


Correlation Between Maternal Anxiety During Mid-Pregnancy and Subsequent Infant Sleep Issues: A Cross-Sectional Study from 2015 to 2016

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Purpose: To explore the correlation between maternal anxiety during mid-pregnancy and infant sleep issues based on the anxiety status of mothers in mid-pregnancy.

Patients and Methods: A cohort of 2122 primigravida women from Ma'anshan City, Anhui Province, was followed from pregnancy until 6 months postpartum. The study analyzed the impact of maternal anxiety on infant sleep patterns, including primary caregivers, encompassing insufficient sleep duration, frequent nocturnal awakenings, prolonged nocturnal awakening durations, and elongated sleep latency.

Results: A total of 1891 mother-infant pairs were included in this analysis. After adjusting for confounding factors, a positive correlation was found between maternal anxiety during mid-pregnancy and insufficient sleep duration (OR=1.69, 95% CI:1.13–2.52), and elongated sleep latency (OR=2.26, 95% CI:1.61–3.18).

Conclusion: Maternal anxiety during mid-pregnancy is associated with sleep issues in infants. Addressing maternal mental health during pregnancy may enhance sleep quality for mothers and infants, promoting overall maternal-infant health.

Keywords: pregnancy anxiety, pregnancy, infant, sleep

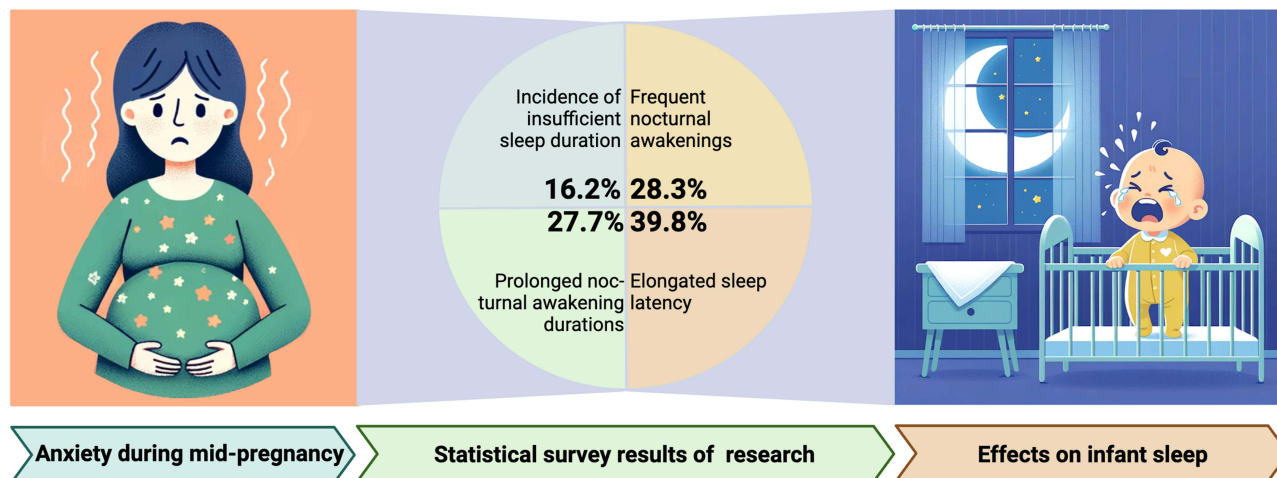
Introduction

Many women experience mental health issues during pregnancy or postpartum. Depression and anxiety are the most common mental health concerns during pregnancy, affecting a significant number of expectant mothers. Antenatal anxiety could potentially predict postpartum depressive symptoms.¹ There's a necessity for active assessment and management of stress, anxiety, and depression, starting from early pregnancy and continuing postpartum.² As a prevalent type of prenatal stress, pregnancy anxiety can impair the nervous system, neurocognitive functions, brain processing, functional and structural brain region connectivity, hypothalamic-pituitary-adrenal axis, and autonomic nervous system, thereby affecting offspring development and prenatal health.³ Anxiety during pregnancy can lead to a myriad of problems, including but not limited to, lack of focus, irritability, and in severe cases, suicidal tendencies.⁴ Symptoms such as dry mouth, irritability, sweating, vomiting require attention; severe cases might experience trembling, difficulty in breathing, even suicidal thoughts and actions—these are undoubtedly the most dangerous manifestations of pregnancy syndrome. Factors like hormonal changes during pregnancy, previous miscarriages or problematic pregnancies, and sleep disturbances might contribute to anxiety in expectant mothers.^{5,6} Concerns may range from worrying about the baby's health and birth-related issues, the impact of the new baby on relationships with friends and family, to the financial strain of adding a new member to the family. In the post-pandemic era of 2021–2022, many expectant mothers staying at home for extended periods inevitably find themselves scrolling through news of the pandemic on their mobile phones, exacerbating anxiety. Research suggests that anxiety is a natural emotional response when feeling uneasy or threatened.

Although, from an evolutionary perspective, anxiety serves as a primal instinct for self-preservation when facing the unknown, leading to tension and stress due to the necessity of dealing with and resolving new issues.⁷ However, studies

Graphical Abstract

Impact of Maternal Anxiety During Mid-Pregnancy on Infant Sleep Patterns



have confirmed that anxiety during pregnancy could have negative effects on both the mother and fetus, increasing the risks of preterm birth, low birth weight, and early pregnancy complications. Moreover, maternal anxiety could affect fetal cortical brain development, enhance the fetus's alert temperament, and increase the likelihood of behavioral and emotional management disorders in children later in life.⁸

Currently, infant sleep problems have emerged as a major public health issue. A search through the Wanfang database revealed that in China, the incidence rate of sleep problems among infants and toddlers aged 1–23 months reaches as high as 65.9%.⁹ Among 0–36-month-old infants and toddlers, the incidence of sleep disorders reported by parents is 30.7%. Good sleep is essential for the healthy growth of infants and toddlers, significantly impacting their physical, cognitive, and central nervous system development.¹⁰ Infant sleep problems are influenced by physiological, psychological, and social factors,¹¹ Many studies have confirmed the association between early childhood sleep problems and neurocognition,¹² emotion,¹³ and diseases¹⁴ in children. Infant sleep problems can adversely affect various aspects of an infant's growth, cognition, and socio-emotional interactions and could potentially continue into preschool and school age, even leading to sleep disorders in adulthood, thereby affecting family functioning.¹⁵ Persistent infant sleep problems can have numerous adverse effects on the infant and their family. Therefore, early prevention of children's sleep problems is helpful for both children and families.

This study, through a birth cohort research design, aims to explore the association between maternal anxiety during mid-pregnancy and infant sleep problems, to promote psychological assessment and adjustment during pregnancy, reduce infant sleep problems, and enhance maternal-infant health. By elucidating the positive correlation between maternal anxiety during mid-pregnancy and infant sleep problems, this study provides crucial scientific evidence for promoting attention and improvement in maternal mental health during pregnancy, actively contributing to reducing infant sleep problems and promoting maternal-infant health.

Materials and Methods

Objects

This research is a prospective birth cohort study, encompassing a Ma'anshan city maternal and infant health birth cohort established at the Ma'anshan City Maternal and Child Health Hospital from June 2015 to June 2016.

Inclusion Criteria: The study included healthy pregnant women residing in Ma'anshan city who were between 6 to 12 weeks of gestation and planned to give birth at this hospital, with this pregnancy being singleton. After excluding those who had miscarriages or induced abortions, a total of 2122 pregnant women were included, with follow-ups conducted from pregnancy until the infant reached 6 months of age.

Exclusion Criteria: A total of 231 mother-infant pairs were excluded from the study due to lost follow-up, or incomplete information regarding maternal anxiety during pregnancy or infant sleep conditions.

In this research, a total of 1891 mother-infant pairs were included in the analysis. The study received approval from the Medical Ethics Committee of Ma'anshan City Maternal and Child Health Hospital (Approval Number: 2016–003). All subjects signed an informed consent form.

Methods

Basic Information

Demographic information of both pregnant women and their spouses (age, educational level, per capita monthly household income, etc.) were collected during early pregnancy. At the 6-month mark post-birth, information regarding sleep habits, sleeping environments, and feeding methods were gathered.

Anxiety During Mid-Pregnancy

Anxiety levels during mid-pregnancy were assessed using the Self-rating Anxiety Scale (SAS).^{16,17} This scale comprises 20 items reflecting subjective feelings of anxiety, with scoring based on the frequency of symptoms experienced within a week, categorized into four levels: none or a small amount of time, a small portion of time, a substantial amount of time, and most or all of the time. A standard score is obtained by multiplying the total score of the 20 items by 1.25, where a standard score of <50 indicates no anxiety, and a standard score of ≥ 50 indicates anxiety.

Infant Sleep Conditions

At the 6-month mark, primary caregivers reported “average nighttime sleep duration” and “average daytime sleep duration” for the infants, the sum of which constitutes the total sleep duration. Referring to the guidelines of the “0 to 5 years old Children Sleep Hygiene Guide” and based on a report retrieved from the Wanfang database, sleep duration of <12 hours is defined as “insufficient sleep duration.” Caregivers also reported the “average number of times baby wakes up at night”, with ≥ 3 times per night defined as “frequent nocturnal awakenings”, as per the research standards set by Weng et al.⁹ They reported “how long the baby stays awake during the night (10 PM to 6 AM)”, with total nocturnal wakefulness \geq the 75th percentile of the surveyed population (60 min) defined as “prolonged nocturnal awakening”.⁹ Additionally, the time it takes for the baby to fall asleep at night was reported, with sleep latency of >20 minutes defined as “prolonged sleep latency” as per the “0 to 5 years old Children Sleep Hygiene Guide”.

Control Variables

Referring to previous infant sleep studies, factors that may influence infant sleep conditions were taken as control variables. These include sleep habits, sleeping environments, current feeding methods, and any history of illness in the past three months, based on their known potential influence on infant sleep conditions, as evidenced by previous studies in this field.^{18,19}

Quality Control

The survey questionnaire was finalized under the ethical approval of Ma'anshan City Maternal and Child Health Hospital and under the guidance of medical experts holding the title of associate chief physician or above, after multiple revisions. Questionnaires were distributed by trained investigators who explained the purpose of the study and how to complete the questionnaire. During on-site surveys, questionnaires were uniformly coded. Upon completion by parents, investigators carefully checked the content for missing or unclear information, making on-the-spot corrections or additions as necessary. Reasons for lost follow-ups were noted, and phone reminders were sent to pregnant women and children who missed their scheduled check-ups.

Statistical Analysis

Data was entered into the Epidata 3.0 database and, after verification for accuracy, analyzed using SPSS 13.0 software. Age distribution was represented as $\bar{x} \pm s$, while gender, pregnancy anxiety, insufficient sleep duration, frequent nocturnal awakenings, prolonged nocturnal awakening, and prolonged sleep latency were all count data, described by frequency and percentage. The χ^2 test was employed to compare the distribution of different characteristic variables of infant sleep conditions and maternal anxiety during pregnancy. Multifactorial non-conditional logistic regression models were used to analyze the impact of pregnancy anxiety on infant sleep conditions before and after adjusting for other factors. Two-sided tests were conducted with a significance level of $\alpha=0.05$.

Results

Basic Information

The age of the pregnant women was (26.86±3.73) years, with male infants constituting 51.9% (981/1891) of the cohort. The incidence of insufficient sleep duration in infants was 16.2% (305/1881), frequent nocturnal awakenings was 28.3% (536/1891), prolonged nocturnal awakening was 27.7% (523/1891), and prolonged sleep latency was 39.8% (752/1891).

Distribution of Anxiety During Pregnancy Across Different Characteristic Variables

As demonstrated in Table 1, the detection rate of anxiety during mid-pregnancy was 8.1% (153/1891), indicating a statistically significant correlation ($P<0.05$) between maternal anxiety during mid-pregnancy and factors such as maternal age, nature of work, pre-pregnancy BMI, and pre-pregnancy alcohol consumption. However, there was no statistically significant difference in the distribution of anxiety during mid-pregnancy among groups characterized by maternal educational level, per capita monthly household income, only-child status, or first-time pregnancy.

Table 1 Anxiety Distribution of Pregnant Women with Different Characteristic Variables in the Second Trimester

Characteristic	Number	Anxiety During Mid- Pregnancy		χ^2	P
		No Anxiety			
Age (years)				8.680	<0.05
≤24	494	436(88.9)	55(11.1)		
25~29	1022	953(93.2)	69(6.8)		
≥30	375	346(92.3)	29(7.7)		
Educational Level				7.639	0.054
Junior High School or Below	229	204(89.1)	25(10.9)		
High School or Vocational	363	325(89.5)	38(10.5)		
Associate's Degree	609	568(93.3)	41(6.7)		
Bachelor's Degree and Above	690	641(92.9)	49(7.1)		
Per Capita Monthly Household Income (CNY)				1.076	0.783
<1000	29	26(89.7)	3(10.3)		
1000~	197	180(91.4)	17(8.6)		
2500~	703	642(91.3)	61(8.7)		
>4000	962	890(92.5)	72(7.5)		

(Continued)

Table 1 (Continued).

Characteristic	Number	Anxiety During Mid- Pregnancy		χ^2	P
		No Anxiety			
Only Daughter				0.444	0.505
Y	780	713(91.4)	67(8.6)		
N	1111	1025(92.3)	86(7.7)		
Primigravida				0.724	0.395
Y	1012	925(91.4)	87(8.6)		
N	877	811(92.5)	66(7.5)		
Nature of Work				9.881	<0.05
Primarily Mental Work	878	821(93.5)	57(6.5)		
Primarily Physical Work	59	51(86.4)	8(13.6)		
Balanced Mental and Physical Work	328	291(88.7)	37(11.3)		
Unemployed	626	575(91.9)	51(8.1)		
Pre-pregnancy BMI				9.557	<0.05
Underweight	401	355(88.5)	46(11.5)		
Normal	1243	1158(93.2)	85(6.8)		
Overweight or Obese	213	192(90.1)	21(9.9)		
Pre-pregnancy Alcohol Consumption				6.144	<0.05
N	1495	1386(92.7)	109(7.3)		
Y	396	352(88.9)	44(11.1)		

Notes: In the tables presented within this document, the notation "Y" stands for "Yes" and "N" denotes "No." * $P < 0.05$, ** $P < 0.001$.

Distribution of Infant Sleep Conditions Across Different Characteristic Variables

Our findings (Table 2) suggest that maternal anxiety during mid-pregnancy, paternal educational level, and per capita monthly household income are associated with insufficient infant sleep duration. Factors such as gender, sleep habits, sleeping environments, and feeding methods are related to frequent nocturnal awakenings in infants. Paternal educational level is correlated with prolonged nocturnal awakening in infants. Maternal anxiety during mid-pregnancy, gender, and feeding methods are associated with prolonged sleep latency in infants, with all differences being statistically significant ($P < 0.05$).

Correlation Between Anxiety During Mid-Pregnancy and Infant Sleep Conditions

As shown in Table 3, univariate logistic regression analysis revealed that, compared to no anxiety during mid-pregnancy, anxiety during this period is positively correlated with insufficient infant sleep duration (OR=1.75, 95% CI:1.18~2.58) and prolonged sleep latency (OR=2.26, 95% CI:1.61~3.15). After adjusting for variables such as child gender, history of illness in the past three months, paternal educational level, per capita monthly household income, sleep habits, sleeping environments, and current feeding methods, multivariate logistic regression analysis showed that anxiety during mid-pregnancy was associated with insufficient infant sleep duration (OR=1.69, 95% CI:1.13~2.52) and prolonged sleep latency (OR=2.26, 95% CI:1.61~3.18).

Table 2 Distribution of Infant Sleep Problems Across Various Characteristic Variables

Characteristic	Insufficient Sleep Duration	Frequent Night Awakenings	Prolonged Night Awakening Duration	Prolonged Sleep Latency
Anxiety during Mid- Pregnancy				
N	267(15.5)	497(28.6)	479(27.6)	663(38.1)
Y	37(24.2)*	39(25.5)	44(28.8)	89(58.2)**
Gender				
Male	158(16.2)	315(32.1)	271(27.6)	356(36.3)
Female	146(16.2)	219(24.1)**	250(27.6)	395(43.6)*
Preterm Birth				
Y	13(19.4)	13(19.4)	16(23.9)	31(46.3)
N	291(16.1)	521(28.6)	505(27.7)	720(39.5)
Mode of Delivery				
Vaginal Delivery	167(15.4)	317(29.0)	316(28.9)	431(39.4)
Cesarean Delivery	137(17.3)	217(27.3)	205(25.8)	320(40.3)
Only Child				
Y	228(16.5)	405(29.3)	397(28.7)	568(41.0)
N	55(15.2)	93(25.5)	95(26.1)	130(35.7)
Maternal Age at Pregnancy (years)				
≤24	93(18.9)	146(29.6)	137(27.7)	206(41.7)
25~29	160(15.7)	285(27.9)	284(27.8)	410(40.1)
≥30	51(13.7)	105(28.0)	102(27.2)	136(36.3)
Paternal Age at Pregnancy (years)				
≤24	54(19.4)	76(27.1)	85(30.4)	113(40.4)
25~29	160(15.9)	298(29.5)	285(28.2)	406(40.2)
≥30	88(15.2)	159(27.3)	149(25.6)	227(38.9)
Recent 3-month Medical History				
N	172(16.4)	279(26.3)	283(26.7)	408(38.5)
Y	132(15.9)	257(30.9)*	240(28.9)	343(41.3)
Maternal Education Level				
Junior High School or Below	46(20.1)	69(30.1)	62(27.1)	88(38.4)
High School or Vocational	59(16.3)	106(29.2)	110(30.3)	146(40.2)
Associate's Degree	104(17.2)	181(29.7)	176(28.9)	247(40.6)
Bachelor's Degree and Above	95(13.8)	180(26.1)	175(25.4)	271(39.3)

(Continued)

Table 2 (Continued).

Characteristic	Insufficient Sleep Duration	Frequent Night Awakenings	Prolonged Night Awakening Duration	Prolonged Sleep Latency
Paternal Education Level				
Junior High School or Below	43(21.4)	48(23.8)	47(23.3)	81(40.1)
High School or Vocational	70(17.5)	128(31.8)	118(29.4)	163(40.5)
Associate's Degree	97(16.8)	162(27.8)	187(32.1)	226(38.8)
Bachelor's Degree and Above	91(13.0)*	197(28.1)	170(24.3)*	280(40.0)
Per Capita Monthly Household Income (CNY)				
<1000	4(13.8)	9(31.0)	7(24.1)	12(41.4)
1000~	40(20.5)	65(33.0)	62(31.5)	78(39.6)
2500~	127(18.2)	204(29.0)	203(28.9)	278(39.5)
>4000	133(13.9)*	258(26.8)	251(26.1)	384(39.9)
Sleep Habits				
Poor	236(16.4)	440(30.4)	410(28.3)	586(40.5)
Self-soothing	64(14.8)	95(21.8)**	113(25.9)	163(37.4)
Sleep Location				
Crib	112(18.3)	135(21.9)	182(29.5)	244(39.5)
Co-sleeping with family	189(14.9)	400(31.5)**	339(26.7)	506(39.9)
Feeding Method				
Exclusive Breastfeeding	110(13.8)	274(34.5)	207(26.0)	326(41.0)
Mixed Feeding, Predominantly Breastmilk	97(17.7)	180(32.5)	158(28.6)	238(43.0)
Mixed Feeding, Predominantly Formula	35(16.8)	48(22.9)	71(33.8)	75(35.7)
Formula Feeding	62(18.8)	33(9.9)**	87(26.2)	113(34.0)*

Notes: In the tables presented within this document, the notation "Y" stands for "Yes" and "N" denotes "No." *P<0.05, **P<0.001.

Table 3 Logistic Regression Analysis on the Association Between Second Trimester Anxiety and Infant Sleep Conditions [or (95% CI)]

Category	Insufficient Sleep Duration	Frequent Night Awakenings	Prolonged Night Awakening Duration	Prolonged Sleep Latency
Model One				
Anxiety During Pregnancy				
N	1.00	1.00	1.00	1.00
Y	1.75(1.18, 2.58)*	0.85(0.59, 1.25)	1.06(0.74, 1.53)	2.26(1.61, 3.15)**

(Continued)

Table 3 (Continued).

Category	Insufficient Sleep Duration	Frequent Night Awakenings	Prolonged Night Awakening Duration	Prolonged Sleep Latency
Model Two				
Anxiety During Pregnancy				
N	1.00	1.00	1.00	1.00
Y	1.69(1.13, 2.52)*	0.89(0.60, 1.32)	1.04(0.72, 1.50)	2.26(1.61, 3.18)**

Notes: Model One represents the univariate analysis model; Model Two represents the multivariate analysis model, adjusting for child gender, recent 3-month disease history, father's level of education, average monthly family income, sleep habit, sleeping location, and current feeding method. * $P < 0.05$, ** $P < 0.001$.

Abbreviations: SAS, Self-Rating Anxiety Scale; HPA, Hypothalamic-Pituitary-Adrenal.

Discussion

The stress and anxiety experienced by mothers during pregnancy have long-term associations with the development of their infants.²⁰ Exposure to maternal anxiety in utero is linked with a higher risk of emotional and behavioral issues in children, as well as anxiety and depression levels in adulthood.²⁰ While the incidence of anxiety during pregnancy is not lesser than that of depression during pregnancy,²¹ the majority of existing research concerning maternal mental health and infant sleep primarily focuses on maternal depression²². The impact of anxiety could be as significant as that of depression during pregnancy. This study, by establishing a mother-infant birth cohort, delineates the levels of maternal anxiety during mid-pregnancy and the distribution of infant sleep problems, exploring their interrelation. It underscores the importance and impact of anxiety during pregnancy on maternal mental health and infant sleep quality, alongside the potential role regional variations might play in the incidence of anxiety.

The existing tools for measuring anxiety include those based on Rogers' Self Consistency and Congruence, the Eysenck Personality Questionnaire (EPQ),²³ and the Raven's Standard Progressive Matrices (SPM).²⁴ In China, the Self-rating Anxiety Scale (SAS) is widely used.²⁵ It is a self-assessment scale consisting of 20 items, rated on a four-level scale, designed to evaluate the subjective feelings of anxiety patients. Its structure and specific assessment methods are very similar to those of the Self-rating Depression Scale (SDS), and both are known for their efficiency, simplicity, and ease of analysis, making them suitable evaluation tools. In China, the cutoff values (including severity thresholds) for these scales are based on percentile distributions in the general population and have not undergone clinical validity testing. Internationally, even in developing countries like Brazil, clinical validity tests are conducted for special populations, such as Parkinson's disease patients. Therefore, it is necessary to conduct related clinical validity studies to better utilize these tools in clinical work.

Our findings indicate that the detection rate of maternal anxiety during mid-pregnancy is 8.1%, which is lower than the rate reported by Sun et al⁹ in their study conducted across multiple regions in China. Despite the fact that our study only investigated the anxiety detection rate among pregnant women in Ma'anshan city, it nevertheless unveils the influence of regional variations within the same territory on the incidence of anxiety during pregnancy, suggesting that maternal anxiety might be associated with different socioeconomic conditions, cultural disparities, and the availability of healthcare resources across various regions.²⁶ Our results are similar to those in other countries,^{27–29} these insights call for future research to consider regional differences, potentially necessitating collaborative studies across different regions to gain a more comprehensive understanding and to verify the economic disparities brought about by regional variations, which might, in turn, negatively affect newborns.

However, anxiety does not present as a binary state, but rather exists on a continuum. The cutoff score used for defining "anxiety" in this research, while methodologically useful, should not be interpreted as a definitive demarcation of the absence or presence of anxiety. This approach acknowledges the nuanced and varied manifestations of anxiety symptoms, ranging from mild to severe. Our decision to use a specific cutoff point is a practical choice to facilitate analysis, yet we understand that it does not capture the full spectrum of anxiety experiences. This perspective aligns with

contemporary understandings in psychology that emphasize the dimensional nature of mental health symptoms, and we suggest future studies consider this continuum in their analytical frameworks.

The regulation of sleep-wake cycles and sleep architecture undergo rapid development during infancy and continue to mature throughout childhood. Increasing evidence suggests that childhood sleep problems are associated with adverse developmental outcomes concerning physical health, cognition, emotions, and behavior.^{30,31} Our study identifies a positive correlation between maternal anxiety during mid-pregnancy and insufficient infant sleep duration as well as prolonged sleep latency. That is, infants of mothers who were anxious during mid-pregnancy had higher risks of experiencing insufficient sleep and prolonged sleep latency. Mid-pregnancy is a crucial period for the development of the fetal nervous system, and maternal anxiety may impact fetal neurodevelopment via biological pathways such as cortisol hormone levels. For instance, research indicates that maternal anxiety and stress can affect the fetal Hypothalamic-Pituitary-Adrenal (HPA) axis, which might further impact infant sleep patterns.²⁶ Therefore, early identification and management of anxiety during pregnancy could be key in preventing infant sleep problems.

In addition to the factors already considered, it is important to acknowledge the potential role of genetics in both maternal anxiety and infant sleep issues. Recent studies suggest that genetic predispositions can influence the likelihood of developing anxiety disorders, as well as affect sleep patterns and quality.³²⁻³⁴ These findings imply that the associations observed in our study might be partially influenced by genetic factors. This underscores the complexity of the relationship between maternal anxiety and infant sleep, suggesting that both environmental and genetic factors should be considered in future research to fully understand these associations.

Providing mental health services during pregnancy can not only ameliorate maternal mental health but also may help prevent infant sleep problems and other developmental issues.³⁵ Moreover, collaboration among mental health professionals, obstetricians, and pediatricians may foster a better understanding and addressing of the relationship between anxiety during pregnancy and infant sleep problems. Through interdisciplinary collaboration, more comprehensive and coordinated care can be provided to pregnant women and newborns, thereby improving overall maternal-infant health outcomes.

Conclusion

This study offers valuable insights for physicians and other healthcare professionals to understand and support maternal mental health and its implications on infant sleep quality. It also lays a foundation for public health strategy formulation, particularly in rendering mental health services and education during pregnancy, which holds practical significance for the clinical practice of precision medicine in postnatal care. Additionally, it aids in a more accurate understanding of the relationship between child sleep and caregiver anxiety among other mental health issues. Furthermore, in this research, we employed caregiver-reported questionnaires to collect data on infant sleep outcomes, which could potentially introduce issues due to subjective memory bias. Hence, we recommend the incorporation of objective measurement and diagnostic tools in future research endeavors.

Ethical Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Ma'anshan City Maternal and Child Health Hospital (No. 2016-003). We ensured that all participants were fully informed and provided their written informed consent. All procedures in this study were in compliance with international and national ethical standards and were strictly protective of participants' privacy and personal data.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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