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Jurnal Kesehatan

| ISSN (Online) 2657-1366 |

Scoping Review

IMPACT OF HYPEREMESIS GRAVIDARUM ON PREGNANCY OUTCOMES

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ARTICLE INFORMATION

Received: July 19, 2020
Revised: July 30, 2020
Accpeted: August 28, 2020
Available online: August 30, 2020

KEYWORDS

Impact; Hyperemesis Gravidarum; NVP; Fetus; Child

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A B S T R A C T

Introduction: Hyperemesis gravidarum (HEG) or continuous nausea and vomiting can result in loss or even death in the mother and fetus. For most women who recover from HEG well, there is clear evidence of an increased risk of pregnancy outcomes.

Purpose: The purpose of this scoping review is to map the evidence and conclude the literature about the effects of Hypermesis Gravidarum on pregnancy outcomes.

Methods: In this scoping review, we evaluate the emerging evidence that HEG impacts pregnancy outcomes, by using two databases (Pubmed and ScienceDirect).

Results: some of the effects of HCG, namely: LBW and Premature, Repetition of hyperemesis gravidarum across generations, Reduction of insulin sensitivity in children in childhood, Risk of placental abruption and increased risk of birth for small for gestational age (SGA), Provides a protective effect on the risk of cleft lip in new babies birth, Delayed nerve development in children, increased blood pressure and abnormal fetal brain development.

Conclusion: HEG has an adverse risk to the outcome of pregnancy and can have an impact on the fetus, childhood and adulthood.

INTRODUCTION

Nausea and vomiting in pregnancy (NVP) are natural symptoms that occur in pregnant women but the symptoms become very dangerous if they become hyperemesis gravidarum (HEG) or nausea and vomiting continuously. Hyperemesis gravidarum (HEG), affects 0.3% to 3% of pregnant women and is characterized by intracable vomiting, dehydration, electrolyte imbalance, ketosis, nutritional deficiencies, acidosis, ketonuria, fatigue and weight loss (1), in some women also suffer psychologically (frustrated, vengeful and depressed) and some of them decide to end their pregnancy rather than tolerate severe symptoms (13), or avoid further pregnancy after experiencing HEG in subsequent pregnancies (10).

The prevalence of Hyperemesis gravidarum in pregnant women varies from country to country, in Sweden the incidence of HEG starts from 0.3%, in the United States 1.2% (6) and 3.6% in Japan (11), while in Indonesia 14.8%. HEG is one of the causes of maternal death in DIY. The most common causes of maternal death in DIY are due to heart problems {8}, embolism {1}, shock {3}, Tb {1}, HIV {1}, pneumonia {1}, DHF {1}, MODS {1}, Autoimmune hemolytic anemia {1}, Hyperemesis gravidarum {1} and unknown {1} (5).

The ethylogy of Nausea and Vomiting in pregnancy is unclear, although many logical theories have been proposed, including hormones undergoing changes such as the Human Chorionic Gonadotropin (hCG) hormone and elevated estradiol levels, evolutionary adaptation, psychological predisposition (1), circulating levels of vitamin B6 (19), Helicobacter pylori infection (14), significant changes in olfactory performance (16) and other causes.

DOI: http://dx.doi.org/10.35730/jk.v11i0.604

In a systematic review there are several treatments for nausea and vomiting, namely: ginger, vitamin B6, antihistamines, metoclopramide (mild symptoms), and pyridoxine-doxylamine (moderate symptoms) associated with an increase in nausea and vomiting in pregnancy compared to placebo. Ondansetron is associated with symptomatic improvement for all severity of nausea and vomiting in pregnancy and hyperemesis gravidarum, and corticosteroids are associated with beneficial effects in severe cases (13).

HEG has been shown to affect women's health and well-being during pregnancy. For most women who recover from HEG well, there is clear evidence of an increased risk of pregnancy outcomes. Different pregnancy outcomes between mild-moderate-severe NVP (HEG), indicate that extreme nutritional deficiencies associated with pregnancy have an important role in the quality of life of the fetus later. Therefore in this review we want to evaluate the emerging evidence that HEG has a detrimental impact on pregnancy outcomes.

METHOD

This study is a scoping review, which reviews systematically to interpret the evidence-based results available through journals, used to map the concepts that underlie the research area, sources of evidence, and types of evidence available. so that accurate evidence is obtained.

Determine and align research objectives and questions

This review is guided by the question "What is the effect of hyperemesis gravidarum on the results of the pregnancy?" we searched journals from two databases (Pubmed and sciencedirect) from 2000-2020. For studies that measure the effects of hyperemesis on pregnancy outcomes.

Develop and align inclusion criteria with research objectives and questions

This study uses the PICO Framework (Population, Intervention, Comparation, Outcome) in managing and solving the focus of review. The focus of the search for articles in this review is quantitative research, PICO is considered appropriate for use.

Table 1. PICO Framework

Criteria	Inclusion	Exclusion
Patient/Problem	*Fetus* *Embryo* *Child*	*Species*
Intervention	-	
Comparison	-	
Outcome	*Effect of hyperemesis gravidarum*	

Identifying Relevant Studies

Journal search strategies on databases focus on the keywords used. that is:

Table 2. Search method

Search String	***AND***
*Hyperemesis gravidarum**	*Fetus**
Emesis gravidarum	*Embryo*
	*Child**
Nausea and vomiting in pregnancy	

Study Selection

Table 3. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion criteria
• The past ten years (2000-2020) • In English language • Original research • Humans	• Review article • Systematic review • Species

The article selection process is described using the PRISMA flowchart. PRISMA is considered appropriate because it can improve the quality of publication reporting.

Quality assessment of articles

Critical Appraisal Skills Program (CASP) is used for a critical appraisal to assess the quality of the article. The selected studies are studies with grades A and B.

RESULT AND DISCUSSION

The findings systematically obtained a number of articles published in 2000-2020. From 9 selected articles, 9 articles were obtained using quantitative research designs. Articles obtained from 1 article from Canada, 2 articles from Norway, 1 article from New Zealand, 1 article from Sweden, 1 article from Hungary, 1 article from the United States, 2 articles from the Netherlands.

Impact of hyperemesis gravidarum on pregnancy outcomes: Low Birth Weight and Premature

This is related because, women with hyperemesis have a 2-fold higher risk of gaining a pregnancy weight less than 7 kg (15.4 lb) than women without hyperemesis. Researchers found an increased risk for each neonatal outcome examined among subgroups with hyperemesis and low weight gain. The rate of premature birth is 3 times higher among women with hyperemesis whose weight gain is less than 7 kg (15.4 lb) compared to women who do not have hyperemesis.

DOI: http://dx.doi.org/10.35730/jk.v11i0.604

There is no evidence of an increased risk of any of these outcomes among women with hyperemesis but with a weight gain of 7 kg or more. The results of this study indicate that adverse outcomes in infants associated with hyperemesis are a consequence of, and are largely limited to, women with poor maternal weight gain (less than 7 kg) (6).

Repetition of hyperemesis gravidarum across generations

The results of this study indicate that the risk of recurring intergenerational decline is passed down through mothers to daughters. Girls who are born after a pregnancy complicated by HEG have a 3% risk of experiencing HEG, whereas women born after an unaffected pregnancy have a 1.1% risk. The risk for female partners of boys born after pregnancy with HEG has a risk of 1.2%. This finding suggests that there may be genetic aspects to HEG involving both maternal and fetal genes, although environmental and other factors cannot be ruled out.

The conclusion is HEG is more influenced by maternal genotype compared to fetal genotype (18).

Reduction of insulin sensitivity in children in childhood

This study provides evidence of adverse long-term metabolic outcomes in offspring of mothers suffering from severe HEG. There are no studies examining the long-term consequences of decreasing insulin sensitivity in children. However, longitudinal studies in adults show that a decrease in insulin sensitivity is associated with an increased risk of developing type 2 diabetes mellitus, hypertension, coronary heart disease, stroke, and cancer years later.

This study shows that children exposed to HEG seem to have an isolated abnormality from reduced insulin sensitivity, so that overall glucose removal appears normal as indicated by the disposition index. Higher fasting insulin concentrations in children exposed to HEG are associated with lower serum IGFBP-1 concentrations. Insulin resistance causes an increase in insulin portal secretion, which suppresses the concentration of IGFBP-1. Low hyperinsulinemia and IGFBP-1 are also associated with increased likelihood of cardiovascular disease (2).

Risk of placental abruption and an increased risk of small for gestational age (SGA) births

This study shows a very strong association with an increased risk of preeclampsia, placental abruption and SGA birth in women with HEG in the second semester (3, 17)

Provides a protective effect against the risk of cleft lip in newborns

This is attributed to the presence of nausea and vomiting associated with higher blood levels of hCG and on the steroid hormones, progesterone and estradiol. Peak levels of hCG occur at around 4-5 weeks of pregnancy (embryological period of cleft formation) and decrease at 12 weeks of pregnancy. This could explain that the racial distribution of newborns with mouth gaps is consistent with low levels of gonadotropin and estrogen.

The conclusions of this study indicate that hyperemesis gravidudum provides a protective effect against the risk of cleft mouth in newborns (4).

Delayed nerve development in children

Children who were exposed to HEG in the womb had a 3.28-fold increase in the possibility of a diagnosis of neurodevelopment including attention disorders, learning delays, sensory impairments, and speech and language delays ($P < 0.0005$). Among the characteristics of HEG pregnancy, only the onset of early symptoms (before 5 weeks' gestation) is significantly related to the delay in nerve development. This study found no evidence for an increased risk of 13 emotional, behavioral, and learning disorders, including autism, intellectual impairment, and obsessive compulsive disorder. However, this research is not sufficient to detect rare conditions. Treatment, care, and premature birth were not associated with an increased risk of delayed neurodevelopment.

From this study it can be concluded that women with HEG have a significant risk of having children with neurodevelopmental delays. Common antiemetic treatments are not associated with delayed neurodevelopment, but early symptoms may play a role. There is an urgent need to address whether aggressive treatment which includes vitamin and nutritional supplements in women with early symptoms of severe pregnancy nausea reduces the risk of delay in nerve development (8)

Increased blood pressure

This study found that children born to mothers who suffered severe weight loss during half the gestational age, had a tendency for higher birth weight and BMI and blood pressure to increase slightly at the age of 5-6 years (9).

Abnormal fetal brain development

In this journal it is concluded that there is a strong connection that HEG interferes with the development of the brain in the womb (11).

CONCLUSSION

HEG can be one of the risk factors that is detrimental to the condition of the mother and the outcome of pregnancy and can cause poor health outcomes in offspring ranging from the fetus, childhood to adulthood.

Further research is still needed on the impact of HEG on pregnancy outcomes.

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PRISMA Flowchart

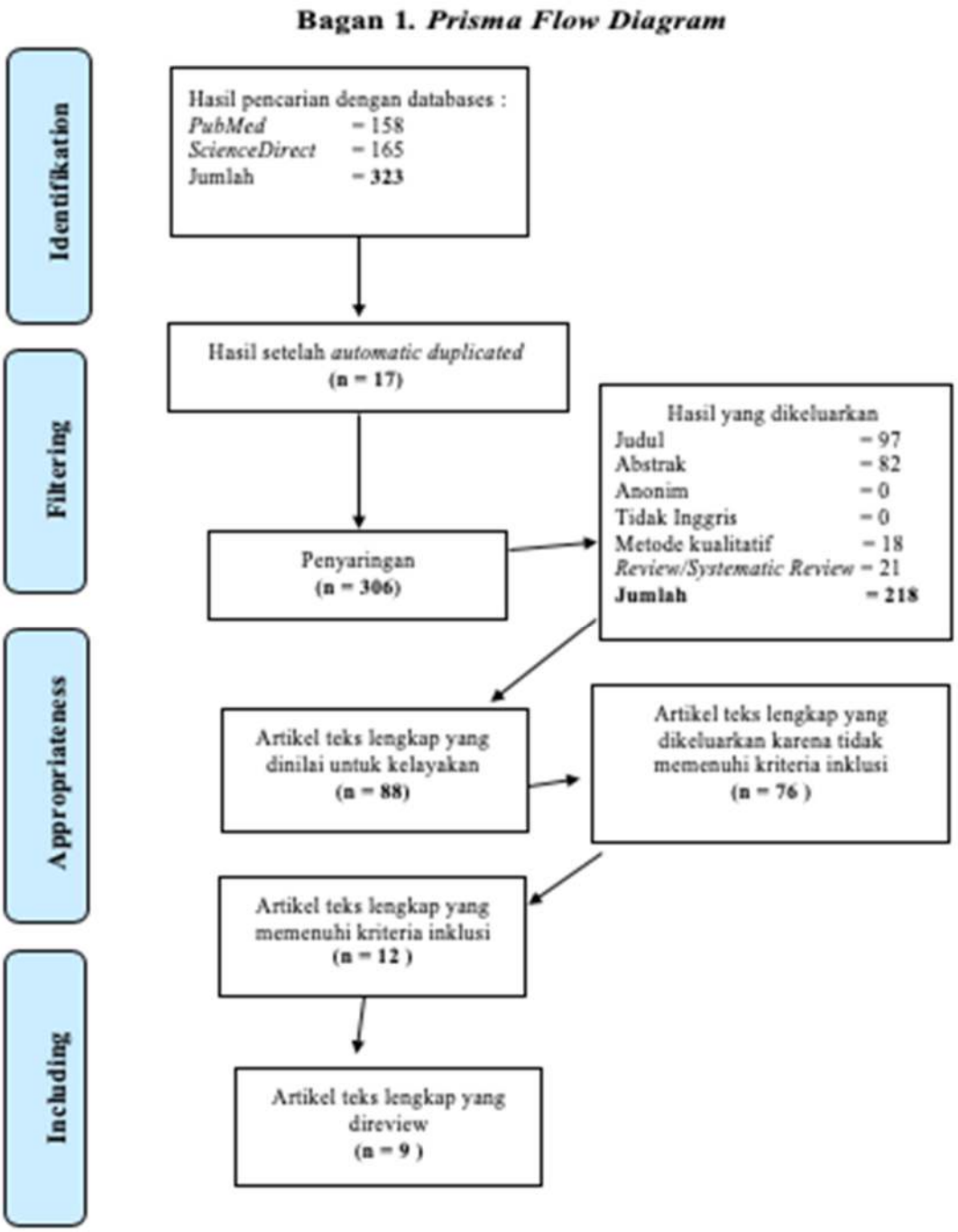

Table Extraction Data

No	Title/Author/Year/Grade	Country	Aim	Type Of Research	Data Collection	Participant/ Sample Size	Result
1.	*Outcomes of Pregnancies Complicated by Hyperemesis Gravidarum (6)*	Canada	The aim of this study was to evaluate the results of mothers and newborns who were exposed to hyperemesis during pregnancy .	*Kuantitative study*	Retrospective cohort. 1. Population based on all single deliveries at 20 weeks of gestational age or more and weighing 500 g or more in Nova Scoyia (1988-2002). 2. Clinical and other information for this study was obtained from the Nova Scotia Atlee Perinatal Database. 3. Researchers study the relationship between hyperemesis and labor outcomes.	156.091 women with a single pregnancy.	The results of this study indicate that of 156,091 women with a single pregnancy, a total of 1270 pregnant women have acceptance of hyperemesis. Babies born to women with hyperemesis and who gain weight in low pregnancies (<7 kg [15.4 lb]) are more likely to have low birth weight, are born before 37 weeks' gestation and have an Apgar score <7 for 5 minutes. The results of this study indicate that poor outcomes in infants exposed to hyperemesis are largely limited to women with poor maternal weight gain.
2.	*Recurrence of hyperemesis gravidarum across generations: population based cohort study (18)*	Norway	This study was conducted to estimate the outcome of pregnancy that is complicated by HEG, in girls and boys' partners.	*Kuantitative study*	Retrospective cohort. 1. Secondary data obtained through medical birth registration containing data from 1967 to the present. 2.3 million births were obtained and the identification number for a single child (male or female) was linked to the identification number of the mother or father of a single child. 2. Researchers selected women who had given birth to at least two daughters, both of which were registered or at least one registered pregnancy.	544.087 mothers and daughters who gave birth and 399.777 units of mother and son children who had a partner who gave birth.	Girls born after a pregnancy that is complicated by hyperemesis have a 3% risk of experiencing hyperemesis in their own pregnancy, whereas women born after an unaffected pregnancy have a 1.1% risk (unadjusted odds ratio 2.9, 95% confidence interval 2.4 to 3.6). Female partners of boys born after pregnancy complicated by hyperemesis have a 1.2% risk (1.0, 0.7 to 1.6). Girls born after pregnancy that are not complicated by hyperemesis have an increased risk of the condition if the mother has hyperemesis in a previous or subsequent pregnancy (3.2 (1.6 to 6.4) if hyperemesis occurs in one of the mother's previous pregnancies and 3.7 (1.5 to 1.5) 9.1) if it occurs in the next pregnancy). Adjustments for maternal age at delivery, birth period, and parity did not change estimates. Limits for older children do not affect results.
3.	*Severe Hyperemesis Gravidarum Is Associated With Reduced Insulin Sensitivity in the Offspring in Childhood (2)*	New Zealand	The aim of this study is to assess whether severe hyperemesis gravidarum affects glucose homeostasis and body composition in offspring in childhood.	*Kuantitative study*	Retrospective cohort 1. Conduct a code of ethics. Ethical approval for this study was provided by the North Y Regional Ethics Committee (Ministry of Health, New Zealand). Written informed	78 children (42 children in the control group and 36 children in the SHG group).	Insulin sensitivity in SHG children is 20% lower than in controls (8.49 vs 10.60 10 4 min 1 (mU / L); P 014). SHG children also had higher fasting insulin (6.88 vs. 5.04 mIU / L; P = 0.024) and lower IGF 1 binding protein (11.8 vs 19.0 ng / mL; P = 0.004) concentration rather than control. Initial cortisol concentrations were 22% higher in SHG offspring (256 vs 210 nmol / L; P021). Children in both groups were anthropometrically similar.

 DOI: http://dx.doi.org/10.35730/jk.v11i0.604

consent was obtained from parents or guardians as well as verbal or written consent from each child according to their age.
2. Healthy, normally developing prepubertal children aged 4 to 11 years were recruited for this study from June to November 2011.
3. All children are assessed at the Maurice & Agnes Paykel Clinical Research Unit (Liggins Institute, University of Auckland). Data on each child was collected during a single visit to the clinic. A number of neonatal parameters were recorded, including birth weight and gestational age. Birth weight data was changed to SDS (20).
4. Insulin sensitivity is assessed using a glucose tolerance test (FSIGT) which is taken routinely for 90 minutes, modified with insulin, and analyzed using Bergman's minimal model software.
5. Height of children is measured using a Harpenden stadiometer.
6. Glucose concentration was measured on a Hitachi 902 autoanalyzer (Hitachi High Technologies Corporation, Tokyo, Japan) with an enzymatic colorimetric test (Roche, Mannheim, Germany), with a coefficient of

					variation between variations (CV) of 2.1%. Insulin concentration was measured using the Abbott AxSYM system (Abbott Laboratories, Abbott Park, Illinois) by the microparticle enzyme immunoassay, with a CV of 5.7%. HDL-C, LDL-C, and total cholesterol concentrations were measured using a Hitachi 902 autoanalyzer, with CVs of 11.4%, 10.1%, and 8.9%, respectively.		
4.	*Hyperemesis gravidarum and risks of placental dysfunction disorders: a population-based cohort study (13)*	Sweden	To study the effects of hyperemesis gravidarum in the first (<12 weeks) or the second trimester (12-21 weeks) associated with impaired placental dysfunction,	*Kuantitative study*	Retrospective cohort 1. Data obtained from the Swedish Medical Birth Register (MBR). Enter all data of single births born at 22 weeks of gestation or more (1997-2009).	1.142.763 pregnant women, with complaints of hyperemesis (n = 10,186) and second trimester (n = 2084)	Women with hyperemesis gravidarum in the first trimester have little risk of pre-eclampsia. Women with hyperemesis gravidarum with first admission in the second trimester have more than double the risk of premature preeclampsia (<37 weeks), threefold increased risk of placental abruption and an increased risk of 39% of SGA births (adjusted odds ratio [95% confidence interval] are: 2.09 [1.38-3.16], 3.07 [1.88-5.00] and 1.39 [1.06-1.83], respectively). 1.
5.	*Protective Effect of Hyperemesis Gravidarum for Nonsyndromic Oral Clefts (4)*	Hungary	The purpose of this study is to evaluate whether hyperemesis gravidarum decreases the risk of Nonsyndromic Oral Clefts or cleft lip and to examine the relationship between hyperemesis gravidarum, birth weight, and gestational age.	*Kuantutative study*	Retrospective cohort 1. Secondary data were obtained from Hungarian country-based abnormalities data collection notes. 2. Maternal data from subjects and controls were obtained from 3 sources, namely: a. Prenatal notebooks, childbirth and all other medical records regarding their illness or inborn anomaly of children. b. Structured questionnaire. c. Interview by regional district nurses.	1368 baby	Fewer mothers of newborns with oral cleft have early onset hyperemesis gravidarum than control mothers (cleft lip with or without cleft palate: 83 cases and 121 controls, odds ratio [OR] 0.67, 95% confidence interval [CI] 0.50, 0.89; cleft palate: 42 cases and 64 controls, OR 0.63, 95% CI 0.42, 0.94). The use of dimenhydrinate is more common among mothers of subjects with cleft palate (OR 2.47, 95% CI 1.11, 5.49), whereas iron appears to have a protective effect against this condition (OR 0.26, 95 % CI 0.09, 0.80). Gestational age and birth weight were not significantly associated with hyperemesis gravidarum. This study shows that hyperemesis graviarum provides a protective effect against the risk of mouth opening in newborns.

 DOI: http://dx.doi.org/10.35730/jk.v11i0.604

6	*Neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum (8)*	United States of America	The purpose of this study is to determine the frequency of emotional, behavioral, and learning disorders in children exposed to hyperemesis gravidarum (HG) content and to identify prognostic factors for this disorder.	*Kuantitative study*	Retrospective cohort 1. Eligible patients are recruited primarily through advertisements on the Hyperemesis Education and Research Foundation Web site at www.HelpHer.org between 2007 and 2011. Inclusion criteria for this case are the diagnosis of HG in first pregnancy and treatment with IV fluids and / or total parenteral nutrition / nasogastric interval, over 18 years, having a child and a single pregnancy.	292 women	Children exposed to HG had a 3.28-fold increase in the likelihood of diagnosing neurological development including attention disorders, learning delays, sensory impairments, and speech and language delays (P <0.0005). Among the characteristics of HG pregnancy, only the onset of early symptoms (before 5 weeks of pregnancy) is significantly related to the delay in nerve development. We found no evidence for an increased risk of emotional, behavioral, and learning disorders, including autism, intellectual impairment, and obsessive-compulsive disorder. However, this research is not strong enough to detect rare conditions. Drugs, treatments, and preterm birth were not associated with an increased risk of delayed neurodevelopment.
7	*Weight loss in pregnancy and cardiometabolic profile in childhood: findings from a longitudinal birth cohort (9)*	Netherlands	The aim of this study is to investigate the consequences of weight loss in pregnancy on pregnancy outcomes and cardiometabolic profile in childhood.	*Kuantitative study*	Retrospective cohort 1. The study data was obtained from the Amsterdam Born Children and their Development (ABCD) profile. The ABCD Study is a large prospective birth cohort that was established in 2003. 2. Midwives recruited pregnant women who lived in Amsterdam between January 2003 and March 2004 to take part in this study. 3. A total of 8266 pregnant women who have been recruited responded to questionnaires about lifestyle, health, environment, psychosocial pressure and ethnic background. 4. Information about pregnancy and neonatal outcomes is provided through midwifery nurses through contact with the Dutch Perinatal Registry (PRN) and Adolescent Health Care Registration. 5. Next, the neonatal	7818 mother-daughter pair	SWL results occur in 6.8% of cases. Women with SWL had similar preterm birth rates compared to women without these complaints (adjusted OR 1.1, 95% CI 0.7, 1.7). Birth weight (adjusted difference - 31 g, 95% CI 76, 15) and BMI at 5- Age 6 years (adjusted difference 0.2 kg / m2, 95% CI 0.0, 0.5) were similar at children born to mothers with and without SWL, but blood pressure rises. For diastolic blood pressure, this relationship does not depend on confounding (adjusted difference of 1.4 mmHg, 95% CI 0.4, 2.4). Lipid and glucose levels did not differ significantly between these groups.

					questionnaire was sent 3 months postpartum (phase 2). 6. After 5 years, 6,161 mothers are approached to follow up on their child. This reduction in the number of follow-ups is largely due to addresses or migrations that cannot be traced. In total, 4488 mothers returned the questionnaire and gave approval for follow-up. This resulted in 3,321 physical examinations and fasting blood samples were also taken in a sample of 2108 children (phase 3).		
8	*Hyperemesis gravidarum and cardiometabolic risk factors in adolescents: a follow-up of the Northern Finland Birth Cohort 1986 (10)*	Netherlands	To investigate the long-term consequences of hyperemesis gravidarum exposure during pregnancy with prenatal cardiometabolic risk.	*Kuantitative study*	Retrospective cohort 1. NFBC1986 recruited women in the provinces of Oulu and Lapland who gave birth on July 1, 1985 and June 30, 1986. 2. In total 9362 maternal and 9479 infants were obtained. 3. NFBC1986 data are collected prospectively at the first antenatal visit and beyond. 4. Mother fills in the questionnaire about her background. 5. Data on antenatal visits, hospital births and birth outcomes are obtained from maternity health centers and hospital medical records. 6. This cohort was followed up in 2002 when the offspring reached 16 years of age. Follow-up focused on children's health and well-being. Teens and their parents give consent to use their data for scientific research.	9479 children →6462 children	Results Multivariate regression analysis did not show differences in hereditary BMI (kg / m 2; difference in percentage adjusted for HG versus reference, 2.2; 95% CI 0.1, 4.6), systolic blood pressure (adjusted difference in 2.1 mmHg; 95% CI 1.5, 5.6), and fasting blood glucose (mmol / l; adjusted percentage difference, 2.3; 95% CI 0.6, 5.4), between adolescents born to mothers with and without HG.

 DOI: http://dx.doi.org/10.35730/jk.v11i0.604

					researchers only included a single pregnancy that was still alive.		
9	*Is hyperemesis gravidarum associated with placental weight and the placental weight-to-birth weight ratio? A population-based Norwegian cohort study (17)*	Norway	To explore the relationship between HEG and placental weight in a population-based cohort	*Kuantitative study*	Retrospective cohort 1. Data obtained from MBRN, which was founded in 1967. 2. All single births of primiparous women. 3. Women who are registered with clinical conditions related to placental abnormalities are excluded. 4. Bivariate analysis between HG and placental weight and PW / BW ratio below or above the 10th percentile was performed using the Pearson Chi Square test. A similar analysis was performed for the 90th percentile. A value of p <0.05 was determined as a cut-off for statistical significance. 5. Yield variables are then analyzed both continuously (grams) and dichotomous results using each linear and logistic regression analysis. In logistic regression analysis we categorized the placental weight and PW / BW ratio either under the 10th percentile or above the 90th percentile. The odds ratio and odds ratio are calculated as an estimate of relative risk with a 95% confidence interval (CI). SPSS for windows v.20.0 (SPSS Inc., Chicago, IL) was used for all calculations.	2589 women	The prevalence of HG is 1.2%. Women with HG and girls have a significantly higher risk of PW / BW ratio above the 90th percentile (OR 1 OR4 1.17, 95% CI: 1.03e1.34). The ratio of HG and PW / BW under the 10th percentile is inversely related (OR 1⁄4 0.70, 95% CI: 0.56e0.89). For boys no relationship was observed for HG and PW / BW ratios below 10 or above the 90th percentile.