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Anxiety at the Onset of Active Phase of Labor and some of its Predictors in Iranian Women

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Abstract

Background and Aim: Severe anxiety during labor can result in adverse maternal and neonatal outcomes. Due to limited studies in Iran and other countries, this study aimed to assess the prevalence of women's anxiety at the onset of active phase of labor and some of its predictors.

Materials and Methods: In this cross-sectional study, the participants included 700 low-risk singleton pregnant women with gestational age of 37^0-41^6, hospitalized for vaginal delivery at two teaching hospitals in Tabriz, Iran. The anxiety state [by using the Spielberger's State Anxiety Inventory (SAI)] and dehydration were assessed at cervical dilatation of 4-6 cm. Variables correlated with the anxiety score with P<0.2 in the unadjusted analysis were included in the multiple linear regression model to determine the predictors.

Results: The mean of the anxiety score was 49.3 (SD 11.7) out of the attainable score of 20-80. About two-thirds of the women had severe (39.6%) or moderate (26.6%) anxiety. The predictors of high anxiety score were: high fear (β=0.610), labor induction (β=0.196), dehydration ≥ 3 h (β=0.109) and < 3 h (β=0.073), second-hand smoke during pregnancy (β=0.087), and no attendance at childbirth preparation classes (β=0.054). The proportion of variance by all these factors was 62%.

Conclusion: Anxiety was very common intrapartum. The during-labor factors including high fear, labor induction, and dehydration were important predictors of the women's anxiety. It seems that providing the women with appropriate counselling services during pregnancy and responding to their needs during labor could play a significant role in decreasing their anxiety.

Keywords: Anxiety; Prevalence; Labor; Iran

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Introduction

Stress and anxiety during pregnancy and labor can lead to release of several hormones and result in complications such as prolonged labor, emergency Caesarean section [1], and long-term neonatal complications [2]. The World Health Organization has emphasized on the importance of addressing mental health problems of pregnant women and integrating mental healthcare into maternal health programs [3].

High and significantly different prevalence rates have been reported for anxiety among pregnant women: 23.6% in Saudi Arabia [4], 30.9% in Amsterdam, the Netherlands [1], and 43% in the third trimester of pregnancy in Bandar Abbas, Iran [5]. Some studies have reported a higher prevalence of anxiety in the third trimester of pregnancy. In a study conducted in Tabriz (Iran), the prevalence of anxiety was 17% in the first and 27% in the third trimesters [6]. In Brazil, these rates were 23% and 29%, respectively [7]. However, in a study conducted in Spain, the prevalence of anxiety was not higher in the third trimester (17.2%) than in the first (19.5%) [8].

Few studies have analyzed the prevalence of anxiety in women during labor. In a study conducted in Australia, anxiety was the most common feeling expressed by women during the first stage of labor. In this study, 30% of women experienced anxiety while entering the maternity ward [9]. High prevalence of moderate or severe anxiety at the onset of the active phase of labor was also reported in baseline evaluation of clinical trials carried out to reduce labor anxiety in Iran [10] and Turkey [11].

Feeling of anxiety may emerge before pregnancy [12] or after pregnancy [13], and continue until the postpartum period [14]. However, specialists may overlook the importance of assessing women's mental state and their anxiety levels during labor [15].

A literature review showed that unemployment, having a history of unintended pregnancy [4], cigarette smoking [1], engagement in family disputes, positive history of mental disorders, insufficient household income, history of negative childbirth experiences [16], no history of

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childbirth, positive history of fetal death or abortion, experiencing domestic violence [17], and fear of childbirth [18] affected the anxiety levels expressed by pregnant women. However, we found no study addressing factors affecting the anxiety level of women at the onset of labor.

Due to the importance of this research subject and lack of relevant studies, this study aimed to assess the prevalence of anxiety in women at the onset of the active phase of labor and find the predictors of anxiety in them.

Methods

This cross-sectional study was part of an extensive study entitled "Birth experiences, predictors and some maternal and neonatal outcomes with labor dystocia: A mixed method study", approved scientifically and ethically by Tabriz University of Medical Sciences. The study method has been explained in detail in previously published articles [19,20]. Thus, herein, only the parts related to this paper are explained.

Study setting:

The study setting included the delivery rooms of Al-Zahra and Taleghani Hospitals, the only teaching maternity hospitals in Tabriz, Iran (the capital of East Azerbaijan Province with a population of over 1.7 million). Taleghani Hospital is a third-level referral center in the provincial level, and Al-Zahra is a third-level referral center in the Northwestern Pole of Iran. There are about 500 deliveries per month in each of these centers. In these centers, an intravenous cannula is inserted for women upon admission to the delivery room with Ringer's solution infusion commenced only upon the physicians' orders, usually for labor induction or augmentation. The fetal heart rate and uterine contractions are constantly monitored using a monitoring device. Women have access to foods and/or drinks (based on the stage of labor). However, since they are lying on the bed, could not have a companion, and there is not enough staff, they are usually not given adequate liquids. In each working shift, a midwife is responsible for taking care of two or three parturients, carrying out residents' orders and monitoring the fetal heart rate and uterine contractions. Gynecology residents are also directly responsible to examine women and prescribe medications during labor and delivery. Vaginal deliveries are performed by

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gynecology residents, midwifery students, or midwives.

The inclusion criteria were: parity of three or less, having a live single fetus with cephalic presentation at 37^0-41^6 weeks of gestation, and normal tococardiography at admission. The exclusion criteria included: advanced first stage of labor (> 6 cm cervical dilatation), psychological, speech, hearing or visual disorders, having any contraindication for vaginal delivery (according to the physician's diagnosis), history of Caesarean section, and planned Caesarean section.

Data collection:

The first author selected the participants using the convenience sampling method and collected the data. The eligibility criteria were assessed by using a checklist.

The Spielberger's State Anxiety Inventory (SAI) [21] was used to measure the anxiety score, which is a 20-item self-report inventory, with response options of not at all (score 1), somewhat (score 2), moderately (score 3), and very much so (score 4), and some of the items are scored inversely. The sum of scores can range from 20-80. The total scores of 20-40 are considered as mild, 41-54 as moderate, and ≥ 55 as severe anxiety. Mahram (1993) [22] confirmed the validity of the Persian version of SAI in Iran. The internal consistency of the inventory was also confirmed in this study with a Cronbach's alpha coefficient of 0.94.

Sociodemographic characteristics:

The age, number of deliveries, and pre-pregnancy or early pregnancy weight of participants were extracted from their medical records. Height was measured using a stadiometer. The participants were asked about their family income levels, level of education, their occupation, their spouse's occupation, intended or unintended pregnancy, fetal gender preference, participation in childbirth preparation classes, cigarette smoking, hookah or alcohol consumption, exposure to physical, mental, or sexual violence during pregnancy, and their desired mode of delivery.

The participants' BMI was calculated by dividing their pre- or early-pregnancy weights (kilograms) by the square of their heights (meters). Those with BMI values of <18.5, 18.5-24.9, 25-29.9, and >30 were considered underweight, normal, overweight, and obese, respectively. Based on the BMI

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values, normal weight gain during pregnancy can range from 13 to 18, 11 to 16, 7 to 11, and 5 to 9 kg, respectively [23].

The participants' exposure to emotional, physical, and sexual violence during pregnancy was assessed by asking one question for each aspect (e.g., "has your spouse ever hurt you emotionally?") with three response options (i.e., never, sometimes, and often). The last two responses were considered as a positive experience of emotional violence.

Women's fear was assessed through the following item, "I feel scared" with four response options (i.e., very little, little, much, and very much), and the last two responses were merged to represent an experience of fear.

The participants were observed for the symptoms of dehydration, abnormal amniotic fluid status (oligo- or poly-hydramnios), and labor induction. The signs and symptoms of dehydration included dry mouth and lips (in cases where a participant had not received medications like atropine), thirst, and dry or sticky mouth making it difficult for women to talk or swallow foodstuff. Any of these symptoms or signs indicated dehydration [24]. Positive cases were asked, "For how long have you felt thirsty?" We considered "no dehydration" if they reported less than 30 min thirsty and had no other signs of dehydration.

The content validity of the data collection tools (except the SAI) was determined using the expert opinion of 10 gynecologists and midwives.

The socio-demographic questionnaire was completed through face-to-face interview with the participants when they had no painful contractions. Anxiety state and dehydration were assessed at cervical dilatation of 4-6 cm.

Sample size and data analysis:

A minimum of 10 participants per predictor variable were required to determine the predictors using linear regression equations with six predictors or more. However, 30 participants per predictor variable would provide a better opportunity to detect predictors with small effect sizes [25]. Therefore, a sample size of 700 sufficed to identify at least 17 potential predictor variables, even variables with small effect sizes.

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The data were analyzed using SPSS 21 (SPSS, Chicago, IL, USA). Normal distribution of the anxiety scores was confirmed by using the skewness and kurtosis. The univariate general linear model was used to analyze the relationship between each independent variable and the anxiety score. After defining the dummy variables for qualitative factors with more than two values, variables with $P<0.2$ in the unadjusted analyses were entered into the linear multiple regression model with backward strategy to design three models for predicting the anxiety score: a. pre-labor, b. during-labor, and c. both pre- and during-labor (the overall model). Before applying the models, the regression assumptions such as normality of residuals and no perfect multicollinearity were checked. The adjusted R-squared was used to show how well variations in anxiety score were explained by the independent variables.

Ethical considerations:

The study was approved by the Ethics Committee of Tabriz University of Medical Sciences under the code IR.TBZMED.REC.1397.624. We followed all the Helsinki declaration and national ethical standards. All participants were ensured about the matter of confidentiality, and written informed consent was obtained from the participants. For cases under 16 years of age, written informed consent was also obtained from their husbands before data collection.

Results

The data were collected from October 2018 until June 2019. We did not draw a flow-diagram for this study since it is present in our previously published article [19]. Out of 700 participants, 354 (50.6%) were hospitalized in Al-Zahra Hospital and 57.4% were primiparous women. There was no case of hookah smoking or alcohol consumption, and only one woman reported cigarette smoking during pregnancy. In total, 21 individuals experienced gestational hypertension, and 300 individuals (43%) underwent labor induction. The mean anxiety score of the participants was 49.3±11.7, and two-thirds of the participants had severe (39.6%) or moderate (26.6%) anxiety.

Association of pre- and during-labor factors with anxiety:

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In the unadjusted analysis, the following factors had significant relationships with high anxiety scores: primiparity, gestational age over 40 weeks, obesity, excessive weight gain during pregnancy, exposure to tobacco smoke during pregnancy, no participation in childbirth preparation classes, tendency towards the Cesarean section before labor, emotional, physical and/or sexual violence during pregnancy, insufficient household income, dehydration and thirst during labor, extreme fear, labor induction, and abnormal amniotic fluid status. Inadequate weight gain was associated with lower anxiety score. Anxiety scores had no significant relationships with age, history of abortion, time interval between current and previous deliveries, pregnancy intention, educational level of women, or fetal gender preference (Table 1)

Table 1: Relationship of some factors with women's anxiety score during labor (n=700)

Variables		N	Mean (SD)	MD (95% CI)	P value
Parity	Primiparous	402	50.8 (11.9)	3.5 (1.8 to 5.3)	<0.001
	Multiparous	298	47.3 (11.2)	reference	
Age (years)	21 to 34	495	49.5 (11.8)	reference	
	20 ≥	123	48.5 (11.1)	-1.0 (-3.9 to 1.8)	0.752
	35+	82	49.3 (11.8)	-0.2 (-3.6 to 3.1)	0.997
Woman's level of education (years)	Less than 8	383	48.2 (11.4)	-1.5 (-3.3 to 0.2)	0.088
	≥ 9	317	50.2 (12.0)	reference	
Household income	Sufficient	320	48.1 (11.1)	reference	
	Insufficient	380	50.4 (11.3)	2.3 (0.6 to 4.0)	0.010
Couple's preferred fetal sex	Yes	25	45.1 (12.1)	reference	
	No	16	51.6 (9.7)	6.5 (-2.4 to 15.5)	0.224
	Does not matter	659	49.4 (11.7)	4.3 (-1.4 to 10.0)	0.194
Planned pregnancy	Yes	583	49.5 (11.9)	reference	
	No	117	48.4 (10.9)	-1.2 (-3.4 to 1.2)	0.344
Positive experience of physical violence during pregnancy	No	639	48.9 (11.8)	reference	
	Yes	61	53.4 (10.5)	4.4 (1.4 to 7.5)	0.004
Positive experience of emotional violence during pregnancy	No	507	48.2 (11.6)	reference	
	Yes	193	52.3 (11.6)	1.4 (2.2 to 6.1)	<0.001
Positive experience of sexual violence during pregnancy	No	625	48.5 (11.5)	reference	
	Yes	75	56.2 (11.5)	7.7 (4.9 to 10.4)	<0.001
Amniotic fluid status	Normal	693	49.3 (7.1)	reference	
	Abnormal	7	59.2 (8.0)	9.9 (1.2 to 18.6)	0.026
	No	627	49.8 (11.7)	3.7 (0.9 to 6.6)	0.010

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Participation in birth preparation classes	Yes	73	46.0 (4.1)	reference	
Dehydration	No	365	45.2 (10.9)	reference	
	Less than 3 h	276	52.5 (11.1)	7.3 (5.2 to 9.3)	<0.001
	More than 3 h	59	59.7 (8.0)	14.4 (10.8 to 18.1)	<0.001
Labor induction	No	400	44.4 (10.5)	reference	
	Yes	300	55.9 (9.9)	11.4 (9.9 to 13.0)	<0.001
Body mass index‡	Normal	359	48.3 (0.6)	reference	
	Overweight	257	49.8 (0.7)	1.5 (-1.0 to 4.1)	0.538
	Obese	84	53.0 (1.3)	4.7 (0.9 to 8.4)	0.006
Weight gain during pregnancy	Normal	249	48.9 (11.7)	reference	
	> normal	268	52.2 (11.3)	3.3 (0.9 to 5.7)	0.003
	< normal	183	45.7 (11.3)	-3.2 (-5.9 to -0.6)	0.012
History of abortion	No	587	49.5 (11.7)	reference	
	Yes	113	48.4 (11.8)	-1/0 (-3.4 to 1.3)	0.385
Fear††	Low	296	39.2 (6.9)	reference	
	High	404	56.7 (8.6)	17.4 (16.2 to 18.6)	<0.001
Exposure to tobacco smoke during pregnancy	No	525	47.8 (11.5)	reference	
	Yes	175	53.9 (11.1)	6.1 (4.1 to 8.0)	<0.001
Interval between current and previous deliveries (years)	3 ≥	62	46.2 (11.1)	reference	
	3.5 to 6	120	46.6 (10.8)	0.4 (-3.7 to 4.6)	0.992
	≥ 6	116	48.6 (11.6)	2.4 (-1.8 to 6.6)	0.428
Woman's preference for delivery mode	Vaginal/does not matter	598	48.4 (11.7)	reference	
	C-section	102	54.7 (10.4)	6.2 (3.8 to 8.7)	<0.001
Gestational age (weeks)	37^0 to 39^6	444	48.2 (11.6)	reference	
	40^0 or more	256	51.1 (11.7)	2.9 (1.1 to 4.7)	0.002

All analyses were done using unadjusted general linear model. SD: standard deviation; MD: mean difference

Anxiety was assessed using the SAI (dilation 4-6 cm) with score range of 20-80 (higher scores indicated higher anxiety) [21].

* Presence of one dehydration sign or symptom (dry mouth and lips, thirst, dizziness, weakness, trouble swallowing dry food, dry, sticky mouth that makes it hard to talk, a swollen, cracked or dry tongue) [24].

‡ Body mass index<18.5 was considered low, 18.5 to 24.9 as normal weight, 25 to 29.9 as overweight and 30 or more as obese, based on the BMI values, normal weight gain during pregnancy can range from 13 to 18, 11 to 16, 7 to 11, and 5 to 9 kg, respectively.

†† Fear was assessed using one question "I am scared" with four options (not at all/somewhat: low fear, moderately so/very much so: high fear [21].

Pre-labor predictors of anxiety:

The most important predictors included: Primiparity (β=0.217), exposure to tobacco smoke during pregnancy (β=0.159), and no participation in childbirth preparation classes (β=0.095). The pre-labor variables explained 18% of the variance of the anxiety score (Table 2).

During-labor predictors of anxiety:

Extreme fear (β=0.622), labor induction (β=0.205), dehydration and thirst for 3 hours or more (β=0.131), and dehydration and thirst

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for less than 3 hours (β=0.082) predicted high anxiety during labor. The during-labor variables explained 61% of the variance of the anxiety score (Table 2).

Overall predictors of anxiety:

In general, the predictors of high anxiety included extreme fear (β=0.610), labor induction (β=0.196), dehydration, and thirst for 3 hours or more (β=0.109), dehydration and thirst for less than 3 hours (β=0.073), exposure to cigarette smoke during pregnancy (β=0.087), and no attendance in childbirth preparation classes (β=0.054). In total, these variables explained 62% of the variance of anxiety (Table 2).

Table 2: Pre-labor and during-labor predictors of women's anxiety score at the onset of the active phase of labor

Predictors	Beta	B (95% CI)	P
1. Pre-labor predictors*			
Constant	--	38.6 (35.5 to 41.8)	<0.001
Primiparous	0.217	5.1 (3.4 to 6.9)	<0.001
Exposure to tobacco smoke during pregnancy (Ref: no smoker)	0.159	4.3 (2.4 to 6.2)	<0.001
Experience of sexual violence during pregnancy	0.138	5.2 (2.5 to 7.9)	<0.001
Gestational age of 40^{+0}– 41^{+6} w (Ref: 37^{+0}– 39^{+6})	0.111	2.7 (1.0 to 4.4)	<0.001
Woman's preference for the Cesarean section (Ref: vaginal delivery)	0.110	3.7 (1.3 to 6.0)	0.002
No participation in birth preparation classes	0.095	3.6 (1.0 to 6.3)	0.007
Over-normal gestational weight gain* (Ref: Normal)	0.086	2.1 (0.2 to 3.9)	0.030
Less than normal gestational weight gain* (Ref: Normal)	-0.094	-2.5 (-4.5 to -0.4)	0.017
Low household income	0.071	1.7 (0.2 to 3.3)	0.047

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2. During labor predictors†			
Constant	--	37.5 (36.6 to 38.4)	<0.001
High fear	0.622	14.7 (13.5 to 15.9)	<0.001
Labor induction	0.205	4.8 (3.6 to 6.1)	<0.001
Dehydration (Ref: no)			
3 h or less	0.131	5.5 (3.4 to 7.7)	<0.001
More than 3 h	0.082	2.0 (0.7 to 3.2)	<0.001
3. All variables‡			
Constant	-	34.9 (32.9 to 36.9)	<0.001
High fear	0.610	14.4 (13.2 to 15.7)	<0.001
Labor induction	0.196	4.6 (3.4 to 5.9)	<0.001
Dehydration (Ref: no)			
3 h or less	0.109	4.6 (2.4 to 6.8)	<0.001
More than 3 h	0.073	1.7 (0.5 to 2.9)	0.005
Exposure to tobacco smoke during pregnancy (Ref: no smoker)	0.087	2.3 (1.0 to 3.6)	<0.001
No participation in birth preparation classes	0.054	2.1 (0.3 to 3.9)	0.025

Anxiety was assessed by the SAI (at 4-6 cm cervical dilation) with score range of 20-80 (higher scores indicated higher anxiety) [21].

All analyses were done using multiple linear regression model with backward strategy. The Sidak test was used to adjust for the multiple comparisons.

❋Other pre-labor variables with a relation of $P < 0.2$ in the unadjusted analysis (variables of physical and emotional violence and obesity at the early pregnancy were removed from the model). adjusted $R^2 = 0.176$.

†Amniotic fluid status with a relation of $P < 0.2$ in the unadjusted analysis was removed from the model. $R^2 = 0.607$

‡ Adjusted for all variables entered in the above models. $R^2 = 0.616$.

Discussion

To the best of the authors' knowledge, this study appears to be the first study with sufficient sample size to assess the prevalence of anxiety in women at the onset of the active phase of labor and identify

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predictors of the anxiety by analyzing several potentially related factors. Anxiety was highly prevalent among the participants, as two-thirds of them experienced severe (39.6%) or moderate (26.6%) anxiety. During-labor factors including extreme fear, labor induction, and dehydration were the important predictors and predicted 61% of variance of the anxiety score. The pre-labor factors explained less than one-fifth (18%) of the variance of the anxiety score. In general, the predictors of high anxiety included extreme fear, labor induction, dehydration and thirst during labor, exposure to tobacco smoke during pregnancy, and failure to attend childbirth preparation classes.

The results regarding high prevalence of anxiety at the onset of the active phase of labor were consistent with the results of baseline evaluation of a clinical trial conducted in Tabriz, where about two-thirds (64%) of the participants had moderate or severe anxiety (score ≥ 5 on a 10-cm visual analogue scale), and about one-third (35%) had severe anxiety (score ≥ 7) [10]. The mean anxiety score obtained in this study was higher than the value obtained for the control group in a clinical trial conducted in Turkey [11]. This difference might be due to the fact that the Turkish study only enrolled women whose labor pain had initiated spontaneously. In our study, the mean anxiety score was also significantly lower in women with spontaneously initiated labor than in those with induced labor.

The present findings regarding the significant effect of fear of childbirth on anxiety scores were consistent with results of previous studies conducted in Iran [18], Norway [26], and Hungary [27]. Fear of childbirth is likely to trigger cortisol responses in the body and cause anxiety [28].

According to the results of the present study, labor induction predicted high anxiety scores. In a study conducted in the Netherlands, there was a correlation between labor induction and anxiety in multiparous women [1]. Induction may increase the anxiety level by inflicting greater pain. On the other hand, anxiety may inhibit uterine contractions and increase the need for labor induction by increasing the catecholamine levels [29].

Dehydration and thirst predicted high anxiety scores. The authors found no study examining such a correlation during labor.

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However, a review study reported that even mild dehydration could lead to mood impairment, even in healthy young adults [30].

The present results indicated high levels of anxiety in women who were exposed to tobacco smoke. Accordingly, a study in France revealed high prevalence of mental disorders in non-smokers who were exposed to tobacco smoke [31], and researchers in Amsterdam found high levels of anxiety in pregnant smokers [1]. A review study also showed that smoking can lead to anxiety disorders through affecting the nervous system, the immune system, oxidative stress markers, neurotrophins, neurogenesis process, and mitochondrial and epigenetic functions [32].

The present results regarding high prevalence of anxiety in women who had not participated in any childbirth preparation classes were consistent with the results of the studies conducted in Iran [33] and Ireland [34]. This is probably due to unfamiliarity of these women with the labor process and proper exercises that can facilitate this process. The present results revealed poor participation of women in pregnancy preparation classes; therefore, pregnant women should be informed about the importance of such classes.

Most pre-labor predictors of high anxiety score such as primiparity, women's pre-labor preference for the Caesarean section, sexual violence during pregnancy, over-normal gestational weight gain, gestational age of 40^{+0}–41^{+6} weeks, and insufficient household income were excluded from the final model; whereas, pre- and during-labor predictors were included. Fear of childbirth, and fear and concerns about fetal health are probably the main causes of anxiety in women with most of the pre-labor predictors. The association of insufficient household income with high levels of anxiety during labor which was also reported in a study conducted in Nigeria [35], might be due to high concerns of women about covering the hospital and newborn expenses.

Limitations

Sufficient sample size in the present study can be considered as a strength, which provided the possibility of detecting the predictive effect of many factors, even factors with small effect sizes. In addition, the participants had been admitted from

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different cities of several neighboring provinces with different cultures; thus, the results are more generalizable.

In this study, we were unaware of the participants' anxiety state before or during pregnancy; hence, it was unclear when a woman's anxiety started or intensified. This study also failed to assess the effects of some during-labor factors such as level of support received from the medical staff and interventions made during labor (duration of induction) on women's anxiety levels because the anxiety was assessed at the beginning of the active phase of labor. In addition, this was a cross-sectional study; therefore, the relationships between the variables could not be described as cause-and-effect relationships. To discover relevant cause-and-effect relationships, further longitudinal observational studies are recommended focusing on factors affecting women during pregnancy or in the latent phase of labor. Also, clinical trials should be carried out in order to assess the effects of some of the predictive factors such as childbirth preparation classes or other interventions aimed at reducing anxiety levels during labor.

Conclusion

Anxiety is highly prevalent in women at the onset of labor. Extreme fear, labor induction, dehydration and thirst, no attendance in childbirth preparation classes, exposure to tobacco smoke during pregnancy, sexual violence during pregnancy, obesity, gestational age over 40 weeks, tendency towards the Cesarean section, and low family income were identified as the main predictors of anxiety during labor. It seems that most of the predictive factors are preventable, and maternal anxiety can be reduced by providing appropriate counseling services to women during pre-pregnancy and prenatal care, meeting the mothers' needs during childbirth and having fewer interventions.

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Conflicts of Interest

The authors declare no conflict of interests.

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