Genetic, Epidemiological and Clinical Risk Factors in Perinatal Anxiety and Depression: Protocol for a Two-point Prospective Observational Study

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Abstract

Background: Perinatal anxiety and depression can significantly impact maternal well-being, infant development, and mother-child bonding. There is a relative lack of research that investigates the overall burden and risk factors of perinatal and postpartum depression and anxiety in the Middle Eastern region.

Objective: To investigate the Genetic, Epidemiological, and Clinical risk factors of anxiety and depression in antenatal and postnatal mothers.

Methods: Two-point cross-sectional observational study of pregnant women to be seen at a tertiary care hospital in Dubai, United Arab Emirates to evaluate point prevalence of depression and anxiety with the Edinburgh Postnatal Depression Scale, Generalized Anxiety Disorder-7 scale and Rahe's stress index and analyse the risk factors in affected and unaffected women. The patients with severe depression and anxiety will be evaluated by genomic testing to identify rare disease causal variants.

Results: Prevalence of depression, anxiety, stress and risk factors will be noted in the antenatal and postnatal period. The association of genetic, social, and demographic risk factors with depression and anxiety will also be evaluated.

Conclusions: This research aims to identify genetic variants associated with perinatal anxiety and depression in Middle Eastern women and to develop a comprehensive risk assessment tool for identifying women at high risk for perinatal anxiety and depression. Clinical Trial: no

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Title

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Keywords

Depression; anxiety; antepartum; postpartum.

Introduction

BACKGROUND

The World Health Organization's guide for integrating perinatal mental health into maternal and child health services reflects the global recognition of this crucial health concern. [1] The impact of mental health disorders on the workforce is significant, with 15% of working-age adults worldwide suffering from such conditions. Anxiety and depression alone lead to the loss of 12 billion working days annually. [2] During pregnancy, untreated depression and anxiety in the perinatal and postpartum periods have far-reaching consequences beyond economic implications. These conditions are associated with obstetric complications,[3] poor birth outcomes, and [4] reduced health-seeking behaviour during and after pregnancy. [5] Furthermore, these conditions can impair mother-child

bonding,[6] with infants of mothers with such conditions at a higher risk for physical, emotional, and behavioural issues. [4] Addressing perinatal mental health is therefore crucial for the well-being of the mother, child, and the wider family unit in both the short and long term.

Previous publications[6], [7], [8], [9], [10] on perinatal mental illness in the United Arab Emirates, reveal a wide range in reported prevalence from 10% to 85.6%. Women from Middle Eastern ethnicity were more prone to depression (50%) and anxiety (48.5%). Globally rates of perinatal depression and anxiety are estimated at one in ten in high-income countries and one in five in low- and middle-income countries.[1] Given these increased local rates, factors causing mental health issues in the obstetric population in this region must be addressed as a priority. There are very few systematic reviews or primary studies of good value from the Middle-east North African region to assess the accurate prevalence of the disorders.[6]

A pilot study conducted in the tertiary care hospital in the previous year found that only 0.65% of pregnant patients treated in the Department of Obstetrics and Gynecology had anxiety, depression, or both documented in their diagnoses. This critical gap in identifying and treating perinatal mental health conditions underscores the urgent need for comprehensive research in this field.

Several risk factors are thought to increase the risk of poor perinatal mental health.[8] These factors encompass socio-demographic, genetic, lifestyle, clinical and endocrine risk factors. Some of these include depression during the second and third trimesters of pregnancy, the number of children, religion, and the use of formula for feeding. Additionally, factors like educational level, lack of breastfeeding, stressful life events,[1] gestational diabetes[11] and employment status after delivery were found to be of borderline significance.[8] These risk factors are crucial for early identification, underscoring the importance of screening pregnant women during pregnancy and postpartum. We therefore aim to evaluate the most relevant socio-demographic risk factors for perinatal anxiety and depression among pregnant women in Dubai. Studying the specific risk factors in our local population will help identify region-specific factors that could allow for more tailored interventions to improve outcomes for mothers and infants in Dubai.

Recent studies have identified multiple genes that contribute to both depression and anxiety, with many genes being common to both conditions.[12] Analysis of Genome-Wide Association Studies from the Psychiatric Genomics Consortium database found a very strong correlation between anxiety and depressive disorders and also revealed a complex interplay of multiple genetic variants that underlie these psychiatric disorders. Studies also indicate that variations in genes related to the hypothalamic-pituitary-adrenal axis, serotonin transporter, and other neurotransmitter systems probably increase the risk of anxiety and depression.[13], [14], [15]

Understanding these genetic risks in greater depth is critical for determining the underlying molecular mechanisms of these disorders, which may lead to the development of more tailored therapeutic strategies. Furthermore, understanding the interplay of genetic and environmental risk factors during the perinatal period should inspire preventive treatments that improve both maternal health and newborn development.

To the best of our knowledge, no previous study has analysed perinatal mental health by looking at both genetic, clinical and socio-demographic risk factors in the United Arab Emirates. These socio-demographic, genetic and clinical risk factors need to be identified to prevent, screen, diagnose and treat anxiety and depression during this vulnerable period.

OBJECTIVES

This study aims to investigate the socio-demographic, genetic, lifestyle and clinical risk factors associated with anxiety and depression in perinatal and postnatal women in Dubai, UAE. (Textbox 1)

Textbox 1. Objectives

Primary Objectives:
To investigate the point prevalence of anxiety and depression in antenatal and postnatal

mothers using the Edinburgh Postnatal Depression scale, Generalized Anxiety Disorder-7 scale in Dubai Hospital, Dubai, UAE.

Secondary Objectives:

1. To identify genetic variants in severe cases of depression and anxiety.
2. To correlate the stress, demographic, social, clinical and lifestyle factors associated with the mental health of antenatal and postnatal women.

The prevalence of anxiety and depression in perinatal and postnatal women in Dubai, UAE is higher than global averages and associated with a unique cluster of socio-demographic, genetic, lifestyle and clinical risk factors. Cultural factors, traditional family structures and social expectations could be protective or may hinder access to mental health services in this region. There is a need to assess the prevalence rate and associated genetic factors in the Middle Eastern region. Similar to type 2 diabetes and obesity, genetic susceptibility to psychiatric disorders could be more prevalent in the Middle Eastern region compared to other populations. Understanding these genetic risks in greater detail is crucial for uncovering the underlying biological mechanisms of these disorders, potentially leading to the development of more targeted therapeutic interventions. Moreover, elucidating the interplay between genetic and environmental risk factors during the perinatal period could inform preventive strategies that benefit maternal health and infant development.

Methods

RECRUITMENT

A cross-sectional observational study will be conducted at Dubai Hospital, a tertiary centre that receives patients from all 7 emirates of the UAE. Participants recruited will be pregnant women who, after 20 weeks of gestation, attend antenatal clinics and inpatient admissions at Dubai Hospital. The age range of our participants will be 15 to 50 years. Informed consent will be obtained from all participants, and they will be provided clarification on the aim of the study and assurance about information confidentiality. The women can withdraw consent from participation in the study at any point. Women identified as having severe depression or anxiety will be referred to our hospital psychologist immediately. Women identified as suicidal will be promptly referred to psychiatry services.

INTERVENTIONS

Figure 1 outlines the following variables to be obtained from women who consent to participate in the study, with further details provided below.

Patient Flow

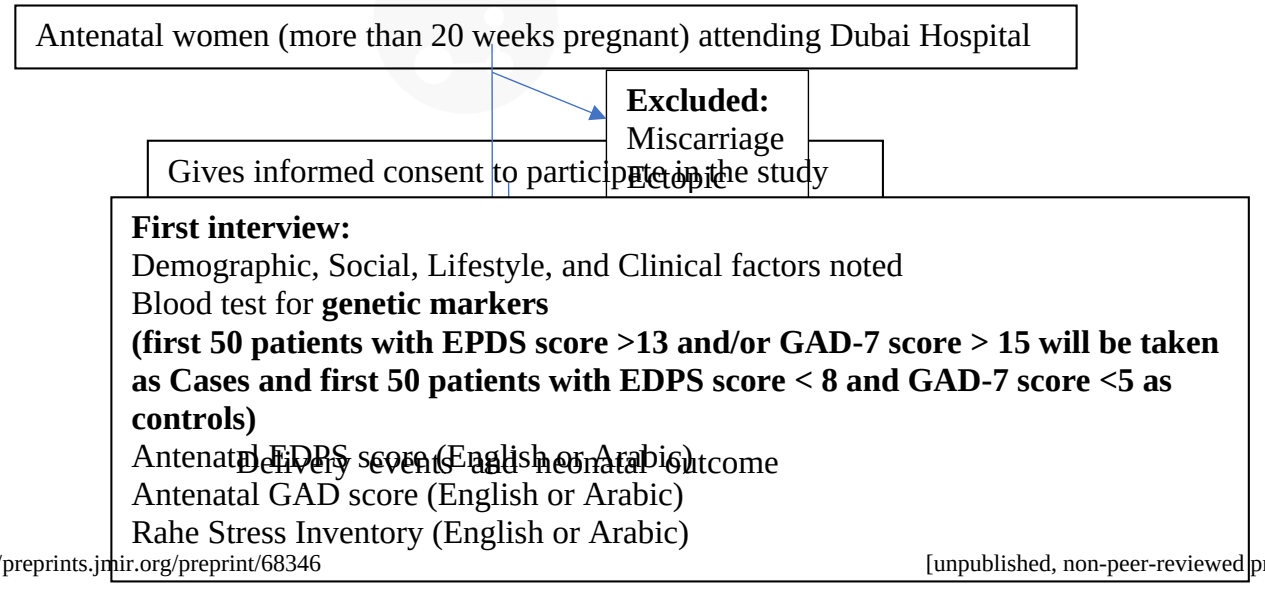

Figure 1.: Patient Recruitment and Study Interventions

Second interview:
Reconfirm consent
Postnatal factors noted
Repeat EDPS, GAD-7 score and Rahe stress inventory at **6 to 12 weeks** postnatal visit

Demographic information such as age, nationality, the emirate of residence, body mass index, marital status, educational level, occupation, long working hours, temporary employment, healthcare worker and total monthly income will be noted. Her partner's education, occupation, consanguinity, military service and the age difference between the partners will be asked.

To evaluate the genetic factors, we will utilise a long-read genome sequencing platform. The sequencing data will be analysed using a flamingo server, a high-performance computing cluster. This computational infrastructure will enable the robust and efficient processing of the genomic data required for our analysis. The system requires 8-10ml blood and high molecular weight DNA. After a long read of whole genome sequencing, established pipelines for genome mapping and variant detection will be utilized. We will try to identify rare variants that might play a vital role in the aetiology of the condition.

Social factors such as family size (nuclear or extended), loss of a parent in childhood, number of years of marriage, polygamous marriage, Intimate partner violence, partner mental illness, planned or unplanned pregnancy, support network including extended family, financial difficulties, loneliness, body image, drug and alcohol abuse and chronic illness will be noted. Personal or family history of mental illness will be asked.

Lifestyle factors like diet, caffeine intake, sleep disturbance, Vitamin D deficiency, exercise of at least 30 minutes a day and sedentary habits will be evaluated. Clinical high-risk factors such as grand multiparity, poor obstetric history, assisted conception, Gestational Diabetes Mellitus, Pregnancy Induced Hypertension, cigarette or alcohol use during pregnancy or any pre-existing medical disorders will be mentioned.

Delivery events and postnatal factors such as birth by caesarean section, intrapartum complications, congenital malformations, Neonatal Intensive care Unit admission and duration of admission, crying, sleeping or feeding problems of the neonate, gestational age at delivery, husband/family presence at delivery, gender of baby, baby’s birth weight will be noted. History of postnatal emotional support from family, poor maternal sleep, and maternity leave, will be obtained from the postnatal women at the second interview.

Mental Health Assessment tools:

Depression symptoms will be assessed by the Edinburgh Postpartum Depression Scale, which is validated for both English and Arabic.[7], [17], [18] It is a self-reporting, 10-item scale questionnaire, scoring from 0 to 3, with the minimum and maximum total scores ranging from 0 to 30 points. A cut-off point of ≥10 is used for identifying depression, ≥13 for severe depression, and a “yes” response to question 10 for suicidal ideation.

Anxiety symptoms will be assessed using validated English and Arabic-translated versions of the Generalized Anxiety Disorder (GAD-7) score.[19] The 7-item score assesses tension, restlessness, and irritability by scoring from 0 to 3 and by adding an overall score range from 0 to 21. A score of ≥5 will be considered to indicate a risk of anxiety and will be used as a cut-off in our study.

The Rahe Stress Inventory [20] will be used to identify the level of stress, with Life Change Unit values. The cumulative impact of these life changes can significantly affect one's health, emphasizing the importance of managing and mitigating stress. 150 points or less indicates a relatively low amount of life change and a low susceptibility to stress-induced health breakdown 150 to 300 points

indicate a 50% chance of health breakdown in the next 2 years and 300 points or more imply an 80% chance of health breakdown in the next 2 years.

Method of sampling:

Convenient sampling of pregnant patients attending Dubai Hospital during the study period will be employed. Patient interviews will be conducted while the women are waiting in the clinic for their antenatal care appointments. A similar study[10] conducted during the COVID-19 pandemic revealed that patients were very willing to discuss their mental health issues confidentially in a safe environment. After the interview, the patient will be directed to give the blood sample for genetic testing. We aim to evaluate 100 patients for genetic causes, The first 50 patients with EPDS score >13 and/or GAD-7 score > 15 will be taken as Cases and first 50 patients with EDPS score < 8 and GAD-7 score <5 as controls. The timing of the blood sample collection will coincide with the 24-week glucose tolerance test. This scheduling will prevent any additional discomfort to the pregnant women.

Sample size

The sample size for the prevalence study was calculated with an expected prevalence of 33% in a previous study[21] for postnatal depression in Dubai (expressed as 0.33), a desired precision of 5% (expressed as 0.05), and a 95% confidence level. The required sample size is approximately 350 participants. We will however aim to recruit 420 women to allow for a 20% dropout rate. We are confident we will achieve this number given the number of pregnant women seen at Dubai Hospital in one year.

Statistical analysis

Statistical analysis will be done using IBM SPSS Statistics, version 25.0 (IBM Corp, Armonk, NY). Univariate statistics and distribution will be assessed, and continuous variables will be presented as mean and standard deviation or median and interquartile range. Categorical variables will be expressed as frequency and percentage. Initial associations between genetic variants of the serotonin gene (5-HTTLPR) and oxytocin gene (OXTR) with depression and anxiety will be tested using the Chi-Squared Test. The Fisher's exact test will be used to evaluate genotype-phenotype relationships. To account for potential confounding factors, logistic regression will be used. Linear regression will be applied to continuous outcomes like severity scores. The correlation between demographic factors, clinical factors, lifestyle factors, Stress and antenatal EPDS and GAD scores and the correlation between postnatal factors and EPDS and GAD scores of postnatal patients will be calculated using chi-square tests. The Mann−Whitney U test will be used for 2 independent samples and the Kruskal-Wallis test for >2 independent demographic variables.

Ethical approval:

Ethical approval will be obtained from the Hospital Ethics Committee and the Dubai Scientific and Research Ethics Committee.

Discussion

Principal Results

The point prevalence of prenatal and postnatal depression and anxiety will be determined at Dubai Hospital following the pandemic. The genetic markers associated with depression and anxiety in Middle Eastern ethnicity will be identified, and the relationship between other risk factors and their mental health impact will be investigated in the enrolled patients.

Comparison with Prior Work

There are only a few studies on perinatal anxiety and depression in the Middle Eastern region. Previous research[21] conducted before COVID-19 showed a 33% prevalence of postpartum depression. A comparable study[10] conducted at the same location during the pandemic found a 43.6% prevalence of depression and 42% of anxiety. However, the risk factors were not assessed in the study. We discovered just one study [22] that examined the relationship between genetic markers and postnatal depression in Jordanian women. The frequency of perinatal depression and anxiety, as well as associated risk factors, in the Middle East and North Africa region must be further investigated.

Limitations

While this study design provides useful information about perinatal mental health, some limitations should be addressed. The recruitment of participants from a single tertiary care hospital in Dubai may impact the generalizability of our findings. The calculated point prevalence may not accurately reflect the true burden of perinatal mental health problems in the population. The study population may not accurately reflect the larger community, particularly those who do not have access to tertiary healthcare services.

Measurement constraints include the use of self-reported screening measures like the Edinburgh Postnatal Depression Scale and GAD-7. Although validated, these tools are susceptible to reporting bias and may be influenced by cultural variables influencing how women in this region perceive and report mental health symptoms. The targeted method for identifying genetic factors may overlook other relevant genetic variants. Furthermore, the cross-sectional design limits our capacity to assess how these genetic factors interact with environmental cues during the perinatal period.
Despite these limitations, this study is an essential step towards better understanding perinatal mental health in the Middle East, and the data will be useful for future longitudinal and more extensive studies in this field.

Conclusions

A deeper understanding of the multifaceted factors contributing to anxiety and depression in antenatal and postnatal women will be achieved. By engaging in this research, clinicians will gain expertise in utilizing validated mental health assessment tools like the EPDS and GAD-7 scales, and in understanding the implications of genetic causes for depression and anxiety. Furthermore, the study's comprehensive approach, which includes socio-demographic, lifestyle, and clinical factors, will enable obstetricians and gynaecologists to adopt a more holistic and informed approach to patient care. This enriched understanding will enhance the ability to identify at-risk individuals, implement early interventions, and collaborate effectively with mental health professionals.

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Conflicts of Interest
None declared.

Abbreviations

UAE= United Arab Emirates
PPD=Post Partum Depression
EPDS = Edinburgh Postnatal Depression Scale

GAD = Generalized Anxiety Disorder

Data Availability

The data supporting the findings of this study will be available from the corresponding author upon reasonable request. The data will not be publicly available due to reasons privacy/confidentiality concerns.

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Supplementary Files

Figures

Patient Recruitment and study interventions.

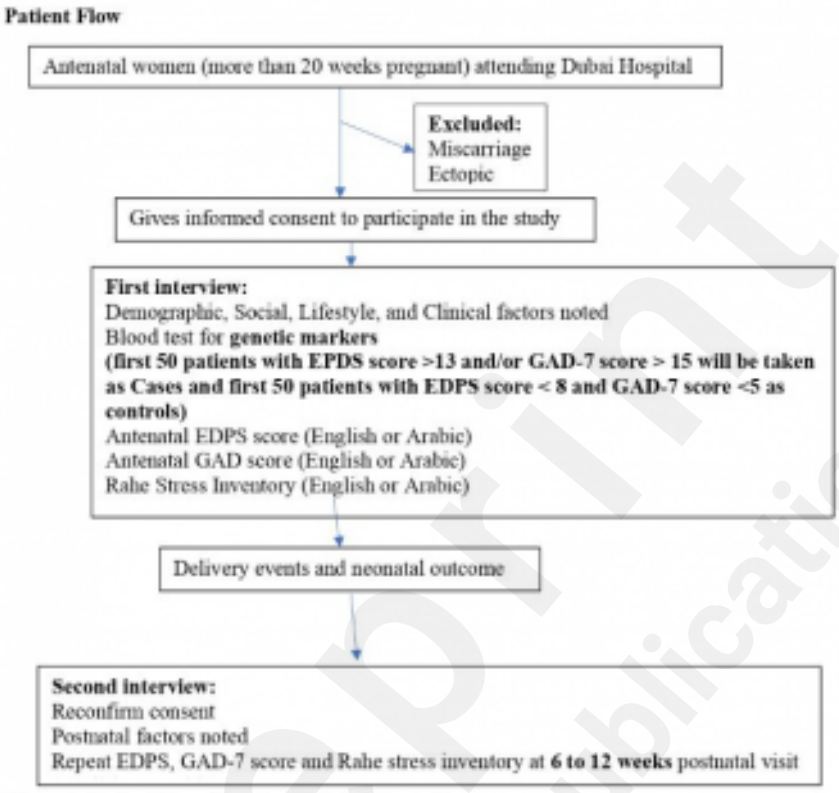

Figure 1.: Patient Recruitment and Study Interventions