ความสัมพันธ์ระหว่างโรคเบาหวานในขณะตั้งครรภ์ของมารดาและโรคสมาธิสั้นในบุตร

The Association between Gestational Diabetes Mellitus (GDM) in Mothers and Attention Deficit/Hyperactivity Disorder (ADHD) in Their Offspring

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บทคัดย่อ

วัตถุประสงค์ เพื่อศึกษาความสัมพันธ์ระหว่างมารดาที่เป็นโรคเบาหวานขณะตั้งครรภ์และโรคสมาธิสั้นในบุตร

วิธีการ รูปแบบในวิจัยเป็น case-control study ผู้เข้าร่วมวิจัยคือคู่มารดาและบุตรจำนวน 132 คู่ ประกอบด้วย คู่มารดาและบุตรที่ได้รับการวินิจฉัยโรคสมาธิสั้น 66 คู่ (กลุ่มสมาธิสั้น) และคู่มารดาและบุตรที่ไม่เคยได้รับการวินิจฉัยโรคสมาธิสั้น 66 คู่ (กลุ่มที่ไม่ใช่สมาธิสั้น) ข้อมูลทางประชากรศาสตร์และประวัติทางสูตินรีเวชของบุตรทั้งที่ได้รับและไม่เคยได้รับการวินิจฉัยโรคสมาธิสั้นมาจากมารดาและบุตรซึ่งมารับการรักษาที่หน่วยจิตเวชเด็กและวัยรุ่นและหน่วยโรคเด็กทั่วไปของโรงพยาบาลมหาราชนครเชียงใหม่ ส่วนประวัติโรคเบาหวานขณะตั้งครรภ์ในมารดาได้รับจากการสัมภาษณ์มารดา ในขณะที่โรคสมาธิสั้นในบุตรนั้นได้รับการวินิจฉัยจากจิตแพทย์เด็กและวัยรุ่น

ผลการศึกษา เราพบว่าอัตราส่วนของเด็กผู้ชายกับผู้หญิงในกลุ่มสมาธิสั้นและกลุ่มที่ไม่ใช่สมาธิสั้นเท่ากับ 2.882:1 และ 2:1 ตามลำดับ (P = 0.446) ลักษณะทางประชากรและสูติศาสตร์นรีเวชไม่มีความแตกต่างกันอย่างมีนัยสำคัญระหว่างกลุ่ม พบมารดาที่เป็นเบาหวานขณะตั้งครรภ์ในกลุ่มบุตรที่เป็นโรคสมาธิสั้น 7 คน (10.61%) และพบมารดา 2 คนที่เป็นเบาหวานขณะตั้งครรภ์ในกลุ่มที่บุตรไม่เป็นโรคสมาธิสั้น (3.03%) มารดาที่มีโรคที่เป็นเบาหวานขณะตั้งครรภ์จะมีความเสี่ยงในการมีบุตรเป็นโรคสมาธิสั้นเพิ่มขึ้น 3.1 เท่า แต่ไม่มีนัยสำคัญทางสถิติ (OR = 3.797, 95% CI = 0.752-19.009, P = 0.105)

สรุป โรคเบาหวานขณะตั้งครรภ์ในมารดาไม่เป็นปัจจัยเสี่ยงของโรคสมาธิสั้นในบุตร

คำสำคัญ โรคเบาหวานขณะตั้งครรภ์ในมารดา โรคสมาธิสั้น บุตรที่เกิด

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ABSTRACT

Objective : To examines the association between gestational diabetes mellitus (GDM) in Thai mothers and attention deficit/hyperactivity disorder (ADHD) in their offspring.

Method : The case-control study was conducted. We enrolled 132 mother-child pairs, consisting of 66 mothers with ADHD in their offspring (ADHD group) and 66 mothers without ADHD in their offspring (non ADHD group). Demographic data and obstetric and neonatal history affecting ADHD in offspring were obtained from mothers and corresponding children seeking treatment from the Child and Adolescent Psychiatric Unit and General Child Disease Unit of Maharaj Nakorn Chiang Mai Hospital. Maternal GDM history was obtained by an interview. The ADHD in the offspring was diagnosed by certified Thai child and adolescent psychiatrists.

Results : We found the ratio of male vs. female children in the ADHD and the non ADHD group to be 2.882:1 and 2:1 respectively (P = 0.446). Demographic and obstetric characteristics were not significantly different between the groups. Maternal GDM was found in seven mothers in the ADHD group (10.61%) and two mothers in the non ADHD group (3.03%). In comparison with mothers without GDM, mothers with GDM had an increased risk of having offspring with ADHD, but without statistical significance (OR = 3.797, 95% CI = 0.752-19.009, P = 0.105).

Conclusion : GDM is not the factor that increased the risk of ADHD diagnosis in children. However, it performs the trend of association that GDM might increase the risk of ADHD.

Keywords : gestational diabetes mellitus, attention deficit/hyperactivity disorder, offspring

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Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the neurodevelopmental disorders that can be found in children. This disorder can be diagnosed from childhood and can continue into adulthood. Children with ADHD may face problems with inattention, impulsivity, and hyperactivity[1-4].

The number of ADHD children changes continuously. A survey by the American Psychiatric Association used the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria[5] to determine that five percent of children in the world have ADHD, and this has tended to increase[6].

In Thailand, one survey found four to five percent of primary students suffer from ADHD, which conformed to the survey results in the United States[7-8].

The causes of this disorder are quite complicated because of factors related to genetics and the environment[9-16]. There are several obstetric and neonatal risk factors for ADHD. One of the risk factors mentioned leading to ADHD is gestational diabetes mellitus (GDM) that develops in the second or third trimester[17]. The prevalence of GDM among Thai citizens has increased in recent years[18]. Likewise, the development of GDM coincides with a period of rapid fetal brain development and may increase risk of neurodevelopmental disorders in offspring[19-20]. Some reviews and theories were mentioned in the mechanisms of the relationship between gestational diabetes mellitus and ADHD in children. The first is GDM causes inflammation in the uterus while pregnant, which may lead to neurodevelopmental diseases in the child[21]. The second is that epigenetic change[22-23] can lead to impairment in anatomical and psychological brain development processes. The results from a few studies which have examined GDM affects deficits in fine and gross motor skills[24], lower verbal intelligence quotient (IQ) [25] and greater inattention and hyperactivity[24]. However, it was inconclusive because Daraki et al[26] found GDM was not associated with ADHD. Besides, there were a few studies in this field and no any study in Thailand. We were also interested GDM increases the risk of ADHD diagnosis in offspring.

Material and Methods

This is a case-controlled study and was approved by the Research Ethics Committee Faculty of Medicine, Chiang Mai University (Research ID: 5076/Study Code: PSY-2560-05076). All mothers included in this study gave informed consent before participating.

1. Participants

Participants included mothers and their children between the ages of 4-17 years old who had been diagnosed with ADHD in the medical records of the child and adolescent psychiatrists at the Child and Adolescent Psychiatric Unit, Maharaj Nakorn Chiang Mai Hospital. They used the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) and DSM-5 international diagnosis systems for

diagnosis. Another group was mothers and their children of the same age who were never diagnosed as ADHD. They were patients at the Children's General Unit (All children in the latter group had not any underlying disease. Those were healthy and came for follow-up upper respiratory tract infection and acute gastroenteritis). The total number of participants was 134. We selected all participants who came to the hospital between January and August 2016.

The inclusion criterion consists of; (1) the participants understood the Thai language and were the birth mother of the child; (2) the mother's gestational diabetes mellitus had to be diagnosed using the International Association of the Diabetes and Pregnancy Study Groups criteria (IADPSG) two-step method during the pregnancy (which is when 50-g glucose and 100-g, 3-hour oral glucose tolerance tests are both positive); and (3) all children with ADHD had to be taking medication for their ADHD.

The exclusion criterion consists of; (1) participants being unable to communicate in Thai language; (2) the mother participating in the research having had diabetes before pregnancy (Excluding 1 participant because the mother was diagnosed with); and (3) mothers having children diagnosed with Autism Spectrum Disorder (ASD), intellectual disability (ID), learning disability (LD), or central nervous system diseases (excluding one participant because the child had epilepsy). The last criterion was collected from medical records.

From both the historical data and current clinic patients, we compiled a total number of 132 mothers willing to attend the study (Figure 1).

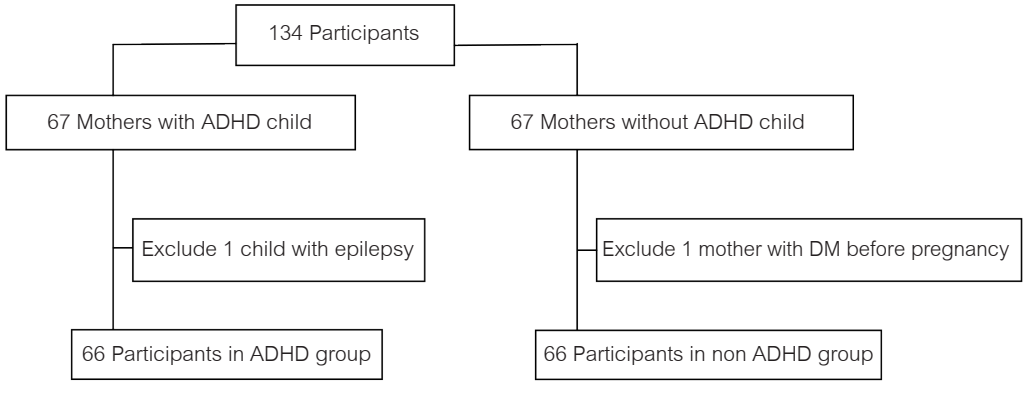

Figure 1 Participant Enrolment, Exclusion, and Inclusion in the Data Analysis.

2. Clinical Variables

Data collection consisted of four parts.

Part 1: Sociodemographic data, including hometown, educational level, ethnicity, nationality, marital status, occupation, child gender, primary caregiver, mother's age, and child's age. (questionnaire)

Part 2: Obstetric and neonatal history, consisting of body mass index (BMI) (weight and height) at pregnancy period, mother's age before pregnancy, history of smoking and alcohol drinking during pregnancy (yes or no), gestational age (weeks), birth weight (grams), type of delivery (normal delivery, assisted delivery and Caesarean section), and period of time (months) the child was breastfed. (questionnaire)

Part 3: Gestational diabetes mellitus interviewing, which consisted of being diabetic while pregnant and treatment for diabetes during pregnancy? The researcher asked "During pregnancy at about 6-7 months, were blood glucose levels monitored by the method of drinking or swallowing sugar? Were there any abnormalities?" In Thailand, we use the "two-step method" to screen and diagnose such states (17). We examine the 'yes' result from the mother by management checking (Pregnant women who had GDM diagnosis were checked the blood glucose level in every visit until delivery, while healthy pregnant women were not).

Part 4: Swenson, Nolan, and Pelham IV (SNAP-IV) Thai version (Cronbach's alpha = 0.93-0.96) was used for ADHD screening in children (27). This questionnaire is a 26-item parent and teacher report symptom designed to screen for ADHD symptoms in children. Based on subjective evaluation, each item is rated as 0 (no symptoms), 1 (a little symptom), 2 (moderate symptoms), and 3 (extreme symptoms). There are three symptom dimensions. Each of the three symptom dimensions comprises 8-9 items. There are inattention, hyperactivity/impulsivity, and oppositional defiant disorder dimensions. The parent cut-offs are 16-14-12 respectively, while the teacher cut-offs are 18-11-8. In this research, only parent cut-offs were used to screen children in 'mothers without ADHD children' group (no positive cut-offs score in any domain).

3. Statistical Analysis

We used the G power program for sample size calculation. We used α error equal 0.05, power equal 0.8 and odd ratio from recent research (28) equal 2.20. The outcome was 77 participants. In total, we collected 132 participants. All participants were informed about the details and had to provide written consent before participation.

Research analysis was performed using the R Commander Program. For categorical variables, we compared the mothers with ADHD children group with the mothers without ADHD children group using the Chi-square χ^2 test. For continuous variables, we compared the mean difference between groups using the independent sample t-test.

The association between GDM and ADHD of the child will be shown as a crude odds ratio (OR) with 95% confidence intervals (CIs).

Binary logistic regression analysis was used to evaluate the eight variables mentioned on ADHD in this research; alcohol drinking, birth weight, BMI, duration of breastfeeding, gestational age, GDM in mothers, type of delivery and mother's age before pregnancy. The OR and 95% CIs were used to observe the associations.

Results

1. Sociodemographic Data

132 participants were Thai nationality (not shown in the table) and most of them were located in the north of Thailand (90.9%). The educational level was mostly bachelor's degree or higher (66.7%). Almost all participants were of Thai ethnicity (97.72%), and in both groups, there were more male children than female children, at 2.88:1 and 2:1 respectively. The primary caregiver to the children was the mother (95.42%), and there was no significant difference in the age of participating mothers and children between the two groups (Table 1).

Table 1 Sociodemographic Data of Mother with ADHD Child (ADHD) Group and Without ADHD Child (Non-ADHD) Group

Sociodemographic data	ADHD n (%)	Non ADHD n (%)	χ^2	P-value
Hometown	66(50)	66(50)	0.51	0.89
Capital	4(57.1)	3(42.9)		
Central	1(50)	1(50)		
North	59(49.2)	61(50.8)		
Northeast	2(66.7)	1(33.3)		
Education	66(50)	66(50)	6.34	0.27
No	1(100)	0(0)		
Primary	3(37.5)	5(62.5)		
Secondary	12(63.2)	7(36.8)		
Vocational	5(31.2)	11(68.8)		
Undergraduate	36(54.5)	30(45.5)		
Higher	9(40.9)	13(59.1)		
Ethnicity	66(50)	66(50)	0.34	1
Thai	64(49.6)	65(50.4)		
Others	2(66.7)	1(33.3)		
Marital status	66(50)	66(50)	3.21	0.54
Single	6(75)	2(25)		
Married	49(47.1)	55(52.9)		
Divorce	7(58.3)	5(41.7)		
Widow	2(40)	3(60)		
Separate	2(66.7)	1(33.3)		
Occupation	66(50)	66(50)	7.14	0.41
No	3(42.9)	4(57.1)		
Labor	14(53.8)	12(46.2)		
Government/State enterprise	18(42.9)	24(57.1)		
Agriculture	0(0)	1(100)		
Employee	3(50)	3(50)		
Private business	21(63.6)	12(36.4)		
Others	6(37.5)	10(62.5)		

Table 1 Sociodemographic Data of Mother with ADHD Child (ADHD) Group and Without ADHD Child (Non-ADHD) Group (cont.)

Sociodemographic data	ADHD n (%)	Non ADHD n (%)	χ^2	P-value
Child's gender	66(50)	66(50)	0.91	0.45
Male	49(52.7)	44(47.3)		
Female	17(43.6)	22(56.4)		
Caregiver	66(50.4)	65(49.6)	0.0003	1
Mother	63(47.7)	62(47)		
Other	3(2.3)	3(2.3)		
	Mean (SD)	Mean (SD)	Mean difference	P-value
Mother's age	39.26 (6.32)	40.02 (6.35)	0.76	0.49
Child's Age	9.55 (3.05)	9.80 (3.36)	0.26	0.65

2. Obstetric and Neonatal History

The mothers in this research did not smoke (100%) or drink alcohol while pregnant (99.24%). Most children were born at the gestational age of more than 35 weeks (86.89%) and had birth weights of more than 2500 grams (90%). The delivery type was usually by Caesarian section (50.38%) and natural births (40.46%). The mother's age during pregnancy, BMI before pregnancy, and breastfeeding period in both groups were not significantly different (Table 2).

Table 2 Obstetric and Neonatal History of Mother with ADHD Child (ADHD) Group and Without ADHD Child (Non-ADHD) Group

Obstetric and neonatal history	ADHD n (%)	Non ADHD n (%)	X^2	P-value
Alcohol drinking during pregnancy	66(50.4)	65(49.6)	0.99	1
Yes	1(100)	0(0)		
No	65(50)	65(50)		
Gestational age (weeks)	59(50)	63(50)	1.47	0.29
<35	10(62.5)	6(37.5)		
35 and more	49(46.2)	57(53.8)		
Birth weight(g)	66(50.8)	64(49.2)	4.16	0.30
ELBW (<1000)	2(100)	0(0)		
VLBW (1000-<1500)	2(100)	0(0)		
LBW (1500-<2500)	5(55.6)	4(44.4)		
Normal (>2500)	57(48.7)	60(51.3)		
Types of delivery	66(50.4)	65(49.6)	1.04	0.59
Normal delivery	25(47.2)	28(52.8)		
Assisted (forceps or vacuum)	5(41.7)	7(58.3)		
Cesarean	36(54.5)	30(45.5)		
	Mean (SD)	Mean (SD)	Mean difference	P-Value
Mother's age before pregnancy	28.97 (5.09)	29.68 (5.65)	0.71	0.45
Mother's BMI before pregnancy	20.39 (3.43)	20.77 (3.36)	0.38	0.53
Breastfeeding (months)	6.46 (6.00)	6.80 (7.30)	0.14	0.77

3. Association between GDM in Mothers and ADHD in Their Offspring

We interviewed all 132 mothers about GDM. In the mothers with ADHD children group, seven mothers had GDM while pregnant, while in the mothers without ADHD children group, two mothers had GDM while pregnant. When comparing the risk of mothers with GDM having a child with ADHD, there was a greater risk than those mothers with GDM, but with no association (crude OR = 3.76, 95% CI=0.68-38.53, p=0.17).

Based on the univariate analyses to evaluate obstetric and neonatal history, no factors were significantly associated with ADHD in this research (Table 3).

The multivariate logistic regression analysis was conducted to identify obstetric and neonatal factors predicting ADHD. No variables were significantly associated with ADHD. Yet, GDM was the factor which correlated more than the others (OR = 3.78, 95% CI = 0.69-20.60, p = 0.10) (Table 3).

Table 3 Binary Logistic Regression Model to Determine the Obstetric and Neonatal History Mentioned to Affect ADHD

Variables	Model 1				Model 2			
	β	SE β	Adjust OR (95%CI)	P-Value	β	SE β	Adjust OR (95%CI)	P-Value
Low birth weight (reference group: normal birth weight)	-0.86	0.63	0.42 (0.12-1.45)	0.17	-0.85	0.75	0.38 (0.09-1.70)	0.20
Mother's BMI before pregnancy	-0.03	0.05	0.97 (0.87-1.07)	0.53	-0.04	0.06	0.96 (0.85-1.089)	0.55
Duration of breastfeeding	-0.01	0.03	0.99 (0.94-1.05)	0.77	-0.004	0.03	1.00 (0.94-1.05)	0.88
Low gestational age (reference group: <35 weeks)	-0.66	0.55	0.52 (0.18-1.52)	0.23	-0.25	0.65	0.93 (0.24-3.54)	0.92
GDM	1.33	0.82	3.80 (0.75-19.01)	0.13	1.35	0.87	3.78 (0.69-20.60)	0.10
Type of delivery (reference group: Cesarian section)	0.34	0.35	1.40 (0.70-2.78)	0.34	0.29	0.39	1.39 (0.65-2.97)	0.40
Mother's age before pregnancy	-0.03	0.03	0.98 (0.91-1.04)	0.45	-0.04	0.04	0.97 (0.90-1.04)	0.34

Model 1: univariate logistic regression model

Model 2: multivariate logistic regression model adjusted for all variables in table 3 (all variables was mentioned in recent studies that affect ADHD)

ADHD = attention deficit/hyperactivity disorder, GDM = gestational diabetes mellitus

Discussions

The current study examined whether maternal GDM heightens the risk of ADHD diagnosis at ages 4-17 years. To our knowledge, this research was the first to study the association between maternal GDM and ADHD in offspring in Thailand. In our research, prevalence of GDM in the ADHD group was 10.6% and 3.03% in the non-ADHD group. Comparing with the recent study[28], the former group was much more than those (the latter group was equal). However, we found no association between mother and child with ADHD. This might represent a difference between factors of interest. Previous studies have focused on ADHD symptoms which were assessed by testing, while this study focused on ADHD diagnosis by criteria from DSM-IV-TR (45 patients) and DSM-5 (22 patients) only. This is new research that indicates that the association between GDM and ADHD diagnosis was different from GDM and ADHD symptoms.

Few studies have focused on GDM and ADHD in offspring. Ornoy et al[24] study in Tel Aviv, Israel, found that mothers being diabetic before and during pregnancy affected Inattention in children. Nomura et al[29] found that being diabetic during pregnancy had a two-fold increase in the risk of the child having ADHD symptoms. Schmitt et al[28] in Germany found that gestational diabetes mellitus was significantly related to the risk of ADHD diagnosis in children. But this diagnosis in this study used the criteria of ICD-10 version corresponding with the criteria of DSM-IV revision. ICD- 10 criteria did not require for impair social functioning for diagnosis (30). It was easier to code ADHD than the DSM system. That could recruit a lot of the ADHD population in their research. Conversely, Daraki et al[26] in Greece found that gestational diabetes mellitus did not affect ADHD symptom in children because of confounding factors that they could not determine in their research

GDM diagnosis in each country was different (18). In Thailand, this method showed the low prevalence of GDM comparing other methods[31]. That may be another reason that we could not find the association between the interested factors.

While we tried to seek other factors that may be associated with ADHD in offspring, we were unable to do so despite collecting data that relates to those factors. This is probably since the study population in this research was small when compared with previous studies.

There are strengths in this research. ADHD among the participants of this research was diagnosed by the child and adolescent psychiatrists certified by the Thai Royal College of Psychiatrists and were based on DSM-IV and DSM-V which are the international diagnostic criteria widely used by psychiatrists.

Our study also has limitations. First, every participant had Thai nationality and almost all had Thai ethnicity, meaning the research cannot be generalized for other populations. Second, we did not collect the ADHD symptom or diagnosis in the mother because we cannot accurately assess the

ADHD history, we might miss the genetic influence. Third, the test used to divide the non-ADHD group was a screening test. So, we might have missed the data of children who had an ADHD diagnosis but had not yet been to see the doctor. Finally, a recall bias of GDM diagnosis from mother could have occurred. They might feel guilty as if they were the cause of ADHD in their child and gave the GDM data incorrectly

Although the results of this research showed no association between GDM and ADHD, it performs the trend of association that GDM might increase the risk of ADHD. Future studies should be done with a prospective study, a larger sample population and understanding the mechanisms between GDM and ADHD.

Conclusions

GDM was not associated with ADHD diagnosis in children. ADHD can occur from many factors, but the relationship which was found in this study showed the tendency for this factor to lead to ADHD. So, we need to increase the study in terms of the number of sample groups in the research of the Thai population or in other Asian countries to understand the importance of mentioned factors affecting ADHD in children.

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