Maternal Term Pruritus and Long-Term Neuropsychiatric Morbidity in the Offspring

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Research Article

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Abstract

Purpose

Pruritus during pregnancy is associated with adverse maternal, pregnancy, and neonatal outcomes. We opted to assess the association between term pruritus and long-term neuropsychiatric morbidity in the offspring.

Method

In a population-based retrospective cohort study, the incidence of long-term neuropsychiatric morbidity was compared between offspring born to women with or without pruritus at term. Neuropsychiatric morbidity was assessed up to the age of 18 years according to ICD-9 codes associated with hospitalization of the offspring. A Kaplan-Meier survival curve was used to compare cumulative neuropsychiatric morbidity incidence and Cox proportional hazards models were used to control for confounders. The study included 226,918 deliveries of which 600 (0.26%) were in women with term pruritus.

Results

Offspring born to women with pruritus exhibited a higher rate of long-term neuropsychiatric morbidity, specifically developmental and neurodegenerative disorders Kaplan-Meier survival curve demonstrated a significantly higher cumulative incidence of long-term neuropsychiatric morbidity in offspring of women with pruritus. Using several Cox proportional hazards models, being born to a woman with pruritus was independently associated with an increased risk of long-term neuropsychiatric morbidity.

Conclusion

Maternal term pruritus was found to be independently associated with long-term neuropsychiatric morbidity in the offspring.

Introduction

During pregnancy, various hormonal, metabolic, and immunologic changes influence the structure and function of the maternal skin and mucous membranes, such as hyperpigmentation and striae gravidarum, which appear in almost 90% of pregnant women, and melasma as seen in up to 75% of pregnant women. Some physiological hair, nail, and vascular changes may also appear [1]. One of the changes affecting the skin during pregnancy is pruritus, which affects about one-third of all pregnancies in its milder form and is less common in its severe form [2]. Pruritus during pregnancy is mostly attributed to non-pregnancy-specific skin dryness, yet there are several conditions unique to pregnancy that present

with pruritus as a leading symptom. Among these are pemphigoid gestationis, pruritic urticarial papules and plaques of pregnancy (PUPP), intrahepatic cholestasis of pregnancy (ICP), and atopic eruption of pregnancy [3]. Each of the conditions mentioned has a different yet not fully understood pathogenesis [4]. Studies have associated pruritus during pregnancy, particularly caused by ICP and pemphigoid gestationis, with adverse perinatal outcomes such as hypertensive disorders during pregnancy, intrauterine growth retardation (IUGR), intrauterine fetal demise, preterm birth, and low Apgar scores [4–6].

Recently, a growing body of evidence has been built regarding the association between maternal pregnancy complications and long-term neuropsychiatric morbidity in the offspring [7,8]. The fetal environment plays a critical role in early neural processes and can impact fetal brain structure and function, where unfavorable early life environment is associated with increased long-term susceptibility to neurodevelopmental and neuropsychiatric disorders [9,10]. As different conditions that manifest with pruritus during pregnancy affect the fetal environment or the fetus directly - such as ICP and pemphigoid gestationis [3], we hypothesized that offspring born to mothers who suffered from pruritus during pregnancy would have offspring with a higher rate of long-term neuropsychiatric morbidity. As preterm birth has been shown to be independently associated with an increased risk for neuropsychiatric morbidity (14.7% compared to 6% for term birth) [8], we opted to assess the association between term pruritus and long-term neuropsychiatric morbidity of the offspring.

Methods

Settings and population

A population-based retrospective cohort study comparing long-term neuropsychiatric morbidity in offspring to mothers with and without term pruritus was conducted. The study population included all children born to mothers with pruritus during pregnancy in the years 1991–2014 at Soroka University Medical Center (SUMC). SUMC is a tertiary hospital and the only medical center in the Negev, the southern region of the country, which covers 65% of the country's area (about 1.22 million people). Multiple gestations, preterm births, and infants with congenital malformations or chromosomal abnormalities were excluded from the study. Perinatal mortality cases were excluded from the long-term analysis.

Study design

This study investigated perinatal outcomes and long-term neuropsychiatric diseases of children to born mothers with and without pruritus. The predefined set of ICD-9 codes (Supplementary Table) was used as the basis for assessing the total neuropsychiatric diseases of children of mothers with pruritus up to the age of 18 years. These neuropsychiatric diseases included movement disorders, developmental disorders, degenerative disorders, eating disorders, psychiatric emotional disorders, and total neuropsychiatric-related hospitalizations. Follow-up time was determined as time to an event (hospitalization with any neuropsychiatric diagnosis). If any of the following occurred, follow-up ended: first hospitalization with

any neuropsychiatric diagnosis, hospitalization resulting in death, or when the child reached 18 years of age.

Data collection method

Data were collected from two cross-linked and merged computerized databases, each based on maternal and infant ID numbers: the perinatal database of the Obstetrics and Gynecology Department and the pediatric hospitalization database of SUMC (Demog-ICD9). The perinatal database contains maternal demographics, diseases and perinatal results documented immediately after delivery and anonymized before analysis. The pediatric hospitalization database contains demographic data and ICD-9 codes for all medical diagnoses recorded during any hospitalization at SUMC.

Statistical methods

Univariable analysis was performed to compare background characteristics between the 2 study groups. The univariable analysis included t-tests or Mann-Whitney U tests for continuous variables and Chi-square tests for categorical variables, according to their distribution. Cumulative incidence rates were compared using Kaplan-Meier curves, using the log-rank test to determine significant differences between the groups. Cox proportional hazards models were conducted to control for confounders. All models controlled for gestational age at birth. Each model also controlled for each of the following characteristics: maternal age, maternal diabetes mellitus, hypertensive disorders, and cesarean delivery. All analyses were performed using SPSS package 23rd. ed. as well as STATA software 12th ed. All analyses were two-sided with an $\alpha = 0.05$ and $\beta = 0.2$.

Results

During the study period, 226,918 deliveries were included, of which 600 (0.26%) were in women with term pruritus. Women with pruritus had high□er parity order compared to women without pruritus. No significant differences were noted in mean maternal age and need for fertility treatments between the groups (Table 1). Higher rates of hypertensive disorders in pregnancy (9.5% vs 4.5%, $p < 0.001$), maternal diabetes mellitus (10.5% vs 4.8%, $p < 0.001$) and caesarean deliveries (21.5% vs 12.3%, $p < 0.001$) were shown among women with pruritus (Table 2). After excluding all cases of perinatal mortality, the study population included 597 offspring born to mothers with pruritus. Offspring born to women with pruritus exhibited a higher rate of long-term neuropsychiatric morbidity in comparison to offspring born to women without pruritus (4.4% vs 3.0%, $p = 0.054$), specifically developmental and neurodegenerative disorders (0.3% vs 0.1%, $p = 0.049$ and 0.3% vs 0.1%, $p = 0.013$, for developmental disorders and neurodegenerative disorders, respectively, Table 3). Likewise, the Kaplan-Meier survival curve demonstrated a significantly higher cumulative incidence of long-term neuropsychiatric morbidity in offspring of women with pruritus (log rank $p = 0.021$, Figure). In Cox proportional hazards models, controlling for gestational age (at term, all models) and maternal age at birth (adjusted HR 1.5, 95% CI 1.03–2.23, $p = 0.034$), hypertensive disorders (adjusted HR 1.5, 95% CI 1.03–2.21, $p = 0.038$), diabetes mellitus (adjusted HR 1.5, 95% CI 1.02–2.22, $p = 0.036$) and cesarean delivery (adjusted HR 1.4, 95% CI 1.01–2.19, $p = 0.041$), separately,

being born to a woman with pruritus was independently associated with long-term neuropsychiatric morbidity in the offspring.

Discussion

In this large population-based cohort study, offspring born to women with term pruritus exhibited higher rates of long-term neuropsychiatric morbidity, specifically developmental and neurodegenerative disorders, compared to offspring born to women without pruritus.

The association between pruritus during pregnancy and pregnancy complications has been investigated in the past [6,7]. ICP, one of the conditions that causes pruritus during pregnancy, was shown to increase the risk for immediate adverse pregnancy outcomes such as preterm birth, respiratory distress syndrome, meconium-stained amniotic fluid, fetal asphyxia, preeclampsia, and stillbirth [11,12], and long-term maternal morbidity, as well as increasing the risk for diseases of the digestive system, cholelithiasis, cholecystitis, and hypothyroidism [13]. Other pruritic conditions during pregnancy have also been studied, among them pemphigoid gestationis, which was associated with immediate adverse pregnancy outcomes, such as small-for-gestational-age offspring and preterm birth, suggesting low-grade placental insufficiency. Other pruritic dermatoses of pregnancy were not found to be associated with pregnancy complications [14].

The fetal environment plays a critical role in early neural processes and can impact fetal brain structure and function and increase long-term susceptibility to neurodevelopmental and neuropsychiatric disorders [10]. For example, an increase in the level of maternal and fetal serum bile acids, as seen in ICP [15], can cross the blood brain barrier via diffusion or by bile acid transporters [16], and has been reported to interact with receptors involved with neurotransmission. Further, an elevation of bile acids has been found in various neuropsychiatric disorders. It is worth mentioning that while several neuropsychiatric disorders have been correlated with elevated bile acids, others were shown to improve by the supplementation of specific bile acids [17], Another pruritus-causing disease that may inflict damage through neuroinflammation is pemphigoid gestationis, an autoimmune disease where the underlying mechanism is the breakdown of immunotolerance against a protein called BP180, which is expressed both on the skin and in the central nervous system [18], This may lead to autoimmune activity in the brain and thus to neuroinflammation, which may result in neurodevelopmental morbidity.

Our study has several limitations. As an inherent limitation of any observational epidemiologic study, our study cannot infer a causative relationship between pruritus during pregnancy and neuropsychiatric morbidity in the offspring, but rather can only demonstrate association between the two. In addition, numerous factors influence neuropsychiatric development, hence we cannot rule out the possibility of bias due to uncontrolled unknown confounders. Another limitation of our study is that our database is based on childhood hospitalization, while many of the neuropsychiatric morbidities that we evaluated hay have been treated in an ambulatory setting. We therefore believe that the true prevalence of the neuropsychiatric morbidities assessed is actually higher than our data shows. An additional limitation

concerns the actual maternal exposure. As "pruritus" is a term comprising several different diseases with different pathophysiologies, the data does not distinguish between the various pruritic diseases. It is therefore highly likely that only the diseases known to cause pregnancy complications are the ones correlated to our findings, and the association between pruritus and long-term neuropsychiatric morbidity in the offspring may have been stronger if pruritus from benign conditions were excluded.

A significant strength of our study is the fact that all preterm deliveries were excluded from the analysis, hence eliminating a significant confounder of long-term neuropsychiatric morbidity [8]. Moreover, controlling for the age at birth within the term deliveries eliminated early-term deliveries which has also been associated with long-term neuropsychiatric morbidity in the offspring [19]. Another strength of this study is the large and unselected population included, with a long follow-up period that was possible due to the fact that SUMC is the only hospital in the entire region.

In conclusion, in our study, pruritus during pregnancy was found to be associated with a higher risk for long-term neuropsychiatric morbidity in the offspring, specifically neurodegenerative and neurodevelopmental disorders. More studies are needed in order to confirm our findings in varying populations, include cases diagnosed and treated in a community setting, and to further investigate specifically which pruritus-causing diseases are related to neuropsychiatric morbidity. Furthermore, pregnant women with pruritus during pregnancy should consider consulting with their physicians and the long-term neuropsychiatric surveillance of the children should be increased.

Declarations

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Competing Interests:

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions:

Conceptualization, E.S. and G.P.; methodology, E.S.; software, E.S.; validation, E.S.; formal analysis, E.S.; investigation, O.L. and G.P.; resources, G.P.; data curation, E.S.; writing—original draft preparation, O.L.; writing—review and editing, O.L., G.P., E.S., and D.K.; visualization, O.L.; supervision, G.P. and E.S.; project administration, G.P. All authors have read and agreed to the published version of the manuscript.

Ethics approval:

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Soroka University Medical Center (SUMC) (protocol code SOR-19-0357, date of approval 10 October 2019).

Consent to participate:

Patient consent was waived due to the retrospective design using anonymous coding

Consent to publish:

Patient consent was waived due to the retrospective design using anonymous coding.

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Tables

Table 1
Maternal characteristics of the study population

Characteristics	Mothers with pruritus (n = 600)	Mothers without pruritus (n = 226,318)	P-value
Maternal age, years (mean ± SD)	28.3 + 5.7	28.1 + 5.7	0.826
Parity			
1	251 (41.8%)	52,506 (23.2%)	< 0.001
2–4	243 (40.5%)	116,327 (51.4%)	
5+	106 (17.7%)	57,485 (25.4%)	
Fertility treatment			
IVF	8 (1.3%)	2,263 (1.0%)	0.115
Ovulation induction	8 (1.3%)	1,584 (0.7%)	

Table 2
Perinatal outcomes of the study population

Outcomes	Mothers with pruritus (n = 600)	Mothers without pruritus (n = 226,318)	OR	95% CI	P-value
		%			
Hypertensive disorder *	57 (9.5%)	10,184 (4.5%)	2.2	1.70–2.95	< 0.001
Maternal diabetes mellitus **	63 (10.5%)	10,863 (4.8%)	2.3	1.78–3.01	< 0.001
Placental abruption	3 (0.5%)	679 (0.3%)	1.6	0.53–5.21	0.370
Cesarean delivery	129 (21.5%)	27,837 (12.3%)	1.9-	1.61-2.37-	< 0.001
Small for gestational age	23 (3.8%)	10,637 (4.7%)	0.8	0.53–1.24	0.343
Low birth weight	24 (4.0%)	7,695 (3.4%)	1.1	0.77–1.76	0.451
Apgar score < 7 at 1 min	30 (5.0%)	10,184 (4.5%)	1.1	0.77–1.60	0.571
Apgar score < 7 at 5 min	2 (0.3%)	4,300 (1.9%)	0.1	0.04–0.70	0.006
Perinatal mortality	3 (0.5%)	453 (0.2%)	2.6	0.84–8.18	0.085
* Including chronic hypertension, gestational hypertension, and preeclampsia					
** Including pre-gestational and gestational diabetes mellitus					

Table 3
Selected long-term neuropsychiatric morbidity of offspring born to mothers with and without term pruritus

Neuropsychiatric morbidity	Offspring born to mothers with pruritus (n = 597)	Offspring born to mothers without pruritus (n = 225,885)	P-value
Eating disorders	3 (0.5%)	452 (0.2%)	0.052
Movement disorders	17 (2.8%)	4066 (1.8%)	0.051
Psychiatric disorders	3 (0.5%)	1129 (0.5%)	0.933
Developmental disorders	2 (0.3%)	226 (0.1%)	0.049
Degenerative disorders	2 (0.3%)	226 (0.1%)	0.013
Total neuropsychiatric related hospitalization	26 (4.4%)	6777 (3%)	0.054

Table 4
Cox proportional hazards models to predict offspring long-term neuropsychiatric morbidity

Model number	Variables	Adjusted HR	95% CI	P-value
1	Pruritus (vs no pruritus)	1.5	1.03–2.23	0.034
	Gestational age at birth	0.9	0.88–0.91	< 0.001
	Maternal age at birth	0.9	0.99-1.00	0.133
2	Pruritus (vs no pruritus)	1.5	1.02–2.21	0.038
	Gestational age at birth	0.9	0.88–0.92	< 0.001
	Hypertensive disorders	1.1	1.00-1.23	0.044
3	Pruritus (vs no pruritus)	1.5	1.02–2.22	0.036
	Gestational age at birth	0.9	0.88–0.92	< 0.001
	Maternal diabetes mellitus	1.0	0.93–1.14	0.506
4	Pruritus (vs no pruritus)	1.4	1.01–2.19	0.041
	Gestational age at birth	0.9	0.89–0.92	< 0.001
	Cesarean delivery	1.1	1.09–1.25	< 0.001

Figures

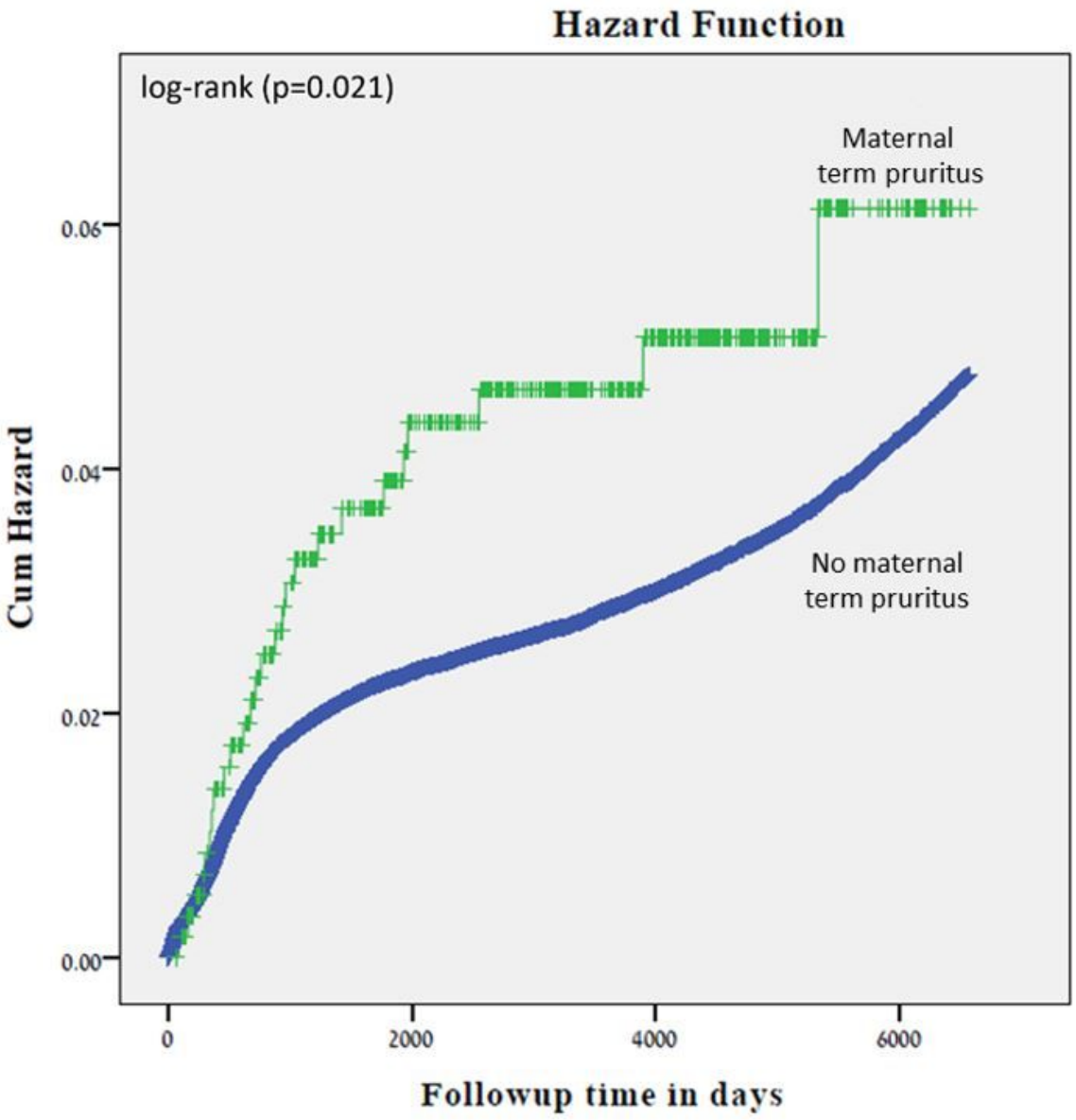

Figure 1

Kaplan-Meier survival curve demonstrating the cumulative incidence of neuropsychiatric morbidities of offspring to mothers with and without term pruritus (log-rank test, p=0.021)

Supplementary Files

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