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Mental Health in Early Pregnancy and Spontaneous Abortion Risk: A Prospective Cohort Study

ABSTRACT

Objective: This study aims to explore the relationship between maternal mental health during early pregnancy and the risk of spontaneous abortion (SA), especially in the context of the Coronavirus disease 2019 pandemic.

Methods: We conducted a prospective cohort study involving 4088 pregnant women at a maternal-child health hospital in China from January to December 2022. During the first trimester, we assessed depression, anxiety, and stress levels using the Depression, Anxiety, and Stress Scale (DASS-21). Pregnancy outcomes were monitored, and univariate and multiple logistic analyses were performed to identify the risk factors. These factors were then used to develop a nomogram model.

Results: Significant differences were found in maternal age, number of embryonic arrests, history of abortion, assisted reproduction, and environmental exposure between the SA group (n = 302) and the normal pregnancy group (n = 3786). After adjusting for potential confounders, higher scores on the DASS-21 subscales were independently associated with an increased risk of SA: Depression (OR [Odds Ratio] = 1.54, 95% CI [Confidence Interval]: 1.39-1.71, $P < .001$), Anxiety (OR = 1.61, 95% CI: 1.44-1.80, $P < .001$), and Stress (OR = 1.69, 95% CI: 1.31-2.20, $P < .001$). The model achieved a concordance index of 0.87 (95% CI: 0.86-0.90) and demonstrated a well-fitted calibration curve, indicating its good clinical applicability.

Conclusion: Our findings indicate that mental health conditions are significantly associated with an increased risk of SA. The nomogram model also demonstrated strong predictive accuracy, indicating its potential usefulness in clinical settings.

Keywords: Spontaneous abortion, mental health, nomograms, risk factors, cohort study

Introduction

Spontaneous abortion (SA), defined as the loss of pregnancy before 20 weeks of gestation without external intervention, affects approximately 10-20% of clinically recognized pregnancies.[1,2] Spontaneous abortion not only leads to adverse physical health effects, but also triggers psychological distress, such as depression and anxiety, in affected women. Emerging evidence suggests a reciprocal relationship where poor maternal mental health could potentially increase the risk of SA, indicating the role of biopsychosocial pathways in pregnancy outcomes.[3-4] Several studies have illustrated the impact of psychological factors on pregnancy outcomes. For instance, elevated stress and anxiety levels have been linked to an increased risk of SA.[5-6] These findings emphasize the necessity of addressing maternal mental health for healthy pregnancies.

The Coronavirus disease 2019 (COVID-19) pandemic has significantly heightened stress and anxiety levels among pregnant women, making it crucial to explore how these psychological stressors impact pregnancy outcomes.[7] Studies have documented increased levels of depression and anxiety among pregnant women during the pandemic, underscoring the urgency of this research.

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This study investigates the relationship between maternal mental health in early pregnancy and the risk of SA during the COVID-19 pandemic. The goal is to develop a predictive nomogram model to offer actionable insights for preventing SA through enhanced mental health interventions.

Materials and Methods

Study Design and Participants

A prospective cohort study was conducted involving 4088 pregnant women at a maternal-child health hospital in China from January to December 2022. Mental health assessments using the Chinese version of the Depression Anxiety and Stress Scale (DASS-21) were performed during the first trimester, and pregnancy outcomes were monitored.[8] Follow-up was conducted regularly, and reasons for loss of follow-up included relocation, withdrawal of consent, and inability to contact the participant. Efforts were made to minimize loss of follow-up by maintaining regular contact and providing flexible follow-up options. Based on their final pregnancy outcomes, they were categorized into either the SA group (n = 302) or the normal pregnancy group (n = 3786).

Inclusion Criteria

1) Women currently pregnant, confirmed through ultrasound to have a normal intrauterine pregnancy, who consent to partake in this research survey.
2) Age range for pregnant participants: 18 to 48 years.

Exclusion Criteria

1) Pregnant participants exhibiting abnormal development of the reproductive system.
2) Those diagnosed with autoimmune disorders, including but not limited to antiphospholipid syndrome, systemic lupus erythematosus, undifferentiated connective tissue disease, and Sjogren's syndrome.
3) Individuals with severe medical conditions affecting vital organs or systems, such as the heart, liver, kidney, or hematopoietic system.
4) Cases where data collection was not comprehensively completed.

For a visual overview of the selection process, refer to Figure 1.

Data Collection

A meticulously crafted questionnaire was formulated to amass a comprehensive dataset, aligning with the predefined survey protocol. This instrument probed a spectrum of determinants, segmented into 3 principal domains:

1) Demographic Characteristics: This encompasses age, gravidity, abortion count, embryonic arrest incidents, body mass index (BMI), educational attainment, and household income.
2) Medical History: This domain surveyed the presence of hypertension, thyroid function anomalies, diabetes mellitus, polycystic ovary syndrome, history of assisted reproductive technologies, and lifestyle choices such as smoking and alcohol consumption, alongside environmental exposures including air pollution and ionizing radiation.
3) Lifestyle Factors: This section evaluated the regularity of nocturnal activities extending beyond conventional hours and any recent domestic refurbishments.

The assessment of psychological well-being was conducted utilizing the Chinese adaptation of the DASS-21.[8] This instrument is comprised of 3 distinct subscales—depression, anxiety, and stress—encompassing a cumulative total of 21 items. Participants rated their affective states over the preceding week using a 4-point Likert scale, which spans from 0 (indicating disagreement) to 3 (indicating strong agreement), with ascending scores reflecting heightened emotional intensity. The aggregate DASS scores facilitated the stratification of psychological distress into 5 categorical levels: normal, mild, moderate, severe, and extremely severe. The scale demonstrated robust internal consistency, as evidenced by a Cronbach's alpha coefficient of 0.890, affirming its reliability and validity in the appraisal of mental health among the pregnant population.[7,8]

Within the initial 6-week gestational period, healthcare professionals facilitated the electronic completion of the questionnaire by pregnant women via smart devices. Systematic transvaginal ultrasound assessments were conducted to ascertain embryonic vitality. Participants encountering embryonic cessation resulting in spontaneous miscarriage were categorized into the SA cohort. Conversely, those maintaining viable pregnancies were classified into the normal gestation cohort. Data entry was meticulously executed in duplicate to ensure veracity. Prior to questionnaire administration, healthcare providers engaged in consultative discussions with the participants, affirming the safeguarding of personal data confidentiality. Informed consent was obtained, underscoring the voluntary nature of participation. The investigative protocol received ethical clearance from the Ethics Committee of Jinan Second Maternal and Child Health Hospital (approval number: 2023-YBD-1-05).

Statistical Methods

Data management was performed using EpiData version 3.1 (The EpiData Association, Odense, Denmark), and statistical analyses were conducted with R software version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were presented as mean ± Standard Deviation (SD) and were compared using Student's *t*-test or the Mann–Whitney *U* test based on the normality of data distribution. Normality was assessed using the Shapiro–Wilk test. Effect sizes were reported as Cohen's *d* for normally distributed data and Cliff's Delta for non-normally distributed data. Categorical variables were presented as frequencies and percentages and were compared using the Pearson Chi-Square test. If there were expected value problems, Fisher's exact test or Fisher–Freeman–Halton test was performed. Pairwise comparisons were performed for statistically significant variables using post hoc tests with Bonferroni correction. Effect sizes for categorical data were reported as Phi coefficients.

MAIN POINTS

- *Our study establishes a strong link between early pregnancy maternal mental health and the risk of Spontaneous abortion (SA).*
- *Utilizing the Depression Anxiety and Stress Scale (DASS-21) helps enhance the accuracy of risk prediction and management.*
- *A pioneering predictive model evaluates SA risk from maternal mental health cues, paving the way for timely intervention.*

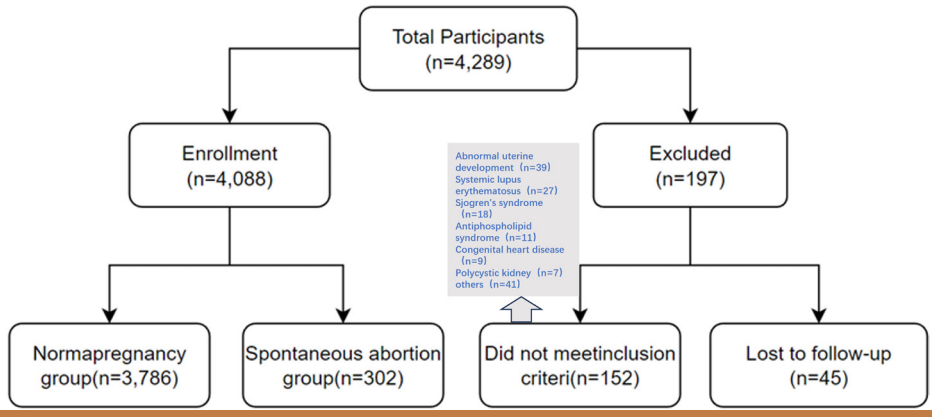

Figure 1. Flowchart of study selection. This figure presents the flowchart of the included samples, starting with 4289 total participants.

Comparisons between groups utilized the Student's *t*-test for continuous variables and the Chi-Square test (χ^2) for categorical variables, with adjusted *P*-values reported to account for multiple testing when applicable. In the multiple logistic regression analysis, variables with *P*-values less than .05 in the univariate analysis were adjusted for to ensure that only predictors with a significant effect on the results were included in the model. The occurrence of SA was designated as the dependent variable. A stepwise logistic regression analysis was conducted to identify potential predictors of SA. A nomogram model was constructed based on multiple analyses using the "rms" package in R. Receiver Operating Characteristic (ROC) curve analysis was performed to determine the optimal cut-off values for the DASS-21 subscales. The Youden Index was employed to identify these cut-off points, maximizing the sum of sensitivity and specificity.

Results

Participant Characteristics

The study encompassed 3786 individuals in the normal pregnancy cohort and 302 individuals in the spontaneous abortion (SA) cohort. The mean age of participants in the SA group was 33.19 ± 6.27 years, which was notably greater than the 30.59 ± 6.02 years observed in the normal pregnancy group ($P < .001$). Furthermore, a significantly larger fraction of the SA group had a body mass index (BMI) of ≥28.0 kg/m^2 (58.0%), compared to the normal pregnancy group (37.1%) ($P < .001$). In contrast, no significant disparities were detected between the cohorts regarding educational attainment ($P = .336$) or a monthly income exceeding 10 000 yuan ($P = .806$). Comprehensive data are presented in Table 1.

Comparison of Past History and Lifestyle Factors

The proportion of primiparous women was comparable between the 2 groups (31.5% and 33.9%, $P = .564$). However, the group experiencing SA had a significantly higher percentage of women with a history of one or more prior embryonic arrests (56.6% compared to 16.8%, $P < .001$). Additionally, a history of previous abortion was significantly more common in the SA group (68.9%) than in the control group (23.9%, $P < .001$).

The incidence of a history of hypertension did not differ significantly between the groups ($P = .572$). The SA group, however, presented higher incidences of abnormal thyroid function (4.0% versus 2.5%, $P = .143$) and a history of diabetes (5.6% versus 3.3%, $P = .031$), with only the latter reaching statistical significance. Furthermore, polycystic ovary syndrome was more commonly observed in the SA group (11.3% compared to 6.5%, $P = .002$).

Additionally, the utilization of assisted reproductive technology was notably higher in the SA group (5.6% compared to 1.3%, $P < .001$). It is important to mention that there were no significant disparities observed between the groups concerning smoking habits ($P = .104$), alcohol consumption ($P = .012$), exposure to environmental pollutants ($P < .001$), or recent home renovations ($P = .154$). Table 1 provides a detailed account of these data.

Assessment of Mental Health Status

The outcomes derived from a univariate analysis concerning the mental health status of the participants revealed statistically significant distinctions between the normal pregnancy group and the SA group across all examined variables ($P < .05$). Specifically, individuals in the SA group exhibited a greater prevalence within the severe and extremely severe spectrums of depression, anxiety, and stress when compared to those in the normal pregnancy group. For comprehensive insights into these findings, refer to Table 2.

Multiple Logistic Regression Analysis

After adjusting for confounding variables, the multiple logistic regression analysis identified several independent predictors of an increased risk of SA. Advanced maternal age was associated with a higher risk (OR [Odds Ratio] = 1.07; 95% CI [Confidence Interval]: 1.05-1.10, $P < .001$), as were previous abortion history (OR = 1.68; 95% CI: 1.44-1.94, $P < .001$), and history of embryonic arrest (OR = 4.45; 95% CI: 3.61-5.49, $P < .001$). Exposure to environmental pollution also showed a significant association (OR = 1.45; 95% CI: 1.10-1.91, $P = .008$). Additionally, mental health issues such as depression (OR = 1.54; 95% CI: 1.39-1.71, $P < .001$), anxiety (OR = 1.61; 95% CI: 1.44-1.80, $P < .001$), and stress (OR = 1.69; 95% CI: 1.31-2.20, $P < .001$) were significantly associated with a heightened risk.

In contrast, no significant correlations were found between SA and factors such as diabetes, polycystic ovary syndrome, assisted reproductive technology usage, or alcohol consumption, as all had *P*-values above .05. Notably, the associations with depression, anxiety, and stress remained significant even after adjusting for potential confounders. For a detailed graphical depiction of these associations, see Figure 2.

Table 1. Univariate Analysis of General Information and Clinical Factors

Variable	Normal Pregnancy (n = 3786)	Spontaneous Abortion (n = 302)	*P*-value	Effect Size* (Cohen's *d*/Phi)	Pairwise Comparison (*P*-value)
Age	30.59 ± 6.02	33.19 ± 6.27	< .001	0.43	–
BMI			< .001	0.26	–
< = 18.4	1110 (29.3)	30 (9.9)			< = 18.4 vs 18.5-27.9: .002
18.5~27.9	1274 (33.6)	97 (32.1)			< = 18.4 vs > =2 8.0: < .001
> = 28.0	1402 (37.1)	175 (58.0)			18.5-27.9 vs > = 28.0: < .001
Educational level			.336	−0.02	–
Below the university	1864 (49.3)	140 (46.4)			
University and above	1922 (50.7)	162 (53.6)			
Monthly household income			.806	0.03	–
< 10000 RMB	1953 (51.6)	158 (52.3)			
≥ 10000 RMB	1833 (48.4)	144 (47.7)			
Fetal number			.564	−0.02	–
1	1284 (33.9)	95 (31.5)			
2	1228 (32.4)	97 (32.1)			
≥ 3	1274 (33.6)	110 (36.4)			
Number of embryonic arrests			< .001	0.49	0 vs 1: < .001
0	3146 (83.1)	131 (43.4)			0 vs 2: < .001
1	284 (7.5)	115 (38.1)			0 vs ≥ 3: < .001
2	86 (2.3)	54 (17.9)			1 vs 2: .003
≥ 3	0 (0)	2 (0.6)			1 vs ≥ 3: .021
Number of abortions			< .001	0.43	0 vs 1: < .001
0	2880 (76.1)	94 (31.1)			0 vs 2: < .001
1	482 (12.7)	96 (31.8)			0 vs ≥ 3: .019
2	287 (7.6)	103 (34.1)			1 vs 2: .012
≥ 3	137 (3.6)	9 (3.0)			1 vs ≥ 3: .045
High blood pressure			.572	−0.01	–
No	3370 (89.0)	272 (90.1)			
Yes	416 (11.0)	30 (9.9)			
Thyroid dysfunction			.143	0.04	–
No	3689 (97.5)	290 (96.0)			
Yes	97 (2.5)	12 (4.0)			
Diabetes			.031	0.05	–
No	3662 (96.8)	285 (94.4)			
Yes	124 (3.3)	17 (5.6)			
Polycystic ovary syndrome			.002	0.08	–
No	3540 (93.5)	268 (88.7)			
Yes	246 (6.5)	34 (11.3)			
Assisted reproduction			< .001	0.09	–
No	3737 (98.7)	285 (94.4)			
Yes	49 (1.3)	17 (5.6)			
Smoking history			.104	0.03	–
No	3731 (98.5)	294 (97.4)			
Yes	55 (1.5)	8 (2.6)			
Drinking history			.012	−0.05	–
No	3517 (92.9)	292 (96.7)			
Yes	269 (7.1)	10 (3.3)			
Exposure to pollution sources			< .001	−0.08	–
No	2388 (63.1)	155 (51.3)			
Yes	1398 (36.9)	147 (48.7)			
Often stay up late			.192	−0.03	–
No	1921 (50.8)	165 (54.6)			
Yes	1865 (49.2)	137 (45.4)			
Recent home decoration			.154	0.03	–
No	1841 (48.6)	134 (44.4)			
Yes	1945 (51.4)	168 (55.6)			

*For normally distributed continuous data, we reported Cohen's *d* values, and for categorical data, we reported Phi effect size values. The "–" indicates that pairwise comparisons are not applicable or not significant for those specific variables. BMI, body mass index; RMB, Chinese yuan.

Table 2. Single-Factor Analysis of the Mental Health Status

Variable	Normal Pregnancy (n = 3786)	Spontaneous Abortion (n = 302)	*P*	Effect Size (Phi)	Pairwise Comparison (*P*)
Depression (% n)			< .001	0.21	Normal vs Mild: .051 Normal vs Moderate: .047 Normal vs Severe: .043 Normal vs Extremely severe: <.001 Mild vs Moderate: .056 Mild vs Severe: .051 Mild vs Extremely severe: <.001 Moderate vs Severe: .065 Moderate vs Extremely severe: <.001 Severe vs Extremely severe: <.001
Normal	652 (17.2)	9 (3.1)			
Mild	753 (19.9)	62 (20.5)			
Moderate	813 (21.5)	56 (18.5)			
Severe	868 (22.9)	56 (18.5)			
Extremely severe	700 (18.5)	119 (39.4)			
Anxiety (% n)			< .001	0.29	Normal vs Mild: .041 Normal vs Moderate: .038 Normal vs Severe: .033 Normal vs Extremely severe: <.001 Mild vs Moderate: .048 Mild vs Severe: .043 Mild vs Extremely severe: <.001 Moderate vs Severe: .051 Moderate vs Extremely severe: <.001 Severe vs Extremely severe: <.001
Normal	694 (18.3)	36 (11.9)			
Mild	756 (20.0)	50 (16.6)			
Moderate	724 (19.1)	46 (15.2)			
Severe	881 (23.3)	53 (17.5)			
Extremely severe	731 (19.3)	117 (38.8)			
Stress (% n)			< .001	0.33	Normal vs Mild: .054 Normal vs Moderate: .049 Normal vs Severe: .045 Normal vs Extremely severe: <.001 Mild vs Moderate: .058 Mild vs Severe: .052 Mild vs Extremely severe: <.001 Moderate vs Severe: .062 Moderate vs Extremely severe: <.001 Severe vs Extremely severe: <.001
Normal	338 (8.9)	31 (10.3)			
Mild	673 (17.8)	16 (5.3)			
Moderate	515 (13.6)	94 (31.1)			
Severe	1273 (33.6)	43 (14.2)			
Extremely severe	987 (26.1)	118 (39.1)			

Development and Verification of Nomogram Model

Employing multiple logistic regression analysis, our study constructed a nomogram to estimate the risk of SA based on 6 determinants (Figure 3). The model's reliability was assessed through bootstrapped internal validation with 1000 resamples, resulting in a robust area under the curve (AUC) of 0.87 (95% CI: 0.86-0.90) (Figure 4). The standard error was 0.02, and the results were statistically significant (*P* < .001). Using the Youden Index, we determined an optimal threshold of 0.79, which achieved 82% sensitivity and 79% specificity.

Discussion

Our study demonstrated that pregnant women experiencing depression, anxiety, and stress have a significantly higher risk of SA. The prevalence of moderate-to-extremely severe depression, anxiety, and stress was notably higher among women who experienced SA compared to those with normal pregnancies. Even after adjusting for potential confounders, depression, anxiety, and stress remained significantly associated with an increased risk of SA.

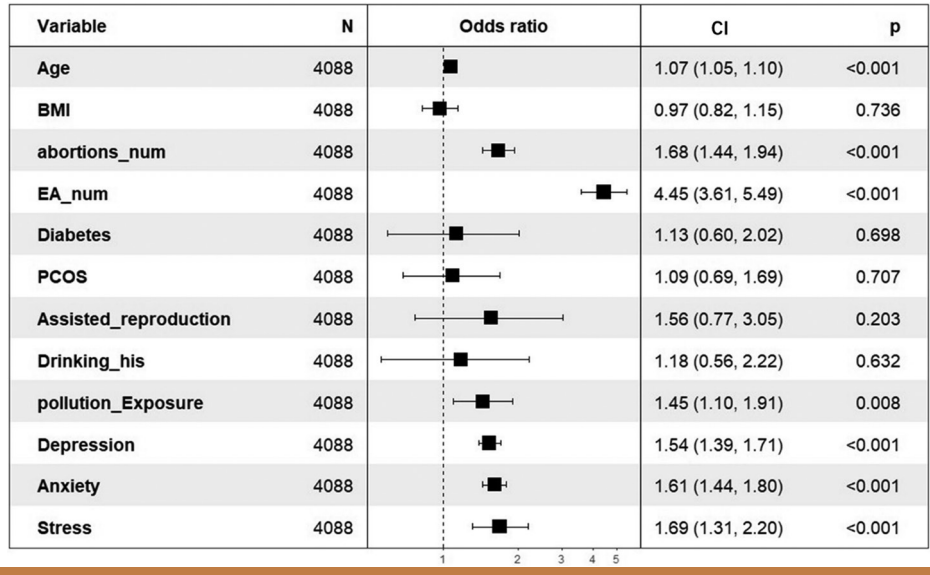

Figure 2. Binary logistic regression analysis after adjustment. This figure displays the results of a binary logistic regression analysis, adjusted for various factors influencing the outcome. The *P*-value for the Binary Logistic Regression model is < .001. abortions_num = Number of abortions, EA_num = Number of embryonic arrests, PCOS = Polycystic ovary syndrome, Drinking_his = Drinking history, pollution_Exposure = Exposure to pollution sources, CI = Confidence Interval, BMI = body mass index.

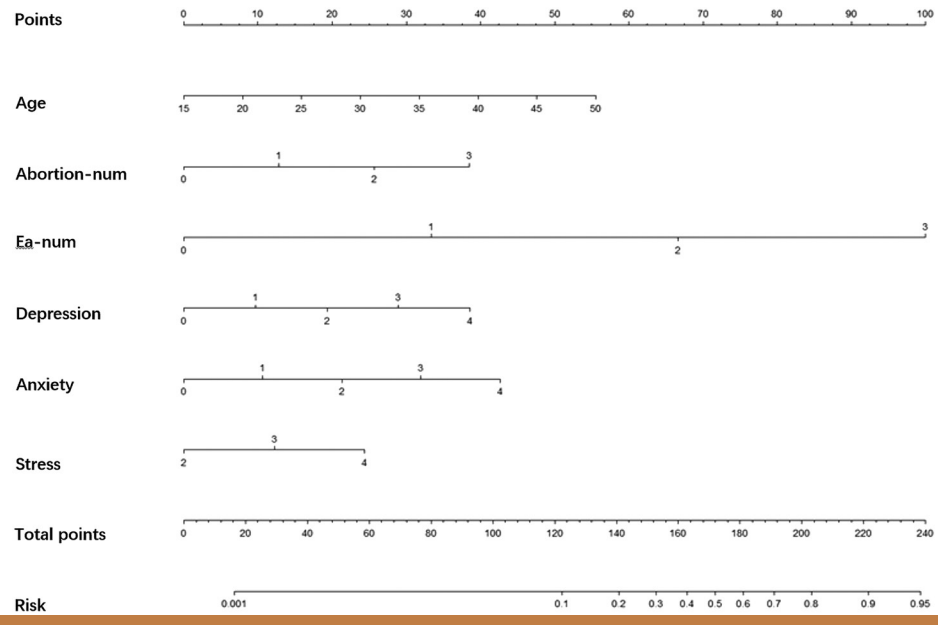

Figure 3. Nomogram for predicting spontaneous abortion risk.

The observed association between negative emotional states and SA risk aligns with previous findings.[9] Proposed mechanisms linking maternal psychological distress to SA include dysfunction of the hypothalamic-pituitary-adrenal axis, increased inflammatory responses, and dysregulation of the autonomic nervous system.[10-11] However, further research is required to elucidate the biological pathways underlying this relationship.

Our findings suggest a significant association between mental health conditions and the risk of spontaneous abortion. Importantly, our study was conducted during the COVID-19 pandemic, a time when pregnant women are likely to experience heightened fear and uncertainty related to childbirth.[12] This could explain the high-stress rates observed in the sample. Previous studies have demonstrated that stress can induce uterine contractions and influence other immune factors that contribute to SA.[13] Some government quarantine and restriction policies during the COVID-19 pandemic have increased levels of stress, anxiety, and depression among pregnant women and affected other factors that lead to miscarriage, including fear of infection, social isolation, and uncertainty about the future. These negative emotional states may adversely affect the maternal-fetal interface, leading to increased inflammation, uterine contractions, and immune dysregulation, which are potential mechanisms of SA.[14] Therefore, our study provides important insights into the context of the COVID-19 pandemic and highlights the need for appropriate screening and intervention for mental health problems in pregnant women, particularly during public health emergencies.[15]

In addition to mental health factors, our study findings also indicate that advancing maternal age, high BMI, previous embryonic arrest, previous

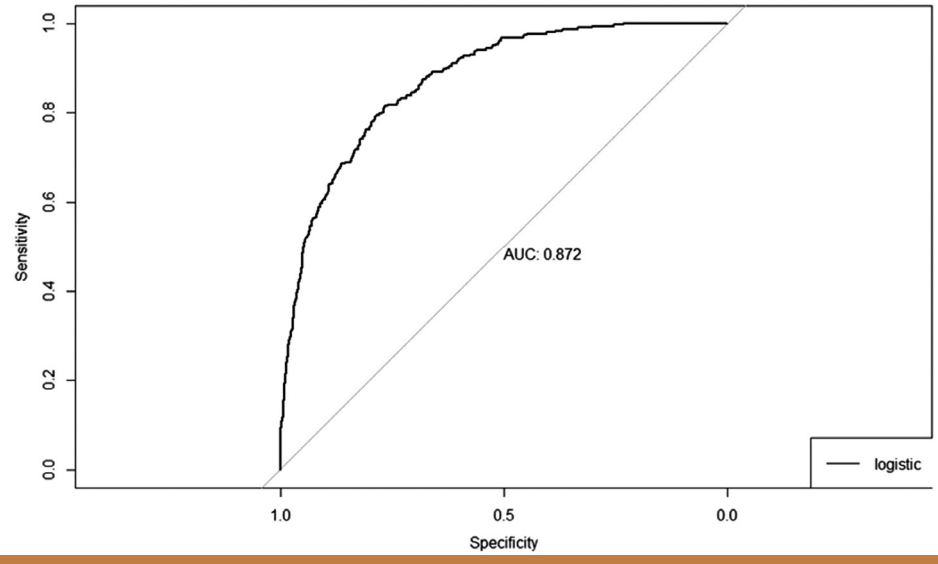

Figure 4. Receiver operating characteristic (ROC) curve for discrimination of early spontaneous abortion.

SA, and use of assisted reproductive technology are associated with an increased risk of SA. Elevated maternal age has consistently been linked to a higher risk of chromosomal abnormalities, diminished endometrial receptivity, and egg quality decline.[16-17] Both low and high BMI may indicate underlying nutritional deficiencies or metabolic abnormalities that can affect embryonic implantation and development.[18-19] A history of previous pregnancy loss may be indicative of genetic, anatomical, infectious, or immunological factors that predispose the mother to recurrent SA.[20-21] The use of assisted reproductive technology introduces external hormones, manipulated gametes, and altered implantation conditions that can increase the chances of SA.[21-22]

In addition to our previous analyses, we formulated and internally validated a nomogram model that demonstrated outstanding diagnostic performance. This model assigns varying scores to each variable, with the cumulative score from 6 key predictors providing an estimate of the risk for SA. Internal validation was conducted using the bootstrap method with 1000 resamples, yielding an Area Under the Curve (AUC) of 0.87, indicative of the model's strong predictive capability. This newly developed nomogram offers clinicians a valuable tool for assessing the likelihood of SA in early pregnancy.[23-24]

Limitations

Our investigation revealed a number of constraints that warrant further consideration. The recruitment of our sample from a single hospital setting may limit the generalizability of our findings to the broader pregnant population. Furthermore, the observational nature of our study design precludes the establishment of causal relationships between maternal mental health issues and the occurrence of SA. Finally, the potential influence of residual confounding variables, stemming from factors either not measured or unidentified, remains an unresolved challenge in our analysis.

Conclusions

This investigation provides compelling evidence indicating that mental health conditions, particularly depression, anxiety, and stress, are significantly correlated with an elevated risk of SA. The implementation of targeted screening and counseling initiatives aimed at identifying and addressing antenatal psychological distress, in conjunction with the management of additional risk factors such as advanced maternal age and abnormal body mass index (BMI), has the potential to mitigate the likelihood of negative pregnancy outcomes. Moreover, the newly developed nomogram model, which encapsulates 6 identified risk factors, offers a user-friendly yet precise tool for predicting the risk of SA.

Availability of Data and Materials: *All data generated or analyzed during this study are included in the article.*

Ethics Committee Approval: *This study was approved by the Ethics Committee of Jinan Second Maternal and Child Health Hospital (Approval No: 2023-YBD-1-05).*

Informed Consent: *Written informed consent was obtained from the participants who agreed to take part in the study.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept – J.L., X.H., M.L.; Design – X.H., M.L.; Supervision – X.H.; Resources – J.L.; Materials – W.F., X.W.; Data Collection and/or Processing – W.F., Z.C.; Analysis and/or Interpretation – J.L., X.W., M.L.; Literature Search – X.W., X.H., Z.C.; Writing Manuscript – J.L., W.F., Z.C.; Critical Review – J.L., W.F., X.W., X.H., M.L.*

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Declaration of Interests: *The authors have no conflict of interest to declare.*

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