mitigate potential risks to infant neurodevelopment.

KEY WORDS: Depression; Heart rate, fetal; Autonomic nervous system; Fetal development.

INTRODUCTION

As a major life event, pregnancy often elicits positive feelings associated with impending motherhood. However, it concurrently serves as a source of considerable stress, which can stem from disruptions of work, ongoing changes in family relationships, physiological and hormonal fluctuations, as well as anxiety related to pregnancy. These distinctive psychosocial features often mask the occurrence of depressive moods [1], even though this period represents a heightened susceptibility to mental health disorders. Antenatal depression seems to serve as a predictive factor for postpartum depression [2], and the results of a cohort study demonstrated elevated depression scores at 32 weeks gestation versus 8 weeks postpartum [3]. Moreover, a substantial multi-cohort study identified a notable increase in the frequency of self-reported de-

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pressive symptoms during pregnancy, from 7 to 14% over a span of 25 years [4]. In the transition from Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV to DSM-5, the pregnancy-related specifier of major depressive disorder was expanded from being solely postpartum to encompassing the peripartum period, which includes the antenatal stage [5]. These changes underscore the essential need to understand, identify, and treat depression during pregnancy.

Depressed mood during pregnancy can have a profound negative impact on both the mother's and child's health, including increased risk of preeclampsia, preterm delivery and fetal growth. Beyond obstetric risks, maternal depressed mood may increase the risk of poor cognitive, social, and emotional development of their infants. Mothers who reported depressive symptoms during pregnancy tended to have infants who were more difficult to soothe [6], and these infants displayed poorer reflexes and exhibited higher baseline levels of cortisol and epinephrine, hormones associated with stress response [7]. Another study indicates that maternal cortisol levels in the third trimester of pregnancy predict increased infant negative reactivity, which supports the idea of the prenatal environment exerting long-lasting programming effects on the fetus [8]. A prospective longitudinal study found that antenatal depression symptoms, particularly during the second trimester, were positively associated with increased infant negative affectivity [9], suggesting a possible period of heightened fetal sensitivity to maternal depression in line with known patterns of fetal brain development. However, since many previous studies retrospectively surveyed self-reports after childbirth, recall bias may exist. Particularly if a mother is experiencing depression while raising her child, it's possible that the characteristics of the child might be reported in a more negative light. In addition, research examining the specific ways in which maternal depression impacts the process of fetal development before birth is scarce.

The autonomic nervous system (ANS) is vital in regulating the body's physiology, impacting organic development, stress response, and cognitive and emotional growth. The ANS development, extending across the prenatal, fetal, and neonatal stages, forms the foundation for individual differences in its function [10]. Early interference with ANS development could significantly impact its developmental trajectory, limit physiological responsiveness, and potentially contribute to later neuropsychiatric disorders [11,12]. While ANS development is typically evaluated during the 3rd trimester when vagus nerve myelination commences, existing literature suggests that potential critical windows influencing ANS maturation may occur earlier [13,14]. Owing to the challenges associated with the direct measurement of fetal ANS development, heart rate variability (HRV) has been employed as a non-invasive and effective assessment tool. HRV estimate the variability of time intervals between successive heartbeats, correlating with ANS development and function [15,16]. For this study, specific HRV parameters were selected based on their relevance to autonomic control during pregnancy. Root mean square of successive differences (RMSSD) was chosen as a robust marker of parasympathetic (vagal) activity, which plays a crucial role in fetal autonomic maturation. Similarly, DFA $\alpha 1$ (detrended fluctuation analysis, short-term scaling exponent) was included to assess the fractal properties and adaptability of the cardiac system, reflecting the integration of autonomic and systemic influences. These indices are particularly valuable during pregnancy, as they provide insights into the dynamic interplay of maternal physiological adaptation and fetal ANS development. Their inclusion builds on prior evidence supporting their utility in studies of autonomic function during gestation. These parameters, along with the broader utility of HRV, can reveal the impact of prenatal stress on fetal brain development and provide valuable diagnostic and prognostic information about fetal well-being and functional autonomic brain age [17].

The 2nd trimester of gestation represents a pivotal juncture for the development of the ANS, with a particular emphasis on parasympathetic maturation. Consequently, depressive mood manifestations during this period might wield a profound influence on fetal socio-emotional development trajectories. In light of this conceptual framework, the present research endeavors to specifically probe the influence of maternal depressive symptoms in the 2nd trimester on both maternal and fetal HRV in the 3rd trimester. This research could provide crucial insights into the effects of depression during pregnancy on physiological adaptations during this period and the development of fetal ANS.

METHODS

Participants

Participants were part of an ongoing research project exploring potential biomarkers of maternal-fetal attachment by collecting psychiatric questionnaires and biological data from pregnant women and their fetuses. This prospective observational cohort study involved a single center—CHA Gangnam Medical Center. The study encompassed pregnant women who had undergone integrated tests or non-invasive prenatal testing, and had been making consecutive antenatal visits from July 2021 through March 2023. All had a healthy pregnancy at the time of recruitment, and none of these participants were taking psychiatric medications. Recruitment procedures allowed participants to enroll at any stage of pregnancy, with 75% of participants registering between 10 to 22 weeks of gestation. The average gestational week at enrolment was 17 + 0 weeks, with a standard deviation of 8.503 weeks. Participants were requested to provide information on demographic variables, including age at enrollment, education year, body mass index (BMI) before pregnancy, annual household income and medical history during their enrollment. They visited a total of six times during the pregnancy period, with one visit in the early and late phase of each trimester. The visits occurred at 6−8 weeks, 9−13 weeks, 14−20 weeks, 21−28 weeks, 29−34 weeks, and 35−41 weeks. At each visit, they filled out several self-report questionnaires assessing depressive mood, sleep quality, subjective mental well-being, and prenatal maternal attachment. A fetal and maternal HRV was conducted during the third trimester of pregnancy.

In this study, we conducted an analysis on 118 women who visited at least once during either the early or late phase of the 2nd trimester, completed the measure of depressed mood, and underwent HRV monitoring for both the mother and fetus. Among them, 97 women completed the questionnaire during the early phase of the 2nd trimester (14−20 weeks), 111 women during the late phase of the 2nd trimester (21−28 weeks), and 80 of these women visited during both phases. Medical records were reviewed to extract relevant information such as the newborn's gender, weight, and Apgar score. All participating pregnant women gave their written informed consent before collecting medical records. The research procedures were approved by the Institutional Ethics Review Committee.

Measures

The Edinburgh Postnatal Depression Scale

The Edinburgh Postnatal Depression Scale (EPDS) is a widely-used self-report tool consisting of ten items scored from 0 to 3 based on the respondent's feelings over the past week, resulting in a total score range of 0−30 [18]. It has been validated for use in prenatal and postnatal periods and has proven reliable in detecting depressive states. The scale covers prevalent depressive symptoms while deliberately excluding somatic indicators, such as fatigue and altered appetite, frequently observed in women during pregnancy. This study used the Korean version of the EPDS scale, which showed good internal consistency (Cronbach's α coefficient 0.84) [19]. Past clinical studies have proposed a cut-off score 12/13 for likely depression and 9/10 for possible minor depression [20]. For this study, we classified participants with EPDS scores of 10 or higher as the "Possible Depressive Group" to investigate the influence of even mild depressive symptoms during pregnancy.

Maternal and fetal cardiotocography recording

We assessed the HRV of the participants in a normal resting state. Following a medical examination, each participant was asked to lie down in a supine position and remain quiet without speaking or making any movements for 5 minutes. The information gathered from subjects is presented as an maternal heart rate (MHR) and fetal heart rate (FHR) graph recorded by the Avalon FM20 (Philips Healthcare) CTG machine. Each cardiotocograph (CTG) record contains time information and signals for the FHR, MHR, and uterine contractions. Skin preparation, electrode placement and impedance testing were performed as per the manufacturer's instructions. In all cases, the CTG monitor applies a proprietary autocorrelation algorithm to determine the heart rates from the raw signals.

Heart rate variability feature extraction

Cardiotocography results were stored as PDF images. The conversion of these images into an analyzable format was accomplished using the prior methodology of this research team, which involved isolating pixels representing waveforms from the background via Red Green Blue channel differences [21]. The red pixels indicating FHR were distinguished from the white background pixels via the R channel's intensity. However, the pixel's position did not directly correspond to the FHR, therefore, we calculated its relative position on the graph, with the upper and lower graph limits fixed at 240 and 30, respectively. An algorithm incorporating the Hough transform [22] as utilized to determine the graph's borderlines, enabling the heart rate calculation based on the relative positions of the separated waveform pixels. This method converted the image file into a CSV file, where the HR value was then converted into an NN interval to calculate HRV features. All processes were executed utilizing Python, and the code pertinent to these procedures is accessible at https://github.com/CMI-Laboratory/Fetal_cardiotocography_extract_code.

The following time domain variables were obtained: the mean values for the standard deviation of all 24-hour NN intervals (SDNN), a measure of overall HRV encompassing both short- and long-term fluctuations; the SD of the averages of NN intervals in all 5-minute segments of the entire recording (SDANN), which primarily reflects long-term variability; the root mean square of the SD of successive NN intervals (RMSSD), which is closely associated with parasympathetic activity; the count and % of NN intervals differing by more than 50 ms (NN50 Count, pNN50%), which reflect beat-to-beat variability and parasympathetic influence; and the count and % of NN intervals differing by more than 20 ms (NN20 Count, pNN20%), a similar measure of short-term variability. In the frequency domain, our assessment considered variables such as absolute power, relative power, and peak for very low frequency (0.0033−0.04 Hz), which may reflect mechanisms such as thermoregulation and hormonal influences; low frequency (LF: 0.04−0.15 Hz), which includes both sympathetic and parasympathetic modulation and baroreceptor activity; and high frequency (HF: 0.15−0.4 Hz), which is widely recognized as an indicator of parasympathetic (vagal) activity. The LF/HF ratio was also assessed as an indicator of the balance between sympathetic and parasympathetic activity, though its interpretation is nuanced due to overlapping influences. We further enriched our analysis by determining non-linear parameters, including the Poincaré plot indicesd SD1 and SD2, which reflect short-term vagal activity and overall HRV, respectively; the SD ratio (SD1/SD2), which indicates sympathovagal balance; sample entropy, which quantifies the complexity and irregularity of heart rate dynamics; and detrended fluctuation analysis (DFA $\alpha 1$, DFA $\alpha 2$, and the α ratio), which characterize short- and long-term correlations in heart rate time series and provide insight into fractal dynamics and regulatory adaptability.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Co.). An Independent t test was used to compare differences in characteristics of demographics, maternal and fetal HRV between the possible depressive group and healthy group at each time point. The threshold of significance used for statistical analysis was set to $p < 0.05$.

Ethics Statement

The study was conducted according to the guidelines of the Declaration of Helsinki. The current study's protocols were approved by the Institutional Review Board of CHA Gangnam Medical Center, Seoul, Republic of Korea (GCI 2020-11-007). Informed consent was submitted by all subjects when they were enrolled.

RESULTS

Demographics

Analyses were conducted on 118 women who completed the EPDS in the 2nd trimester and the maternal and fetal HRV measurements in the 3rd trimester. Out of these, 97 women completed the EPDS between 14−20 weeks, of which 12 were identified as the possible depressive group. A total of 111 women completed the EPDS between 21−28 weeks, among whom 24 were categorized as the possible depressive group.

There were no significant differences in maternal age, education years, pre-pregnancy BMI, and gestational weeks of HRV recording between healthy and possible depressive groups at both 14−20 weeks and 21−28 weeks. The mean age of the entire participant pool was 33.89 (SD: 3.58) years and the average gestational week at the time of HRV measurement was 35 + 4 (SD: 2.41) weeks. Notably, significant differences in EPDS scores were found between the two groups at 14−20 weeks and

21−28 weeks, with the possible depressive group scoring 12.42 (SD: 2.47) and 12.79 (SD: 3.27), respectively. At both observed time points, no significant differences were detected between the groups concerning gestational weeks at delivery, gender of neonates, birth weight, and Apgar scores at 1 and 5 minutes (Tables 1, 2).

To further examine the impact of depressed mood in the 2nd mester on maternal and fetal HRV, we analyzed 80 women who completed the measure during both the early and late phases of the 2nd trimester. Among these, women who reported depressive symptoms above the cutoff on the EPDS at least once were categorized into the possible depressive group, while others were categorized as the healthy group. The healthy group consisted of 59 women, and the possible depressive group had 21 women. There were no differences between the groups based on factors other than the EPDS. The average EPDS score for the possible depressive group during the 2nd trimester was 9.69 (SD: 2.86), which was lower than the scores for the possible depressive groups in both the early and late phases of the 2nd trimester (Table 3).

The Influence of Maternal Depressed Mood at 14 to 20 Weeks on Maternal Heart Rate Variability

Upon examining the maternal and fetal HRV in relation to the reported depressed mood during the early phase of the 2nd trimester (14−20 weeks), we observed that in the maternal HRV, the PNN50% was higher in the possible depression group. Additionally, DFA $\alpha 2$ was notably lower in the possible depressive group, while the α ratio was elevated (Table 4). However, other indices of the maternal HRV showed no significant differences between the

Table 1. Baseline demographics of the healthy and possible depressive group in the early phase of the 2nd trimester (14−20 weeks) of pregnancy

Mother	Healthy group (n = 85)	Possible depressive group (n = 12)	*p*
Age (yr)	33.33 (3.31)	34.76 (3.14)	0.162
Education (yr)	16.28 (1.16)	16.00 (1.48)	0.448
BMI before pregnancy	21.37 (3.47)	21.31 (1.97)	0.953
EPDS score	3.67 (2.48)	12.42 (2.47)	< 0.001
Gestation weeks of HRV recording (wk)	35.42 (2.59)	35.94 (1.94)	0.415
Neonates			
Gestation weeks of delivery	38.86 (1.34)	39.33 (1.07)	0.187
% of men	50	50	< 0.999
Weight (g)	3,167.8 (385.6)	3,251.7 (422.6)	0.528
Apgar score at 1 min	7.76 (0.77)	7.75 (0.62)	0.951
Apgar score at 5 min	8.90 (0.61)	9.00 (0.00)	0.572

Values are presented as mean (standard deviation) or percentage only.
BMI, body mass index; EPDS, Edinburgh Postnatal Depression Scale; HRV, heart rate variability.

Table 2. Baseline demographics of the healthy and possible depressive group in the late phase of the 2nd trimester (21−28 weeks) of pregnancy

Mother	Healthy group (n = 87)	Possible depressive group (n = 24)	*p*
Age (yr)	33.68 (3.30)	33.34 (3.77)	0.672
Education (yr)	16.23 (1.12)	16.33 (1.27)	0.698
BMI before pregnancy	21.33 (3.15)	21.30 (2.90)	0.964
EPDS score	4.14 (2.46)	12.79 (3.27)	< 0.001
Gestation weeks of HRV recording (wk)	35.63 (2.35)	36.35 (2.22)	0.183
Neonates			
Gestation weeks of delivery	39.03 (1.10)	38.83 (1.81)	0.522
% of men	51.8	43.5	0.480
Weight (g)	3,214.7 (370.2)	3,090.0 (446.0)	0.175
Apgar score at 1 min	7.80 (0.64)	7.87 (0.34)	0.593
Apgar score at 5 min	8.94 (0.33)	8.96 (0.21)	0.816

Values are presented as mean (standard deviation) or percentage only.
BMI, body mass index; EPDS, Edinburgh Postnatal Depression Scale; HRV, heart rate variability.

Table 3. Baseline demographics of the healthy and possible depressive groups who experienced depressive symptoms at least once during either the early or late phase of the 2nd trimester of pregnancy

Mother	Healthy group (n = 59)	Possible depressive group (n = 21)	*p*
Age (yr)	33.37 (3.18)	33.37 (3.59)	0.999
Education (yr)	16.24 (1.29)	16.19 (1.25)	0.886
BMI before pregnancy	21.48 (3.45)	21.54 (3.08)	0.951
Average EPDS score during 2nd trimester	3.58 (1.96)	9.69 (2.86)	$<$ 0.001
Gestation weeks of HRV recording (wk)	35.55 (2.49)	36.32 (2.19)	0.213
Neonates			χ^2/p
Gestation weeks of delivery	38.92 (1.10)	38.94 (1.83)	0.946
% of men	50	52.4	0.035/0.852
Weight (g)	3,188.6 (357.3)	3,132.8 (447.6)	0.572
Apgar score at 1 min	7.80 (0.62)	7.81 (0.51)	0.969
Apgar score at 5 min	8.96 (0.27)	8.95 (0.22)	0.856

Values are presented as mean (standard deviation) or percentage only.
BMI, body mass index; EPDS, Edinburgh Postnatal Depression Scale; HRV, heart rate variability.

Table 4. Means, standard deviations, and group comparisons for maternal HRV in the healthy and possible depressive group in the early phase of the 2nd trimester (14−20 weeks) of pregnancy

Maternal HRV indexes	Healthy group (n = 85)	Possible depressive group (n = 12)	Independent samples *t* test		
			t	df	*p*
pNN50%	0.036 (0.060)	0.081 (0.095)	−2.238	95	0.028
DFA α2	1.615 (0.082)	1.540 (0.100)	2.872	95	0.005
DFA α ratio	1.185 (0.057)	1.226 (0.054)	−2.354	95	0.021

Values are presented as mean (standard deviation).
HRV, heart rate variability; pNN50%, the count and % of NN intervals differing by more than 50 ms; DFA, detrended fluctuation analysis.

Table 5. Means, standard deviations, and group comparisons for fetal HRV in the healthy and possible depressive group in the late phase of the 2nd trimester (21−28 weeks) of pregnancy

Fetal HRV indexes	Healthy group (n = 87)	Possible depressive group (n = 24)	Independent samples *t* test		
			t	df	*p*
RMSSD	3.677 (2.709)	2.930 (0.819)	2.229	108.06	0.028
SDSD	3.172 (2.771)	2.375 (0.739)	2.392	108.97	0.018
SD1	2.600 (1.916)	2.072 (0.582)	1.909	61.68	0.028

Values are presented as mean (standard deviation).
HRV, heart rate variability; RMSSD, root mean square of the successive differences of successive NN intervals; SDSD, standard deviation of successive RR interval differences; SD1, Poincaré plot standard deviation perpendicular the line of identity.

groups (Supplementary Table 1; available online). Moreover, there were no meaningful differences observed between the two groups in terms of fetal HRV indices (Supplementary Table 2; available online).

The Influence of Maternal Depressed Mood at 21 to 28 Weeks on Fetal Heart Rate Variability

Upon analyzing the maternal and fetal HRV in relation to the reported depressed mood during the late phase of the 2nd trimester (21−28 weeks), all indices of the maternal HRV exhibited no discernible differences between the groups (Supplementary Table 3; available online). In the fetal HRV, both RMSSD, standard deviation of successive differences (SDSD) and SD1 were significantly lower in the possible depressive group compared to the healthy group (Table 5). Other indices of the fetal HRV showed no significant differences between the groups (Supplementary Table 4; available online).

Table 6. Means, standard deviations, and group comparisons for maternal and fetal HRV in the healthy and possible depressive groups who experienced depressive symptoms at least once during either the early or late phase of the 2nd trimester of pregnancy

Maternal HRV indexes	Healthy group (n = 59)	Possible depressive group (n = 21)	Independent samples t test		
			t	df	p
DFA α1	1.910 (0.044)	1.883 (0.059)	2.137	78.007	0.036
Fetal HRV indexes					
RMSSD	3.741 (3.048)	2.866 (0.814)	2.012	74.869	0.048
SDSD	3.249 (3.128)	2.321 (0.750)	2.115	72.745	0.038
SD1	2.645 (2.155)	2.026 (0.576)	2.012	74.869	0.048
SD2	35.002 (13.91)	29.742 (8.577)	2.018	57.586	0.048

Values are presented as mean (standard deviation).
HRV, heart rate variability; DFA, detrended fluctuation analysis; RMSSD, root mean square of the successive differences of successive NN intervals; SDSD, standard deviation of successive RR interval differences; SD1, Poincaré plot standard deviation perpendicular the line of identity; SD2, Poincaré plot standard deviation along the line of identity.

The Influence of Maternal Depressed Mood Reported at Either the Early or Late Phase of the 2nd Trimester on Maternal and Fetal Heart Rate Variability

For women who experienced depressive symptoms during either the early or late phase of the 2nd trimester, the maternal HRV parameter DFA alpha 1 was lower. Additionally, in terms of fetal HRV, RMSSD, SDSD, SD1, and SD2 were significantly lower in the possible depressive women (Table 6). More detailed information on the differences between groups in maternal and fetal HRV can be found in Supplementary Tables 5 and 6 (available online).

DISCUSSION

Using data from a cohort of pregnant women, the current study investigated the associations between depressed prenatal mood and maternal and fetal resting HRV, an indicator of parasympathetic regulation and development of ANS. One particular strength of this study is the concurrent assessment of maternal and fetal HRV, a methodology scarcely seen in prior research, providing new insights into these intertwined physiological processes. We notably examined the influence of maternal depressive mood experienced during the second trimester, a critical window for developing the parasympathetic division of the ANS. Women who experienced depressive mood exhibited an augmentation in pNN50% and a diminution in DFA alpha within HRV indices, insinuating alterations in hemodynamic adaptations during late pregnancy. Correspondingly, their fetuses demonstrated reductions in RMSSD, SDSD, SD1, and SD2, thereby suggesting attenuations in the parasympathetic variables of fetal HRV. These alterations may predispose the children to be susceptible to physiological and neurological changes that influence emotional, cognitive, and social developmental trajectories, potentially increasing the risk of unfavorable outcomes. HRV, as a physiological biomarker, may provide the groundwork for predicting neurodevelopmental outcomes, offering valuable insights for early intervention strategies in children at risk of altered neurodevelopment due to prenatal depression.

Pregnancy is a period characterized by significant physiological changes across virtually all body systems, including increased blood volume, heart rate, and cardiac output, alongside a decrease in peripheral resistance and blood pressure [23,24]. These adaptations aim to optimize the nutrient and oxygen supply to both maternal and fetal tissues. The ANS appears to play a crucial role in the onset and sustainment of these physiological changes, as evidenced by existing research [25-27]. One study explored HRV changes throughout a healthy pregnancy, discovering a shift from dominant cardiac parasympathetic activity in early pregnancy to dominant cardiac sympathetic activity in late pregnancy. This shift was evidenced by decreasing markers of parasympathetic activity (SDSD, pNN50, and HF) and increased LF, representing primarily sympathetic-induced activity, throughout pregnancy [28]. This suggests that as pregnancy progresses, pregnant women exhibit a diminished heart rate responsiveness, implying a reduced cardiac autonomic control plasticity, which can be interpreted as developing a defective adaptive capacity to protect the fetus. In a previous study measuring depressive symptoms and maternal HRV at the 27 gestational weeks, it was suggested that depression during pregnancy is linked with decreased HRV, specifically in time domain measures such as SDNN and SDANN [29]. This finding is indicative of a potential decrease in vagal influences among pregnant women experiencing depression, a conclusion that is consistent with the documented impact of depression on HRV in the general population [30]. In our study, these parameters did not show significant differences between groups, which may reflect either limited statistical power or physiological resilience in the maternal autonomic system. The adaptations during pregnancy may buffer the impact of depressive symptoms on overall and long-term HRV variability. On the other hand, our study demonstrated that the group potentially experiencing depression between 14－20 gestational weeks exhibited a higher pNN50%, suggesting an increased parasympathetic tone compared to the healthy group. Furthermore, DFA alpha, which provides insight into the fractal-like correlation attributes of R-R interval data and typically increases during parasympathetic withdrawal [31], was lower in the possible depressive group. This observation might be interpreted as a lower parasympathetic tone within the healthy pregnant group. In contrast to previous studies that assessed depressive symptoms and HRV simultaneously, our study confirmed the influence of depressive feelings in the second trimester on subsequent maternal HRV, reflecting ANS adaptation during pregnancy. These findings suggest potential deficiencies in hemodynamic adaptation in depressive pregnant women, which should typically progress as women approach the later stages of pregnancy. Consequently, this might lead to a decrease in the appropriate regulation of blood supply to the fetus.

In this study, fetuses of mothers who experienced depressed mood during the 21－28 gestational weeks exhibited a significant decrease in RMSSD, SDSD and SD1. This reduction in RMSSD and SDSD, which are key indicators of HRV representing short-term variations in successive heartbeats, suggests autonomic dysmaturation. In fetuses of mothers who experienced depressed mood at any point during the second trimester, SD1 and SD2 were also notably reduced. SD1, reflecting short-term HRV, represents beat-to-beat variability and is primarily influenced by the parasympathetic nervous system. On the other hand, SD2 indicates longer-term HRV and captures changes in heart rate due to the cycle of day and night, stress, and other factors, integrating both parasympathetic and sympathetic influences. This reduction in SD1 and SD2 suggests a potential disruption in the balance and maturation of the ANS in these fetuses.

Building on these findings, the broader context highlights the developmental origins of health and disease (DOHaD) hypothesis, which suggests that early life environmental exposures shape individual variations in lifelong health and disease susceptibility, including psychopathology [32]. This hypothesis has been fortified by numerous potential mechanisms, incluindg alteration in the fetal hypothalamic-pituitary-adrenal axis [33], long-term changes in the epigenome [34], maternal immune activation [35], and modifications in the intestinal microbiome [33]. Additionally, techniques that assess fetal neurobehavioral development, such as FHR, fetal heart rate variability (FHRV), and the correlation between fetal movement and FHR, can provide valuable insights into how maternal depressed mood reaches the fetal brain via ANS development. ANS undergoes a prolonged development and maturation process during fetal and neonatal life, making it susceptible to various physiological and environmental stimuli disruption. The sympathetic division of the ANS, responsible for heart rate and blood pressure variability, progresses steadily throughout the fetal period and plays an important role in heart rate and blood pressure variability [36]. In contrast, the parasympathetic nervous system begins development during the 1st trimester with the differentiation of the lateral hypothalamus and increased vagus nerve myelination, but it doesn't exert much influence until around 25－30 weeks gestation, with a steep increase in vagal tone occurring around 37－38 weeks [13,37,38]. The parasympathetic nervous system undergoes continuous maturation during late pregnancy and the postnatal period, impacting the resting heart rate [39,40]. This system and the sympathetic branch interact with the central autonomic network, influencing higher cortical functions, including cognition control, emotional regulation, and behavior, and adapting complex non-linear interactions in response to environmental stimuli [14,41]. The findings of this study reveal that fetuses at 37－38 weeks of gestation from mothers who experienced depressed moods during the mid-pregnancy exhibit reduced HRV. This supports previous research suggesting that the risk of poor cognitive, social, and emotional development in infants born to mothers who were depressed during pregnancy arises from 'programming' that begins in the fetal stage. Maternal depression during pregnancy is just one of the numerous factors that can influence a child's future, but importantly, it's a factor that can often be adjusted. Offering supportive interventions to pregnant women dealing with distress not only aids these women but also may bring about positive outcomes for their children.

This study has objectively confirmed the influence of depressive symptoms during mid-pregnancy on the mother and fetus through physiologic effects. The study suggests that in addition to the already known biological biomarkers involved in the pathogenesis of perinatal depression, maternal and fetal HRV can also be used as reliable biomarkers. Moreover, it provides information about the timing, one of the important moderators of the DOHaD hypothesis on the fetal origins of child psychopathology. However, some limitations should be noted. First, the possible depressive group was not clinically diagnosed but was classified based on self-report EPDS scores. While the EPDS is a validated tool with high sensitivity for detecting depressive symptoms during pregnancy, it does not replace a formal clinical diagnosis. This limitation highlights the potential for misclassification, which could impact the interpretation of the findings. Despite this, the use of the EPDS allowed us to detect even minor depressive symptoms, which might otherwise be underestimated during pregnancy. Future studies should aim to incorporate clinical evaluations to enhance diagnostic accuracy. Second, due to incomplete measures from some mothers in the cohort, we could not confirm HRV changes associated with the mother's depressive changes over time. In other words, we could not consider the impact of depression experienced in the first or third trimester of pregnancy on the mother and fetus, aside from during mid-pregnancy. Despite these limitations, the cohort used in this study provides valuable research material that allows us to verify whether these findings are associated with maternal mental disorders or child psychopathology. This is due to the evaluation of the timing of maternal depressive experience, the extent of fetal ANS development, and the plan to conduct postpartum depressive scale, infant HRV, and emotional-behavioral evaluation of the child in the subsequent long-term follow-up.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Kyungun Jhung, Dukyong Yoon, Hee Young Cho, Jin Young Park. Data curation: Dukyong Yoon, Jihoon Seo. Formal analysis: Heeyeon Kim. Methodology: Hee Young Cho, Jin Young Park. Investigation: Hee Young Cho. Project administration: Kyungun Jhung, Hee Young Cho, Jin Young Park. Funding acquisition: Jin Young Park. Software: Dukyong Yoon, Jihoon Seo. Supervision: Hee Young Cho, Jin Young Park. Writing – original draft: Heeyeon Kim. Writing – review & editing: Heeyeon Kim, Kyungun Jhung, Hee Young Cho.

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