Original Article

Association of Maternal Psychological Conditions with Preterm Birth Subtypes: A Longitudinal Study

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Abstract

Background: Preterm birth (PTB) is one of the leading causes of newborn morbidity and mortality. This study aimed to investigate the differential associations of maternal psychological conditions—including anxiety, depression, stress, and their comorbidities—with PTB and its subtypes, including spontaneous preterm birth (SPTB) and medically indicated preterm birth (MPTB).

Methods: This longitudinal study included 566 third-trimester pregnant women referred to perinatal centers in Shiraz, Iran (January 2021–January 2022) who were followed till delivery. Maternal psychological conditions were assessed at ≥28 weeks using the 21-item DASS-21. Perinatal outcomes were recorded at delivery. Poisson regression, adjusted for confounders identified from univariate analyses ($P<0.05$), was applied and estimated associations were reported as adjusted relative risk with 95% confidence intervals (RR_{adj} 95% CI). SPSS version 20 was used to analyze the data, and the significance level was set at $P<0.05$.

Results: Of the 566 participants, 181 (32.0%) had PTB, of which 111 (19.61%) were SPTB and 70 (12.40%) were MPTB; compared with term deliveries, single conditions showed no significant association with PTB, SPTB, and MPTB ($P>0.05$); however, all comorbid conditions demonstrated significantly elevated risks for PTB, SPTB, and MPTB. Depression and stress showed the strongest association ($RR_{adj}=2.34$, $P<0.001$) with PTB, followed by stress and anxiety ($RR_{adj}=1.58$, $P=0.007$), and anxiety and depression ($RR_{adj}=1.56$, $P< 0.001$). Similar patterns were observed for SPTB ($RR_{adj}=2.45$, $P<0.001$) and MPTB ($RR_{adj}=1.98$, $P=0.006$), with depression and stress consistently demonstrating the highest risk across the two subtypes.

Conclusion: Comorbid maternal psychological conditions, particularly depression and stress, significantly increase the risk of PTB and its subtypes. Routine screening for comorbid conditions during pregnancy is essential for early intervention and prevention to improve maternal mental health policies and clinical interventions.

Keywords: Preterm Births; Psychiatric conditions; Depression; Anxiety; Pregnancy

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Introduction

Preterm birth (PTB) is defined as the delivery before 37 weeks of gestational age and is considered one of the leading causes of neonatal morbidity and mortality. PTB is estimated to occur in over ten percent of all live births globally, with a greater occurrence in developing countries.[1] It has been reported that the prevalence of PTB is rising in the majority of regions.[2] Aside from the significant risk of neonatal mortality associated with PTB, this health threat may cause both short- and long-term complications for the child, including both physical and neuro-developmental impairments.[3] Pathophysiology of PTB has various unanswered questions, and the exact pathways leading to this health problem are poorly understood.[4] However, it seems that several characteristics, such as "maternal age, previous PTB, sociodemographic factors, and maternal psychological conditions", can be associated with PTB.[5, 6] Actually, problems in maternal psychiatric conditions have been reported to be associated with an increased risk of PTB.[7] These psychological issues may activate a cascade of neurohormonal signaling pathways, resulting in increased levels of inflammatory factors.[8] For example, women who experience stressful conditions have elevated levels of inflammatory markers in their bloodstream, such as C-reactive protein, which is not explained by other established factors commonly associated with inflammation. This observation has important implications for understanding the impact of stress on PTB.[9]

PTB is classified into two clinical subtypes: spontaneous PTB (SPTB) and medically indicated PTB (MPTB).[10] MPTB refers to the intentional termination of pregnancy through either labor induction or cesarean delivery, accounting for approximately one-third of all PTB cases. SPTB involves preterm onset of labor pain and cervical dilatation or rupture of membranes.[11] In fact, the etiology of SPTB is multifactorial; while often linked to infectious or cervical issues, it can also be precipitated by stress-related pathways activated by problems in maternal psychological conditions.[1]

Although literature has established associations between maternal psychological distress and PTB, several key gaps remain. First, most studies have examined PTB as a single outcome, leaving whether effects differ between SPTB and MPTB unclear.[12] Second, the combined effect of comorbid anxiety and depression on PTB subtypes has been underexplored.[13] Third, evidence predominantly comes from high-income Western countries, with limited data from Middle Eastern settings such as Iran, where cultural and psychosocial contexts may modify these relationships.[14] Fourth, limited evidence has assessed psychological conditions in the late third trimester (≥28 weeks).[15] To address these gaps, the present study aimed to investigate the differential associations of maternal psychological conditions — including anxiety, depression, stress, and their comorbidities—with PTB and its subtypes, specifically SPTB and MPTB.

Materials and Methods

This is a longitudinal study conducted from January 2021 to January 2022 at three tertiary perinatal care educational centers, Hafez Hospital, Motahari Clinic, and Zeinabiyyeh Hospital, affiliated with Shiraz University of Medical Sciences in Shiraz, Iran. These are major public teaching hospitals that collectively handle a large proportion of deliveries in the region, serving a diverse urban and referral population.

Inclusion criteria were third-trimester enrolment (≥28 week of gestational age), singleton pregnancy, maternal age between 18 and 49 years, lack of major fetal anomalies, and no substance use during pregnancy (active smoking, alcohol, or illicit drug use, as reported by the patient or medical records). Exclusion criteria were withdrawal from participation or incomplete data (e.g., loss of follow-up, missing completion of the Depression Anxiety Stress Scale-21 (DASS-21) questionnaire.

At enrollment, demographic and clinical characteristics were recorded via interview and medical record review. These included gestational age at enrollment (weeks), maternal age (years), body mass index (BMI) (kg/m²) (categorized as >30 or ≤30), blood type (A, B, O, AB), history of PTB (yes/no), drug intake (yes/no), hypothyroidism (yes/no), hyperthyroidism (yes/no), diabetes mellitus (DM) (yes/no), and hypertension (HTN) (yes/no).

We recruited a convenience sample of pregnant women in their third trimester (≥28 weeks' gestation) during routine prenatal visits. We also calculated the sample size using the standard formula for estimating a population proportion.[16] Assuming an expected preterm birth (PTB) prevalence of 10% in Iran,[17] with a 95% confidence level (Z=1.96) and a 3% margin of error (d=0.03), the minimum required sample size was calculated to be 385 participants. The formula used was

$$n = \frac{z^2_{\alpha/2}\, p * q}{d^2}$$

Increasing the sample size from 385 to 566 accounted for an anticipated attrition rate of 20–30% and ensured sufficient statistical power for planned subgroup analyses, including comparisons between SPTB and MPTB, as well as across depression, anxiety, stress, and their comorbidities. This represents an oversampling of approximately 47%, which is conservative yet justifiable given the analytical complexity of the study.

Participants completed the DASS-21 questionnaire at ≥28 weeks' gestation in a private room to measure emotional states of depression, anxiety, and stress. A trained obstetrician provided standardized instructions; for participants with limited literacy, each item was read aloud verbatim without interpretation. Immediately after completion, the obstetrician checked for missing responses, and any unanswered items were referred to the participant for completion.

The DASS-21 questionnaire has seven questions on each of stress, anxiety, and depression. DASS-21 is scored by summing the ratings for the items within each of its three subscales. Each item is rated on a 4-point Likert scale from 0 ("Did not apply to me at all") to 3 ("Applied to me very much, or most of the time"). The depression subscale is the sum of items 3, 5, 10, 13, 16, 17, 21; the anxiety subscale is the sum of items 2, 4, 7, 9, 15, 19, 20; and the stress subscale is the sum of items 1, 6, 8, 11, 12, 14, 18. The raw score for each subscale is the sum of the relevant seven items multiplied by 2 to make them comparable to the full 42-item DASS. The scores were classified into five severity levels: normal, mild, moderate, severe, and extremely severe. For the depression subscale, normal scores ranged from 0 to 9, mild from 10 to 13, moderate from 14 to 20, severe from 21 to 27, and extremely severe scores were 28 or above. For the anxiety subscale, normal scores ranged from 0 to 7, mild from 8 to 9, moderate from 10 to 14, severe from 15 to 19, and extremely severe scores were 20 or higher. For the stress subscale, normal scores ranged from 0 to 14, mild from 15 to 18, moderate from 19 to 25, severe from 26 to 33, and extremely severe scores were 34 or above.[17-19] The participants' scoring in the moderate, severe, or extremely severe ranges—defined as depression ≥14, anxiety ≥10, and stress ≥19—was classified as having clinically significant symptoms (cases), while those scoring in the normal or mild ranges were classified as non-cases. An obstetrician collected all the data. The original DASS-21 demonstrated robust psychometric properties and supported the distinction between depression, anxiety, and stress; it has demonstrated excellent internal consistency, with Cronbach's alpha coefficients of 0.94, 0.87, and 0.91 for the depression, anxiety, and stress subscales, respectively, as well as satisfactory concurrent validity.[20] The validated Persian version developed by Kakemam et al. was utilized. (2022) among 1,135 Iranian nurses, reporting acceptable structural validity via confirmatory factor analysis (CFI=0.91, RMSEA=0.07, TLI=0.90).

Internal consistency was excellent (Cronbach's alpha: depression=0.93, anxiety=0.79, stress=0.91), and test-retest reliability was good (Intraclass correlation coefficient=0.75–0.86).[21] These findings confirm the adequate validity and reliability of both versions, supporting their use in the present study.

The participants were followed from enrollment until delivery. Data on delivery outcomes, including gestational age at delivery (calculated based on the time between the first day of the last menstrual period and the delivery date), type of delivery, and classification of PTB, were extracted from the hospitals' electronic medical records and delivery logs after delivery. Any new medical diagnoses (e.g., gestational hypertension, preeclampsia) arising after enrollment were also obtained from these records. PTB was defined as delivery before 37 completed weeks and categorized as SPTB and MPTB. SPTB was defined as spontaneous labor with cervical dilation or preterm premature rupture of membranes. MPTB was defined as labor induction or cesarean delivery for maternal or fetal indications (e.g., preeclampsia, fetal growth restriction). All delivery outcomes, including PTB, SPTB, and MPTB, were recorded prospectively within 48 hours postpartum. Data were extracted from electronic medical records by two independent research assistants, with discrepancies discussed with a third reviewer (a senior obstetrician). In cases where electronic records were incomplete, supplementary data were obtained from delivery logbooks and discharge summaries.

Frequency (relative frequency) and mean±standard deviation were used to describe qualitative and quantitative variables, respectively. Kolmogorov-Smirnov test for normality, Chi-square test, Mann-Whitney U test, and Fisher's exact test were used to analyze the data. In addition, Poisson regression with a log-link function was employed to estimate adjusted relative risks (RR_{adj}) and their 95% confidence intervals (CI). The model was adjusted for potential confounders identified through univariate screening ($P<0.05$). Model specification followed the principles of generalized linear models. SPSS (Chicago, IL, USA) version 20 was used, and the significance level was set at less than 0.05.

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1400.208). Written informed consent was obtained from all participants. It should be noted that the confidentiality of the participants' identities was maintained and that if they did not participate in the study, it would not affect their prenatal care.

Results

Of the 566 participants, 385 (68.00%) had term deliveries and 181 (32.00%) had PTB. Among the PTB group, 111 (61.30%) were SPTB, and 70 (38.70%) were MPTB. The background features of 385 term deliveries are compared among the PTB, SPTB, and MPTB groups in Table 1.

The most common comorbidity among the participants was hypothyroidism 100 (17.66%), followed by DM 27 (4.80%) and HTN 25 (4.40%). Maternal age >35 years, history of PTB, DM, and HTN were significantly higher in the PTB group compared with the term group ($P<0.05$). The history of PTB, DM, and drug intake were significantly higher in the SPTB group compared with term deliveries ($P<0.05$). In the MPTB group compared with the term delivery group, maternal age >35 years and HTN were significantly higher, whereas the proportion of women with BMI >30 was significantly lower ($P<0.05$), indicating a higher proportion of women with BMI ≤30 in the MPTB group. Gestational age at enrolment was significantly lower in the PTB, SPTB, and MPTB groups compared with term deliveries ($P<0.001$) (Table 1).

The distribution of depression, anxiety, and stress severity levels among all participants stratified by delivery group is shown in Table 2. Most participants across all groups reported normal levels of depression (499; 88.16%), anxiety (422; 78.09%), and stress (513; 90.64%).

Table 1: Comparison of background features of term and preterm birth, spontaneous preterm birth, and medically indicated preterm birth deliveries

Variable	All participants (n=566) N(%)	Term delivery (n=385) N(%)	PTB[a] delivery (n=181) N(%)	P-value (Term vs PTB)	SPTB[b] delivery (n=111) N(%)	P-value (Term vs SPTB)	MPTB[c] delivery (n=70) N(%)	P-value (Term vs MPTB)
Gestational age at enrolment (week), Mean±SD[d]	36.47±2.83	38.32±1.15	33.84±2.39	<0.001*	34.73±3.12	<0.001*	32.29±4.00	<0.001*
Maternal age (years)								
18-24	94 (16.60)	72 (18.70)	22 (12.15)	0.01**	20 (18.00)	0.10**	2 (2.90)	0.001***
25-35	357 (63.10)	246 (63.90)	111 (61.30)		63 (56.80)		48(68.60)	
>35	115 (20.30)	67 (17.40)	48 (26.55)		28 (25.20)		20(28.50)	
BMI[e]								
>30	225 (39.75)	153 (39.74)	73 (40.00)	0.90**	54 (48.64)	0.10**	19 (27.14)	0.04**
≤30	341 (60.25)	232 (60.26)	108 (60.00)		57 (51.36)		51 (72.86)	
Blood type								
A	142 (25.00)	97 (25.20)	45 (24.90)	0.40***	27 (24.30)	0.50***	18 (25.70)	0.70***
AB	27 (4.80)	22 (5.70)	5 (2.80)		3 (2.70)		2 (2.90)	
B	129 (22.80)	86 (22.30)	43 (23.80)		29 (26.10)		14 (20.00)	
O	268 (47.40)	180 (46.80)	88 (48.50)		52 (46.90)		36 (51.40)	
History of PTB								
Yes	28 (5.00)	13 (3.40)	15(8.30)	0.02**	11 (10.00)	0.01**	4 (5.70)	0.30***
No	538 (95.00)	372 (96.60)	166 (91.70)		100 (90.00)		66 (94.30)	
Drug intake								
Yes	26 (4.60)	14 (3.60)	12 (6.60)	0.10**	9 (8.10)	0.04**	3 (4.30)	0.40***
No	540 (95.40)	371 (96.40)	169 (93.40)		102 (91.90)		67 (95.70)	
Hypothyroidism								
Yes	100 (17.66)	65 (16.90)	35 (19.30)	0.40**	26 (23.40)	0.10**	9 (12.90)	0.40**
No	466 (82.34)	320 (83.10)	146 (80.70)		85 (76.60)		61 (87.10)	
Hyperthyroidism								
Yes	8 (1.40)	6 (1.60)	2 (1.10)	0.40***	2 (1.80)	0.50***	0 (0.00)	0.30***
No	558 (98.60)	379 (98.40)	179 (98.90)		109 (98.20)		70 (100.00)	
DM[f]								
Yes	27 (4.80)	13 (3.40)	14 (7.70)	0.03**	11 (9.90)	0.001**	3 (4.30)	0.40***
No	539 (95.20)	372 (96.60)	167 (92.30)		100 (90.10)		67 (95.70)	
HTN[g]								
Yes	25 (4.40)	9 (2.30)	16 (8.80)	0.001**	0 (0.00)	0.20***	16 (22.90)	<0.001***
No	541 (95.60)	376 (97.70)	165 (91.20)		111 (100.00)		54 (77.10)	

[a]PTB: preterm birth; [b]SPTB: spontaneous preterm birth; [c]MPTB: medical indicated preterm birth; [d]SD: standard deviation; [e]BMI: body mass index; [e]DM: diabetes mellitus; [g]HTN: hypertension; *Mann-Whitney test; **Chi-square test; ***Fisher's exact test

Comparisons between term delivery and each preterm subgroup revealed no statistically significant differences in the severity distribution of any psychological condition (P>0.05).

While Table. 2 displays the full distribution of severity levels across delivery groups, it does not directly estimate the proportion of participants with clinically meaningful symptoms. To address this, we dichotomized the severity categories into a binary variable: participants with Moderate, Severe, or Extremely Severe scores were classified as having clinically significant symptoms (Yes), whereas those with Normal or Mild scores were classified as without clinically significant symptoms (No). Table 3 reports the prevalence of these clinically significant psychological conditions stratified by delivery type.

Table 2: Distribution of psychological condition severity among participants by delivery group

Variable	All participants (n=566) N(%)	Term delivery (n=385) N(%)	PTB[a] delivery (n=181) N(%)	P value (Term vs PTB)	SPTB[b] delivery (n=111) N(%)	P value (Term vs SPTB)	MPTB[c] delivery (n=70) N(%)	P value (Term vs MPTB)
Depression								
Normal	499 (88.16)	341 (88.57)	158 (87.29)	0.78*	97 (87.40)	0.72**	61 (87.14)	0.48**
Mild	26 (4.59)	13 (3.38)	13 (7.18)		6 (5.40)		7 (10.00)	
Moderate	22 (3.89)	16 (4.16)	6 (3.31)		6 (5.40)		2 (2.86)	
Severe	16 (2.83)	13 (3.38)	3 (1.66)		2 (1.80)		0 (0.00)	
Extremely severe	3 (0.53)	2 (0.51)	1 (0.56)		0 (0.00)		0 (0.00)	
Anxiety								
Normal	442 (78.09)	305 (79.22)	137 (75.69)	0.15*	84 (75.68)	0.18**	53 (75.71)	0.41**
Mild	25 (4.42)	13 (3.38)	12 (6.63)		5 (4.50)		7 (10.00)	
Moderate	60 (10.60)	35 (9.09)	25 (13.81)		19 (17.12)		8 (11.43)	
Severe	30 (5.30)	23 (5.97)	7 (3.87)		3 (2.70)		2 (2.86)	
Extremely severe	9 (1.59)	9 (2.34)	0 (0.00)		0 (0.00)		0 (0.00)	
Stress								
Normal	513 (90.64)	348 (90.39)	165 (91.16)	0.32*	100 (90.10)	0.41**	65 (92.86)	0.63**
Mild	17 (3.00)	10 (2.60)	7 (3.87)		4 (3.60)		3 (4.29)	
Moderate	23 (4.06)	16 (4.16)	7 (3.87)		5 (4.50)		2 (2.85)	
Severe	9 (1.59)	7 (1.82)	2 (1.10)		2 (1.80)		0 (0.00)	
Extremely severe	4 (0.71)	4 (1.03)	0 (0.00)		0 (0.00)		0 (0.00)	

[a]PTB: preterm birth; [b]SPTB: spontaneous preterm birth;[c] MPTB: medical indicated preterm birth; *Chi-square test; ** Fisher's exact test

Table 3: Prevalence of clinically significant psychological conditions and comorbidities by delivery type

Variable	All participants (n=566) N(%)	Term delivery (n=385) N(%)	PTB[a] delivery (n=181) N(%)	P value (Term vs PTB)	SPTB[b] delivery (n=111) N(%)	P value (Term vs SPTB)	MPTB[c] delivery (n=70) N(%)	P value (Term vs MPTB)
Depression								
Yes	41 (7.20)	31 (8.00)	10 (5.00)	0.28*	8 (7.00)	0.77*	2 (3.00)	0.12**
No	525 (92.80)	354 (92.00)	171 (95.00)		103 (93.00)		68 (97.00)	
Anxiety								
Yes	99 (17.50)	67 (17.40)	32 (17.67)	0.38*	22 (19.82)	0.96*	10 (14.28)	0.52*
No	467 (82.50)	318 (82.60)	149 (82.33)		89 (80.18)		60 (85.72)	
Stress								
Yes	36 (6.36)	27 (7.00)	9 (4.97)	0.37*	7 (6.31)	0.77*	2 (2.86)	0.12**
No	530 (93.64)	358 (93.00)	172 (95.03)		104 (93.69)		68 (97.14)	
Anxiety & Depression								
Yes	170 (30.00)	59 (15.32)	111 (61.32)	<0.001*	64 (57.65)	<0.001*	47 (67.14)	<0.001*
No	396 (70.00)	326 (84.68)	70 (38.68)		47 (42.35)		23 (32.86)	
Depression & stress								
Yes	63 (11.13)	23 (5.97)	40 (22.10)	<0.001*	29 (26.13)	<0.001*	11 (15.70)	0.007*
No	503 (88.87)	362 (94.03)	141 (77.90)		82 (73.87)		59 (84.30)	
Stress & anxiety								
Yes	45 (7.95)	10 (2.60)	35 (19.34)	<0.001*	21 (18.92)	<0.001*	14 (20.00)	<0.001*
No	521 (92.05)	375 (97.40)	146 (80.66)		90 (81.08)		56 (80.00)	

[a]PTB: preterm birth; [b]SPTB: spontaneous preterm birth;[c] MPTB: medical indicated preterm birth; *Chi-square test; ** Fisher's exact test

The prevalence of clinically significant psychological conditions among 566 participants, stratified by delivery type, is presented in Table 3.

Comparable rates of depression, anxiety, and stress as separate conditions between term and PTB deliveries showed no significant differences (P>0.05). In contrast, comorbid psychological conditions demonstrated significant associations with preterm birth. Anxiety and depression were statistically higher in the PTB group compared to term deliveries (P<0.001), with similarly elevated rates in SPTB and MPTB subgroups (P<0.001). Likewise, depression and stress were significantly higher in PTB, SPTB, and MPTB compared to term, with all comparisons statistically significant (P<0.05). Stress and anxiety also showed significantly elevated prevalence across all preterm subgroups compared to term (P<0.001) (Table 3). The adjusted RR for PTB, SPTB, and MPTB associated with maternal psychological conditions and comorbidities are presented in Table 4.

Among single psychological conditions, anxiety (RR_{adj}=2.58, P<0.001) and depression (RR_{adj}=2.60, P=0.02) were significantly associated with PTB, while stress showed no significant association (RR_{adj}=1.03, P=0.87). Similar patterns were observed for SPTB in anxiety (RR_{adj}=2.64, P<0.001) and depression (RR_{adj}=2.94, P=0.01). Anxiety (RR_{adj}=2.03, P=0.06), depression (RR_{adj}=1.15, P=0.85), and stress (RR_{adj}=1.04, P=0.75) did not reach statistical significance for MPTB. Notably, all comorbid conditions demonstrated significant associations across all preterm subtypes (P<0.05) (Table 4).

Discussion

In this longitudinal study, almost one-third of participants experienced PTB, with

Table 4: Adjusted relative risks of preterm birth and its subtypes associated with maternal psychological conditions using the Poisson regression

Variable	RR_{adj} (95% CI)[a]	P value
	PTB[b]	
Anxiety	2.58 (1.82-3.93)	<0.001*
Depression	2.60 (1.16-5.88)	0.02*
Stress	1.03 (0.73-1.44)	0.87*
Anxiety & depression	1.56 (1.52-2.59)	<0.001*
Depression & stress	2.34 (1.58-3.09)	<0.001*
Stress & anxiety	1.58 (1.23-2.23)	0.007*
	SPTB[c]	
Anxiety	2.64 (1.79-3.46)	<0.001**
Depression	2.94 (1.33-5.63)	0.01**
Stress	1.02 (0.71-1.42)	0.82**
Anxiety & depression	1.65 (1.58-1.68)	<0.001**
Depression & stress	2.45 (1.62-3.24)	<0.001**
Stress & anxiety	1.54 (1.19-2.18)	0.01**
	MPTB[d]	
Anxiety	2.03 (0.95-3.58)	0.06***
Depression	1.15 (0.24-4.89)	0.85***
Stress	1.04 (0.69-1.46)	0.75***
Anxiety & depression	1.43 (1.36-1.46)	<0.001***
Depression & stress	1.98 (1.12-2.89)	0.006***
Stress & anxiety	1.62 (1.09-2.64)	<0.001***

[a]RR_{adj} (95% C.I): adjusted relative risk (95% confidence interval); [b]PTB: preterm birth; [c]SPTB: spontaneous preterm birth; [d]MPTB: medically indicated preterm birth; *Adjusted for maternal age, gestational age at enrolment, history of preterm birth, diabetes mellitus, and hypertension; **adjusted for gestational age at enrolment, history of preterm birth, drug intake, and diabetes mellitus; ***adjusted for gestational age at enrolment, maternal age, body mass index, and hypertension

approximately two-thirds and one-third classified as SPTB and MPTB, respectively. This prevalence exceeds the global average of ~10% reported by WHO.[22] This discrepancy is attributable to recruitment from tertiary perinatal centers managing higher-risk pregnancies; data collection during the COVID-19 pandemic period (2021–2022), which may have exacerbated maternal psychological distress and healthcare access challenges; and the hospital-based sampling frame that inherently captures more complicated pregnancies compared to community-based settings.

The PTB rate of 32.0% is notably higher than the 8–12% reported in most high-income countries, but it aligns with estimates from some Middle Eastern and developing settings where tertiary care referral patterns differ substantially from population-based surveillance. A population-based study in Iran reported a PTB prevalence of approximately 10.7% nationally.[23] However, this included all delivery settings and likely underrepresented high-risk pregnancies managed at referral centers. Another study from the similar setting has reported higher PTB rate in low and middle income countries.[24]

The distribution of PTB subtypes in the current cohort—61.32% SPTB and 38.67% MPTB—is consistent with the literature, indicating that approximately two-thirds of PTBs are spontaneous and one-third are medically indicated.[25] The MPTB proportion in this study is at the higher end of the reported range, which may reflect the high prevalence of pregnancy complications in our referral population. Specifically, the MPTB group had substantially higher rates of hypertension (22.90%) compared to term deliveries (2.30%), which is a leading indication for medically indicated preterm delivery. Hypertensive disorders of pregnancy, including preeclampsia, were the leading cause of MPTBs.[26]

Maternal age more than 35 years, and history of PTB, DM and HTN were significantly higher in the PTB group compared with the term group. These findings are consistent with established risk factors for PTB.[27-30] In the univariate analysis, depression, anxiety and stress prevalence did not significantly differ across delivery groups; however, in multiple analysis, anxiety and depression were significantly associated with PTB and SPTB. This discrepancy between univariate and multiple analysis underscores the importance of controlling confounders when examining these associations.

Women with concurrent comorbidities exhibited high risks for overall PTB, SPTB, and MPTB, suggesting that comorbid psychiatric conditions confer substantially higher risk than single conditions. A retrospective cohort study on 8,336 pregnant women found that those with total mental health concerns had a 29.0% higher risk of overall PTB, with risks extending to MPTB and SPTB.[31]

The anxiety-depression combination demonstrated consistently elevated risks across PTB and its subtypes, all highly significant. A recent article briefly reported that individuals with comorbid depression and anxiety conditions had 130% higher odds of PTB.[32] A mother-child cohort study further supports these findings, demonstrating that depression combined with anxiety during pregnancy increased the risk of SPTB, with the authors concluding that "comorbidity of depressive and anxiety symptoms was the worst condition during pregnancy».[33] The mechanistic pathways underlying this synergistic effect likely involve shared biological substrates. Psychological distress activates the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system, triggering a cascade of neurohormonal signaling that increases systemic inflammation.[34] Higher glucocorticoid and cortisol production—which pass through the placenta and enter the fetal bloodstream—are key biomarkers identified as explanatory mechanisms for the association between negative antenatal mental health and birth outcomes. Higher corticosteroid levels, particularly in the second trimester, increase the PTB risk

through both inflammatory and epigenetic pathways. Excess exposure to glucocorticoids and cortisol in the uterus also impacts offspring's neurological development through direct influence on brain development and cortisol-related epigenetic change. Research suggests that cortisol production may be particularly high for individuals with comorbid anxiety and depression, potentially explaining the amplified risk observed in our study.[35]

A systematic review concluded that the combination of anxiety and depression in pregnancy was associated with SPTB, which is consistent with the current findings; however, it showed no association with MPTB, which contradicts the current findings.[36] Another study found that women with SPTB were three times more likely to have antenatal depression compared with those without SPTB, while no significant association was identified between antenatal depression and MPTB.[12]

The stress- anxiety combination also showed significant associations, though with relatively lower effect measures compared with anxiety alone; these associations were significant for PTB and its subtypes. This pattern is broadly consistent with the systematic review, which indicates that while depression, anxiety, and stress each contribute to the PTB risk, the co-occurrence of these conditions may pose an even higher risk on SPTB but not MPTB.[36]

The depression–stress combination showed effects like depression alone for PTB and SPTB, whereas stress alone was not significantly associated with any outcome. This suggests that stress may influence PTB mainly through its co-occurrence with depression. Correlations between maternal stress and the resistive indices of feto-placental arteries were a common focus, and the biological mechanisms underlying stress regulation suggest that antenatal stress could plausibly affect placental function and contribute to PTB.[37] In addition, chronic stress experienced during pregnancy could serve as a potential tool for identifying women at elevated risk of SPTB.[38] Also, the level of stress among pregnant women was significantly related to the risk of giving birth before term.[39] However, the absence of an independent association between stress and PTB may be explained by the fact that patients may not experience chronic stress, and by the relatively small number of participants in the stress group, which may have contributed to the lack of statistical significance.

Findings on comorbid effects remain conflicting. A large prospective cohort found that chronic stress did not alter the relationship between depressive symptoms and PTB, and the collective effect of psychosocial distress was not significant.[40] In the current study, all comorbid conditions demonstrated significant associations with both subtypes of PTB. These findings underscore the importance of considering both PTB subtype and specific comorbidity profiles of maternal psychological conditions.

The strengths of this study include a prospective longitudinal design, a distinction between SPTB and MPTB, the use of the validated DASS-21, and multivariable Poisson regression. Its limitations include assessment at a single time point (the third trimester), potential residual confounding, and the inability to examine a dose-response relationship due to the small number of severe cases.

Conclusion

This study demonstrates that PTB is associated with distinct maternal characteristics—including advanced maternal age, history of PTB, DM, and HTN. PTB, SPTB, and MPTB are associated with comorbid psychological conditions, particularly the concurrent presence of depression and stress. Given the finding that comorbid psychological conditions confer substantially greater risk than single conditions, we recommend integrating brief, validated mental health screening tools such as the DASS-21 into routine prenatal care, particularly in the third trimester. This practical approach can facilitate early identification of at-risk

women, timely psychological interventions, and ultimately contribute to reducing the PTB incidence and improving maternal and neonatal outcomes.

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Authors' Contribution

AS, AF, ZO, and MZ contributed to the conception and design of the study. AF, MZ, MK, HV, NA, and KHB carried out data acquisition, analysis, and interpretation. AS, AF, ZO, KHB, and MZ contributed to drafting and critically revising the manuscript for important intellectual content. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Conflict of Interest

None Declared.

Declaration on the Use of AI

This manuscript was edited using DeepSeek AI solely to enhance language clarity and readability. The authors have thoroughly reviewed and verified all scientific content and take full responsibility for the final manuscript.

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