BMJ Open

Seremban Cohort Study (SECOST): A prospective study of determinants and pregnancy outcomes of maternal glycemia in Malaysia

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018321
Article Type:	Protocol
Date Submitted by the Author:	23-Jun-2017
Complete List of Authors:	yong, heng yaw; University Putra Malaysia, Nutrition and Dietetics MOHD SHARIFF, ZALILAH; University Putra Malaysia, Nutrition and Dietetics Rejali, Zulida; University Putra Malaysia, Department of Obstetrics and Gynaecology Mohd Yusof, Barakatun Nisak ; University Putra Malaysia, Nutrition and Dietetics Yasmin, Farah; University Putra Malaysia, Nutrition and Dietetics Palaniveloo, Lalitha; Institute for Public Health Malaysia, Center for Nutrition Epidemiology Research
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Nutrition and metabolism, Diabetes and endocrinology
Keywords:	DIABETES & ENDOCRINOLOGY, NUTRITION & DIETETICS, OBSTETRICS, PRIMARY CARE, PUBLIC HEALTH

Study protocol

Seremban Cohort Study (SECOST): A prospective study of determinants and pregnancy outcomes of maternal glycemia in Malaysia

Yong Heng Yaw[1], Zalilah Mohd Shariff[1]*, Zulida Rejali[2], Barakatun Nisak Mohd Yusof[1], Farah Yasmin[1], Lalitha Palaniveloo[3]

[1]Department of Nutrition and Dietetics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia

[2]Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia

[3]Center for Nutrition Epidemiology Research, Institute for Public Health, Ministry of Health Malaysia

* Corresponding author

Email: zalilahms@upm.edu.my

Abstract

Introduction: Both gestational diabetes mellitus (GDM) and hyperglycemia less severe than GDM are associated with risk of adverse pregnancy outcomes. We describe the study design of a prospective cohort of pregnant women recruited in early pregnancy with follow-ups of mothers and infants up to 2 years after birth. The primary aim of the study was to identify the determinants and outcomes of maternal glycemia.

Methods and analysis: Seremban Cohort Study (SECOST) is an on-going prospective cohort study in which eligible pregnant women in first trimester (< 10th weeks of gestation) are recruited from Maternal and Child Health (MCH) clinics in Seremban District, Negeri Sembilan with 7 follow-ups during pregnancy through 2 years postnatal. Infants are followed-up every 6 months after birth until 2 years old. A standard 75g Oral Glucose Tolerance Test (OGTT) is performed between 24th and 32nd of weeks of gestation and as close to 28th weeks of gestation. Pregnancy and birth information are obtained from medical records. Socio-demographic, anthropometric, biochemical, dietary, physical activity, smoking, depression, child feeding, and other data of mothers and infants are obtained at follow-ups.

Ethics and dissemination: This study is approved by the Medical Research Ethics Committee (MREC), Universiti Putra Malaysia (UPM/FPSK/100-9/2-MJKEtika) and the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (KKM/NIHSEC/08/0804/P12-613). Permission to conduct this study is also obtained from the Head of Seremban District Health Office. The research findings will be disseminated at journals and conference presentations.

Strengths and limitations of this study:

1. SECOST is the first prospective study in Malaysia to provide data on determinants and pregnancy outcomes of maternal glycemia.
2. Information on lifestyle factors and weight gain patterns during pregnancy will provide insight on determinants of maternal glycemia.
3. Data on birth and early child growth patterns will inform on the short and long-term outcomes of maternal glycemia.
4. The cohort of pregnant women and their off-springs may not represent the general population of pregnant women and infants in Malaysia due to the location of subject recruitment and study selection criteria.
5. High attrition rate of subjects during pregnancy and infancy is expected.

Introduction

During pregnancy, substantial changes occur in glucose, lipid and protein metabolism as to meet the increasing demands of the fetus. In a normal pregnancy, an increase in insulin resistance will reduce glucose uptake into maternal tissues as to make glucose more readily available for fetal growth. This hyperglycemic state is mainly due to the increased production of placental growth hormones that may interfere with insulin receptor's action and inhibit glucose uptake as pregnancy progresses [1]. Pregnant women will develop elevated blood glucose level (hyperglycemia) or gestational diabetes mellitus (GDM) if the mother's beta cells are unable to increase insulin secretion to compensate for the insulin resistance in pregnancy.

The international multicenter Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study reported that maternal fasting and stimulated glucose levels showed linear associations with risks of increased size at birth, caesarian delivery, neonatal hypoglycemia and fetal hyperinsulinemia (Metzger et al., 2008). On the basis of this landmark study, the International Association of Diabetes in Pregnancy Study Groups (IADPSG) and the American Diabetes Association (ADA) have recommended new lower diagnostic criteria for GDM (2). However, the use of these new criteria has resulted in a dramatic increase in the number of women diagnosed with GDM [3–5]. Increased health care cost and lack of improvement in maternal and infant outcomes are other concerns related to the new diagnostic criteria [6]. Thus, the optimal diagnostic threshold of GDM during pregnancy remains controversial.

Globally, the prevalence of GDM ranging from 1 to 14% of all pregnancies, depends on the population and diagnostic criteria of GDM [5]. In the United States, GDM affected 7% of all pregnancies annually [7]. In Europe, a 2 - 6% prevalence of GDM was reported with a lower prevalence in the Northern Europe (less than 4%) than in the Southern Europe (higher than 6%) [8]. Similarly, in Asian countries, the prevalence of GDM in China [9], Korea [10] and Thailand [11] were 6.8%, 2 – 5% and 5.7%, respectively. GDM rate in Malaysia (8 – 11%) [12,13] is much higher than those reported for most Asian populations (2 – 7%) [9–11]. As the rate of obesity increases among women, a parallel rise in GDM rate is inevitable. The National Health and Morbidity Survey (NHMS) reported that the prevalence of obesity in Malaysian women aged 18 years old and above increased from 5.7% in 1996 to 17.6% in 2011 [14,15]. As more women in reproductive age become overweight or obese prior to pregnancy, they will be at greater risk of maternal hyperglycemia.

At present, limited data are available on determinants and outcomes of hyperglycemia during pregnancy in Malaysia [13,16]. This study will provide important insights on lifestyle factors and weight gain patterns during pregnancy as determinants as well as birth and early child growth data as short and long-term outcomes of maternal glycemia. In light of increasing rates of child and adult obesity, GDM and diabetes mellitus and persistence of child under-nutrition in Malaysia, such information on intergenerational transmission of risk of obesity and non-communicable diseases are pertinent for planning effective strategies that best meet the needs and resources to achieve a future healthy generation.

Materials and methods

Study design

SECOST is an on-going prospective cohort study in which pregnant women and their infants are followed-up through 2 years postnatal. Women in the first trimester (< 10th weeks of gestation) of pregnancy are recruited from three [3] Maternal and Child Health (MCH) clinics in Seremban District, Negeri Sembilan, Malaysia. There are 7 follow-up visits for mothers (3 pregnancy and 4 postnatal visits) and 4 follow-up visits for infants at an interval of 6 months after birth (Table 1).

Participants

Pregnant women attending MCH clinics for antenatal booking are eligible to participate in the study upon screening based on study criteria:

Inclusion criteria:

Malaysian women (age more than 18 years) with singleton pregnancy, BMI ≥ 18.5 – < 40.0, normal glycemia at study enrolment (FPG 3.0 – 6.0 mmol/l) and free from any medical illness or obstetrics complications

Exclusion criteria:

Women with multiple pregnancies, became pregnant with assistance of advanced reproductive technology, unable to complete OGTT within 24 – 32nd weeks of gestation, pre-existing diabetes mellitus (FPG > 7.0 mmol/l), diagnosis of diabetes during this pregnancy, abnormal glycemia (FPG < 3.0 mmol/L or FPG > 6.0 mmol) at study enrolment, previous diagnosis of diabetes requiring treatment with medication outside of pregnancy, BMI > 40.0, other medical problems (e.g. HIV positive, Hepatitis B/C, hypertension, renal disease, anemia, thalassemia) at study enrolment.

Recruitment

Study information leaflet is given to all pregnant women attending the 3 MCH clinics for antenatal booking by nurses. Pregnant women who meet the selection criteria are invited to participate in the study. Study participation is on a voluntary basis and participants can withdraw from the study at any time during the study period. A study manual that outlines the details of study visits and measurements are given to participants. The period of recruitment is from 2013 – 2016.

Sample size

Sample size is estimated using a statistical formula for a proportion by Scheaffer, Mendenhall, Ott, & Gerow (2011). Based on 18.3% of pregnant women in Malaysia had abnormal OGTT [18], 95% confidence level and 5% probability of missing a true difference, a minimum of 230

pregnant women are required as study participants. To account for an attrition rate of 50%, the sample is increased to a minimum of 345 pregnant women.

Measurements

The schedule of measurements for mothers and infants at study enrolment and follow-up visits are summarized in Table 1.

Mothers

Socio-demographics

The socio-demographic information obtained include current age, years of education, ethnicity, marital status, occupation, income, spouse's years of education, spouse's occupation, spouse's income and household income.

Dietary intake

Dietary intake is assessed using one day 24-hours diet recall and Food Frequency Questionnaire (FFQ).

1. Energy and nutrient intakes

A 24-hour diet recall is used to obtain dietary information. Standard household measuring cups, glasses, bowls and spoons are used to assist respondents to estimate food portion size. Dietary data are analysed using Nutritionist Pro Diet Analysis software [19] and comparison of energy and nutrient intakes is made to the Malaysian Recommended Nutrient Intake [20] to determine intake adequacy. Intakes of grains, meat, fish, legumes, fruits, vegetables and dairy product

(gram/day) are calculated as number of servings and compared to the Malaysian Dietary Guidelines [21].

2. Alcohol use

The frequency of drinking alcohol and amount of alcohol (glass) are obtained.

3. Energy density

Energy density is calculated by dividing each subject's daily energy intakes (in kilocalories) by the reported weight of all foods consumed (in grams) [22].

4. Dietary pattern

Food Frequency Questionnaire (FFQ) is utilized to assess food consumption patterns. There are 12 main food groups with 50 sub-food groups which include cereals, meat and meat products, fish and seafood, eggs, fruits, vegetables, legumes and nuts, milk and dairy products, fat and oil, sugar and sugary food, flavouring and beverages [23]. Dietary patterns are determined based on standard procedures [24,25].

5. Dietary glycemic index and glycemic load

Dietary glycemic index (GI) and glycemic load (GL) are calculated from Food Frequency Questionnaire and 24-hour dietary recall. The GI values will be categorized into low GI: ≤55, medium GI: 56 – 70 and high GI: >70. The formulae to calculate dietary GI and GL as used are [26–28]:

Dietary glycemic index = [Glycemic index value of the food x Frequency of servings of the food per day (g) x carbohydrate content of the food (%)] / Total daily carbohydrate (g)

Dietary glycemic load = [Glycemic index value of the food x Frequency of servings of the food per day (g) x carbohydrate content of the food (%)]

Physical activity

Pregnancy Physical Activity Questionnaire (PPAQ) is used to determine physical activity of pregnant women [29]. The PPAQ is a semi quantitative questionnaire that requires participants to report the time spent participating in 32 activities including household/care giving (13 activities), occupational (5 activities), sports/exercise (8 activities), transportation (3 activities), and inactivity (3 activities).

Anthropometry

Weight, height and waist circumference are measured at study enrolment (antenatal booking) using standard instrument (SECA digital weighing scale, SECA body meter and SECA measuring tape). Pre-pregnancy body weight (current pregnancy) and weight at the beginning of first pregnancy are obtained from medical record. Pre-pregnancy BMI is calculated as pre-pregnancy weight (kg) divided by recommendation of World Health Organization [30]. Inter-pregnancy weight change is defined as the difference between weight at the beginning of the first and current pregnancies. Postpartum weight retention is calculated as the absolute difference between weight measured at each of 4th and 5th visit and pre-pregnancy weight. Total gestational weight gain is defined as the difference between measured weight at last prenatal visit and pre-pregnancy weight. Rate of weight gain in first, second or third trimester is defined as the average weekly weight gain in that trimester.

Biochemical

A standard 75g OGTT is performed at 2 time points. The first OGTT is performed for all participants at 10 – 13th weeks of gestation. The second OGTT is performed between 24th and 32nd weeks of gestation (2nd visit) and as close to 28th weeks of gestation as possible. A 2ml fasting venous blood is drawn prior to ingestion of a standard glucose solution. Another 2 ml of venous blood is drawn at 2-hours after ingestion of standard glucose solution. All blood samples are sent for analysis on the same day to determine fasting glucose, 2-hr plasma glucose concentration. Additional blood (3ml) is obtained for analysis of total cholesterol, HDL-cholesterol, triglycerides and vitamin D. Normal fasting plasma glucose for pregnant women is defined according to the Ministry of Health (MOH) (3.0 mmol/l to < 6.0 mmol/l). The cut off values for serum lipid is according to the National Cholesterol Education Program Adult Treatment Panel III [31] guidelines. Vitamin D cut offs for severe deficiency, mild deficiency, insufficiency and sufficiency are < 25 nmol/L, 25 – <50 nmol/L, 50 – <75 nmol/L and ≥ 75 nmol/L, respectively [32].

Blood pressure

Right arm systolic blood pressure (SBP) and diastolic blood pressure (DBP) is measured using OMRON SEM-1 Automatic Blood Pressure Monitor by trained nurses.

Smoking habit

The status of smoking, frequency of smoking and number of cigarettes smoked are obtained.

Food insecurity

A 10 items questionnaire is use to assess women food insecurity. All items are rated on a 3 response point ranging from always, sometimes or never [33]

Depression

Depression during pregnancy and postpartum depression is assessed using a self-administered 10 question Edinburg Postnatal Depression Scale (EPDS) [34]

Maternal birth information

1. Delivery

Mode of birth (normal vaginal birth, assisted breech delivery, instrumental delivery or caesarean section) and gestational age at birth are obtained from medical record. Premature birth is defined as childbirth occurring at less than 37 completed weeks of gestation or 259 days of gestation [35].

2. Birth information of infants

Birth data are obtained from medical record. Birth weight is categorized according to the recommendation of United Nations Children's Fund (UNICEF) and World Health Organization [36]. SGA is defined as an infant weighing less than 10th percentile of birth weight. An infant with >90th percentile of birth weight was classified as large-for-gestational age (LGA), while an infant with the 10th-90th percentile of birth weight as appropriate-for-gestational-age (AGA) [37].

Infants

1. Anthropometry

All infants are measured for weight (to the nearest 0.1 kg), length (to the nearest 0.1 cm), head circumference and mid arm circumference (to the nearest 0.1 cm) using TANITA digital baby weighing scale with recumbent length meter and SECA fibreglass measuring tape, respectively. Infants are measured using standard procedures as described by Gibson, (2005) [38]. Growth data are analyzed using Anthro Plus software that utilizes World Health Organization growth standard [39]. Five growth indicators (weight-for-age, weight-for-height, height-for-age, head circumference-for-age and BMI-age) will be determined. In order to assess subcutaneous fat, triceps and subscapular are measured using Harpenden Skinfold Caliper and recorded to the nearest 0.1mm [40].

2. Dietary intake

A 24-hour diet recall is used to obtain dietary information of infants from parents / guardians with the aid of standard household measurements. Dietary data are then analysed for adequacy of energy and nutrients [19, 20] as well as dietary diversity [41]. Parents are also interviewed on infant feeding practices (e.g. milk feeding, complementary feeding).

Data collection

All enumerators are given an intensive briefing and field training before data collection. Study visits are scheduled on the same day of appointments at MCH clinics. A day before each visit, enumerators are required to remind participants of their clinic appointments through telephone calls. During the visits, participants are interviewed or measured for relevant data. For participants who are not able to be interviewed at the clinics, home visits or telephone interviews are carried out by enumerators.

Data Analysis

Data will be analyzed using IBM SPSS Statistic 22. Descriptive statistics (mean, standard deviation, median, frequency) will be used to describe the data. Multiple logistic regression will be used to determine the relationship between predictors and maternal glycemia, as well as the relationship between maternal glycemia with pregnancy outcomes controlling for confounding variables. Significant level for all statistical analysis will be set at $p<0.05$.

Discussion

Globally, the prevalence of overweight and obesity is increasing among women, particularly during reproductive years. A study on trends of obesity in the United States (US) showed that the prevalence of obesity (BMI ≥ 30 kg/m^2) in US women aged 20 – 39 years increased from 28.4% in 1999 to 34.0% in 2007 [42]. In the Malaysian National Health and Morbidity Survey 1996 (NHMS II), women showed a significantly higher prevalence of obesity (BMI ≥ 30kg/m^2) (17.5%) than man (10.2%). In the period between the NHMS II (1996) and the NHMS (2011), there was an 11.9% increase in the prevalence of obesity (BMI ≥ 30kg/m^2) among females aged ≥18 years old. With increasing prevalence of obesity among women of childbearing age, the risk of having higher pre-pregnancy BMI and excessive gestational weight gain are inevitable [43,44]. These conditions could further increase the risk of pregnant women to have higher blood glucose level and subsequently poor pregnancy outcomes.

Studies have shown that women with hyperglycemia during pregnancy are at higher risk for poor pregnancy outcomes, such as caesarean delivery, pregnancy induced hypertension and preeclampsia [18,45,46]. Apart from that, mothers with hyperglycemia during pregnancy tend to have large-for-gestational-age (LGA) infants and infants with asphyxia and hypoglycemia [46–48]. These conditions can lead to other long-term child health problems such as obesity, type II diabetes, cancer and cardiovascular disease in later life. For the mothers with hyperglycemia, they are at higher risk of developing cardiovascular disease and overt diabetes, mainly type 2 diabetes in later life [49–51]. However, there is no clear threshold above which women are at high risk and below which they are at low risk. Moreover, the impact of maternal hyperglycemia,

which is characterized by value of glucose tolerance intermediate between normal and gestational diabetes on outcomes of pregnancy remains unclear.

Dietary intake and physical activity are important modifiable risk factors for the development of type 2 diabetes, as well as gestational hyperglycemia. While higher total fat and lower carbohydrate intakes during second trimester of pregnancy were associated with maternal hyperglycemia [52], pregnant women in the high quartile of moderate intensity activity and occupational activity during early pregnancy had about 50% decreased risk of abnormal glucose tolerance [53]. A lower energy intake and higher physical activity are known to improve insulin sensitivity and reduce glucose levels, however, there is less information on dietary nutrients intakes, particularly fat types, vitamin D and iron related to maternal hyperglycemia, as well as the optimal distribution of macronutrient intakes during pregnancy to prevent maternal hyperglycemia. Therefore, there is a need for a better understanding of the role of lifestyle factors, especially energy and nutrient intakes, physical activity and sedentary behavior in the development of maternal hyperglycemia.

SECOST is the first prospective study in Malaysia to provide a better understanding of weight gain and lifestyle patterns from early pregnancy until 1 year postpartum and to quantitate the relationship between maternal glucose levels and pregnancy outcomes. As GDM impacts maternal and fetal health, detailed information on lifestyle factors, biochemical parameters and weight gain patterns during pregnancy can provide insight on determinants of maternal glycemia. Data on early child growth and development obtained periodically will not only provide information on short and long-term outcomes of maternal glycemia but also indicate the role of

environment (e.g. infant feeding, diet, parent-infant interaction, home environment) that could potentially impact child growth and development. Despite the modest sample size, this pregnancy cohort study provides an opportunity for many hypotheses related to maternal and infant health and nutrition to be tested or confirmed. SECOST is expected to provide valuable data that can be used not only for strengthening existing strategies but also formulating new strategies that are in accordance with promoting maternal and child health.

Ethics and dissemination

This study is approved by the Medical Research Ethics Committee (MREC), Universiti Putra Malaysia (UPM/FPSK/100-9/2-MJKEtika) and the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (KKM/NIHSEC/08/0804/P12-613). Permission to conduct this study is also obtained from the Head of Seremban District Health Office. All participants are required to provide written informed consent prior to data collection. The research findings will be disseminated through publications and conference presentations. Data sharing is available upon request.

Acknowledgements

The authors would like to thank all women and infants who took part in this study and all nurses, and staff in MCH clinics of Seremban district, Negeri Sembilan for their assistance during data collection.

Author's contributions

ZMS – conceptualized and designed the study; contributed to the development of study protocol; supervise data collection; read, revised and approved the final draft of manuscript

YHY – conceptualized and designed the study; contributed to the development of study protocol; involve in data collection; drafted the manuscript

ZR and BNMY – contributed to the development of study protocol; read and approved the manuscript

FY and LP – involve in data collection

Study funding

Funding is provided by Danone Dumex (Malaysia) Shd. Bhd.

Competing interests

Although SECOST is funded by the Danone Dumex (Malaysia) Shd. Bhd, the company does not influence the study protocol and preparation of this manuscript. As the nature of this study is more of exploratory and does not involve any testing of company product, the researchers are free to report any findings of this study in future publications. All authors declare that they have no competing interests.

References

1. Perkins JM, Dunn JP, Jagasia SM. Perspectives in Gestational Diabetes Mellitus: A Review of Screening, Diagnosis, and Treatment. Vol. 25, Clinical Diabetes. 2007. p. 57–62.
2. Panel IA of D and PSGC. International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. Diabetes Care [Internet]. 2010 Mar 1;33(3):676–82. Available from: http://care.diabetesjournals.org/content/33/3/676.short
3. Cundy T, Ackermann E, Ryan E a. Gestational diabetes : new criteria may triple the prevalence but effect on outcomes is unclear. Bmj [Internet]. 2014;1567(March):1–5. Available from: http://dx.doi.org/doi:10.1136/bmj.g1567
4. Blackwell SC. Enough evidence to treat? The American College of Obstetricians and Gynecologists Guidelines. Clin Chem. 2012;58(7):1098–100.
5. Coustan DR. Medical Management of Pregnancy Complicated by Diabetes [Internet]. Coustan DR, editor. American Diabetes Association; 2013. 188 pages. Available from: https://books.google.com.my/books?id=NDbQlAEACAAJ
6. Langer O, Umans JG, Miodovnik M. Perspectives on the proposed gestational diabetes mellitus diagnostic criteria. Obstet Gynecol. 2013 Jan;121(1):177–82.
7. Hillier TA, Vesco KK, Pedula KL, Beil TL, Whitlock EP, Pettitt DJ. Screening for gestational diabetes mellitus: A systematic review for the U.S. preventive services task force. Vol. 148, Annals of Internal Medicine. 2008. p. 766–75.
8. Buckley BS, Harreiter J, Damm P, Corcoy R, Chico A, Simmons D, et al. Gestational diabetes mellitus in Europe: Prevalence, current screening practice and barriers to

screening. A review. Vol. 29, Diabetic Medicine. 2012. p. 844–54.

9. Zhang Y, Peck K, Spalding M, Xu T, Ragain M. A study to examine the attitudes, knowledge, and utilization of CAM by primary care professional in West Texas. Complement Ther Med. 2010;18:227–32.

10. Jang HC. Gestational diabetes in Korea: incidence and risk factors of diabetes in women with previous gestational diabetes. Diabetes Metab J [Internet]. 2011;35(1):1–7. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3080571&tool=pmcentrez&rendertype=abstract

11. Sumeksri P, Wongyai S, Aimpun P. Prevalence of gestational diabetes mellitus (GDM) in pregnant women aged 30 to 34 years old at Phramongkutklao Hospital. J Med Assoc Thai. 2006;89(Suppl 4):S94-9.

12. Kwapisz J, Bodaghi M. Preliminary Report of National Obstetrics Registry, Jan-December 2010. Jeganathan R, Karalasingam SD, editors. Kuala Lumpur, Malaysia, Malaysia: Jointly published by the National Obstetrics Registry and the Clinical Research Centre (CRC), Ministry of Health Malaysia.; 2013. 1-24 p.

13. Tan PC, Ling LP, Omar SZ. Screening for gestational diabetes at antenatal booking in a Malaysian university hospital: The role of risk factors and threshold value for the 50-g glucose challenge test. Aust New Zeal J Obstet Gynaecol. 2007;47:191–7.

14. IPH. National Health and Morbidity Survey 2011 (NHMS 2011). Ministry of Health Malaysia. Kuala Lumpur.: Institute for Public Health. Ministry of Health, Malaysia; 2011. 258 pages.

15. IPH. The Second National Health and Morbidity Study (NHMS 2). Ministry of Health

Malaysia. Kuala Lumpur.: Institute for Public Health. Ministry of Health, Malaysia; 1996.

16. Kampan N, Azman H, Hafiz I, Mohammad H, Yee CS, Azurah N, et al. Outcome of pregnancy among Malaysian women with diabetes mellitus - A single centre experience. Malaysian J Public Heal Med. 2013;13(2):1–10.

17. Scheaffer R, Mendenhall W, Ott R, Gerow K. Elementary Survey Sampling [Internet]. 7th ed. Cengage Learning; 2011. 480 pages. (Advanced series). Available from: https://books.google.com.my/books?id=TbSjtoy4p-8C

18. Nordin NM, Wei JWH, Naing NN, Symonds EM. Comparison of maternal-fetal outcomes in gestational diabetes and lesser degrees of glucose intolerance. J Obstet Gynaecol Res. 2006 Feb;32(1):107–14.

19. Axxya Systems LLC. Nutritionist Pro Diet Analysis [Internet]. 2011. Available from: http://www.axxya.com/products.html.

20. National Coordinating Committee on Food and Nutrition. Recommended Nutrient Intakes for Malaysia. A Report of the Technical Working Group on Nutritional Guidelines. Ministry of Health Malaysia, Putrajaya.; 2005.

21. National Coordinating Committee on Food and Nutrition. Malaysian Dietary Guidelines 2010. A Report of the Technical Working Group on Nutritional Guidelines. [Internet]. Vol. 1. Ministry of Health Malaysia, Putrajaya.; 2010. Available from: http://www.moh.gov.my/images/gallery/Garispanduan/diet/introduction.pdf

22. Ledikwe JH, Blanck HM, Kettel Khan L, Serdula MK, Seymour JD, Tohill BC, et al. Dietary energy density is associated with energy intake and weight status in US adults. Am J Clin Nutr. 2006 Jun;83(6):1362–8.

23. Ministry of Health Malaysia. The Malaysian Adults Nutrition Survey (MANS)-Findings

Report 2003. Nutrition Section Family Health Development Division, Putrajaya: Ministry of Health Malaysia, Malaysia; 2007.

24. Randall E, Marshall JR, Graham S, Brasure J. Patterns in food use and their associations with nutrient intakes. Am J Clin Nutr [Internet]. 1990 Oct 1;52(4):739–45. Available from: http://ajcn.nutrition.org/content/52/4/739.abstract

25. Nicklas TA, Webber LS, Thompson B, Berenson GS. A multivariate model for assessing eating patterns and their relationship to cardiovascular risk factors: the Bogalusa Heart Study. Am J Clin Nutr. 1989 Jun;49(6):1320–7.

26. Sieri S, Krogh V, Berrino F, Evangelista A, Agnoli C, Brighenti F, et al. Dietary glycemic load and index and risk of coronary heart disease in a large italian cohort: the EPICOR study. Arch Intern Med. 2010 Apr;170(7):640–7.

27. Villegas R, Liu S, Gao Y-T, Yang G, Li H, Zheng W, et al. Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2 diabetes mellitus in middle-aged Chinese women. Arch Intern Med. 2007 Nov;167(21):2310–6.

28. Liu S, Willett W. Dietary glycemic load and atherothrombotic risk. Curr Atheroscler Rep [Internet]. 2002;4(6):454–61. Available from: http://dx.doi.org/10.1007/s11883-002-0050-2

29. Chasan-Taber L, Schmidt MD, Roberts DE, Hosmer D, Markenson G, Freedson PS. Development and validation of a Pregnancy Physical Activity Questionnaire. Med Sci Sports Exerc. 2004 Oct;36(10):1750–60.

30. WHO. Physical status: The Use and Interpretation of Anthropometry. Report of a WHO Expert Committee. World Health Organization, editor. Geneva: WHO Technical Report Series No. 854.; 1995.

31. NCEP. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002 Dec;106(25):3143–421.

32. Hamid Jan, Mohamed, Angela R, Bertram F, Loy SL. Maternal serum and breast milk vitamin D levels: findings from the Universiti Sains Malaysia Pregnancy Cohort Study. PLoS One. 2014;9(7):e100705.

33. Radimer KL, Olson CM, Campbell CC. Development of indicators to assess hunger. J Nutr. 1990 Nov;120 Suppl(December 1989):1544–8.

34. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987 Jun;150:782–6.

35. WHO. International classification of diseases and related health problems. 10th ed. World Health Organization, editor. Geneva.; 1992.

36. UNCF/WHO. Low Birthweight: Country, regional and global estimates. UNICEF, New York. United Nations Children's Fund and World Health Organization, editor. UNICEF, New York; 2004.

37. Bukowski R, Hansen NI, Willinger M, Reddy UM, Parker CB, Pinar H, et al. Fetal Growth and Risk of Stillbirth: A Population-Based Case–Control Study. Fisk NM, editor. PLoS Med [Internet]. 2014 Apr 22;11(4):e1001633. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3995658/

38. Gibson RS. Principles of Nutritional Assessment [Internet]. Oxford University Press; 2005. 908 pages. Available from: https://books.google.com.my/books?id=lBlu7UKI3aQC

39. WHO. Training Course on Child Growth Assessment. [Internet]. World Health Oraganization, editor. Geneva, WHO; 2008. Available from:

http://www.who.int/childgrowth/software/en/

40. Dauncey MJ, Gandy G, Gairdner D. Assessment of total body fat in infancy from skinfold thickness measurements. Arch Dis Child. 1977;52(August 1976):223–7.

41. Food and Agriculture Organization and Food and Nutrition Technical Assistance Project. Guidelines for measuring household and individual dietary diversity. Rome, Italy; 2013.

42. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among us adults, 1999-2008. JAMA [Internet]. 2010;303(3):235–41. Available from: http://dx.doi.org/10.1001/jama.2009.2014

43. Gunderson EP. Childbearing and Obesity in Women: Weight Before, During, and After Pregnancy. Vol. 36, Obstetrics and Gynecology Clinics of North America. 2009. p. 317–32.

44. Li N, Liu E, Guo J, Pan L, Li B, Wang P, et al. Maternal prepregnancy body mass index and gestational weight gain on pregnancy outcomes. PLoS One [Internet]. 2013 Dec 20;8(12):e82310. Available from: http://dx.doi.org/10.1371%252Fjournal.pone.0082310

45. Catalano PM, Tyzbir ED, Wolfe RR, Calles J, Roman NM, Amini SB, et al. Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. Am J Physiol [Internet]. 1993;264(1 Pt 1):E60–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8430789

46. Lowe LP, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TRJ, et al. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: Associations of maternal A1C and glucose with pregnancy outcomes. Diabetes Care [Internet]. 2012 Mar 10;35(3):574–80. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3322718/

47. Leary J, Pettitt DJ, Jovanovič L. Gestational diabetes guidelines in a HAPO world. Vol. 24, Best Practice and Research: Clinical Endocrinology and Metabolism. 2010. p. 673–85.

48. Polin RA, Fox WW, Abman SH. Fetal and Neonatal Physiology [Internet]. Elsevier Health Sciences; 2011. Available from: https://books.google.com.my/books?id=38X8Kc_YMMUC

49. Gilmartin A "Bird" H, Ural SH, Repke JT. Gestational Diabetes Mellitus. Rev Obstet Gynecol [Internet]. 2008;1(3):129–34. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2582643/

50. Negrato C, Gomes M. Historical facts of screening and diagnosing diabetes in pregnancy. Diabetol Metab Syndr [Internet]. 2013;5(1):22. Available from: http://www.dmsjournal.com/content/5/1/22

51. Carr DB, Utzschneider KM, Hull RL, Tong J, Wallace TM, Kodama K, et al. Gestational Diabetes Mellitus Increases the Risk of Cardiovascular Disease in Women With a Family History of Type 2 Diabetes. Diabetes Care [Internet]. 2006 Sep 1;29(9):2078–83. Available from: http://care.diabetesjournals.org/content/29/9/2078.abstract

52. Ley SH, Hanley AJ, Retnakaran R, Sermer M, Zinman B, O'Connor DL. Effect of macronutrient intake during the second trimester on glucose metabolism later in pregnancy. Am J Clin Nutr [Internet]. 2011 Nov 1;94(5):1232–40. Available from: http://ajcn.nutrition.org/content/94/5/1232.abstract

53. Chasan-Taber L, Silveira M, Lynch KE, Pekow P, Braun B, Manson JE, et al. Physical activity before and during pregnancy and risk of abnormal glucose tolerance among Hispanic women. Diabetes Metab [Internet]. 2014 Feb;40(1):67–75. Available from: http://www.sciencedirect.com/science/article/pii/S126236361300178X

Table 1. Schedule of measurements

Measurements	Study enrolment	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit	7th visit
	As early as possible (< 10 weeks)	10-13 weeks of gestation	24-32 weeks of gestation	34-38 weeks of gestation	6 months postpartum	12 months postpartum	18 months postpartum	24 months postpartum
Mother								
Socio-demographic	x							
Obstetrical information	x							
Anthropometric measurements								
Waist	x				x	x	x	x
Height	x							
Weight	x	x	x	x	x	x	x	x
Blood pressure	x	x	x	x	x	x	x	x
Biochemical								
Hemoglobin	x	x	x	x				
Fasting glucose	x				x			
Lipid profile	x				x			
Vitamin D	x				x			
OGTT			x					
Dietary intake								
FFQ	x	x	x	x				
24 dietary recall	x	x	x	x	x			
Physical activity	x	x	x	x	x			
Smoking		x						
Food insecurity			x					
Depression				x	x			
Birth information					x			

Table 1: Schedule of measurements (continue)

Measurements	Study enrolment	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit	7th visit
	As early as possible (< 10 weeks)	10-13th weeks of gestation	24-32nd weeks of gestation	34-38th weeks of gestation	6 months postpartum	12 months postpartum	18 months postpartum	24 months postpartum
Infant								
Anthropometric measurements								
Weight					x	x	x	x
Length					x	x	x	x
Head circumference					x	x	x	x
Waist circumference					x	x	x	x
Skinfold thickness					x	x	x	x
Arm circumference								
Postnatal environment								
Dietary intake					x	x	x	x
Infant feeding practices					x	x	x	x
Diet diversity					x	x	x	x

BMJ Open

Seremban Cohort Study (SECOST): A prospective cohort study of determinants and pregnancy outcomes of maternal glycemia in Malaysia

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018321.R1
Article Type:	Protocol
Date Submitted by the Author:	07-Oct-2017
Complete List of Authors:	yong, heng yaw; University Putra Malaysia, Nutrition and Dietetics MOHD SHARIFF, ZALILAH; University Putra Malaysia, Nutrition and Dietetics Rejali, Zulida; University Putra Malaysia, Department of Obstetrics and Gynaecology Mohd Yusof, Barakatun Nisak ; University Putra Malaysia, Nutrition and Dietetics Yasmin, Farah; University Putra Malaysia, Nutrition and Dietetics Palaniveloo, Lalitha; Institute for Public Health Malaysia, Center for Nutrition Epidemiology Research
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Nutrition and metabolism, Diabetes and endocrinology
Keywords:	DIABETES & ENDOCRINOLOGY, NUTRITION & DIETETICS, OBSTETRICS, PRIMARY CARE, PUBLIC HEALTH

Study protocol

Seremban Cohort Study (SECOST): A prospective study of determinants and pregnancy outcomes of maternal glycemia in Malaysia

Yong Heng Yaw[1], Zalilah Mohd Shariff[1]*, Zulida Rejali[2], Barakatun Nisak Mohd Yusof[1], Farah Yasmin[1], Lalitha Palaniveloo[3]

[1]Department of Nutrition and Dietetics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia

[2]Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia

[3]Center for Nutrition Epidemiology Research, Institute for Public Health, Ministry of Health Malaysia

* Corresponding author

Email: zalilahms@upm.edu.my

Abstract

Introduction: Both gestational diabetes mellitus (GDM) and hyperglycemia less severe than GDM are associated with risk of adverse pregnancy outcomes. We describe the study design of a prospective cohort of pregnant women recruited in early pregnancy with follow-ups of mothers and infants up to 2 years after birth. The primary aim of the study was to identify the determinants and outcomes of maternal glycemia.

Methods and analysis: Seremban Cohort Study (SECOST) is an on-going prospective cohort study in which eligible pregnant women in first trimester (< 10th weeks of gestation) are recruited from Maternal and Child Health (MCH) clinics in Seremban District, Negeri Sembilan with 7 follow-ups during pregnancy through 2 years postnatal. Infants are followed-up every 6 months after birth until 2 years old. A standard 75g Oral Glucose Tolerance Test (OGTT) is performed between 24th and 32nd of weeks of gestation and as close to 28th weeks of gestation. Pregnancy and birth information are obtained from medical records. Socio-demographic, anthropometric, biochemical, dietary, physical activity, smoking, depression, child feeding, and other data of mothers and infants are obtained at follow-ups.

Ethics and dissemination: This study is approved by the Medical Research Ethics Committee (MREC), Universiti Putra Malaysia (UPM/FPSK/100-9/2-MJKEtika) and the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (KKM/NIHSEC/08/0804/P12-613). Permission to conduct this study is also obtained from the Head of Seremban District Health Office. The research findings will be disseminated at journals and conference presentations.

Strengths and limitations of this study:

1. SECOST is the first prospective study in Malaysia to provide data on determinants and pregnancy outcomes of maternal glycemia.
2. Information on lifestyle factors and weight gain patterns during pregnancy will provide insight on determinants of maternal glycemia.
3. Data on birth and early child growth patterns will inform on the short and long-term outcomes of maternal glycemia.
4. The cohort of pregnant women and their off-springs may not represent the general population of pregnant women and infants in Malaysia due to the location of subject recruitment and study selection criteria.
5. High attrition rate of subjects during pregnancy and infancy is expected.

Introduction

During pregnancy, substantial changes occur in glucose, lipid and protein metabolism as to meet the increasing demands of the fetus. In a normal pregnancy, an increase in insulin resistance will reduce glucose uptake into maternal tissues as to make glucose more readily available for fetal growth. This hyperglycemic state is mainly due to the increased production of placental growth hormones that may interfere with insulin receptor's action and inhibit glucose uptake as pregnancy progresses [1]. Pregnant women will develop elevated blood glucose level (hyperglycemia) or gestational diabetes mellitus (GDM) if the mother's beta cells are unable to increase insulin secretion to compensate for the insulin resistance in pregnancy.

The international multicenter Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study reported that maternal fasting and stimulated glucose levels showed linear associations with risks of increased size at birth, caesarian delivery, neonatal hypoglycemia and fetal hyperinsulinemia (Metzger et al., 2008). On the basis of this landmark study, the International Association of Diabetes in Pregnancy Study Groups (IADPSG) and the American Diabetes Association (ADA) have recommended new lower diagnostic criteria for GDM (2). However, the use of these new criteria has resulted in a dramatic increase in the number of women diagnosed with GDM [3–5]. Increased health care cost and lack of improvement in maternal and infant outcomes are other concerns related to the new diagnostic criteria [6]. Thus, the optimal diagnostic threshold of GDM during pregnancy remains controversial.

Globally, the prevalence of GDM ranging from 1 to 14% of all pregnancies, depends on the population and diagnostic criteria of GDM [5]. In the United States, GDM affected 7% of all pregnancies annually [7]. In Europe, a 2 - 6% prevalence of GDM was reported with a lower prevalence in the Northern Europe (less than 4%) than in the Southern Europe (higher than 6%) [8]. Similarly, in Asian countries, the prevalence of GDM in China [9], Korea [10] and Thailand [11] were 6.8%, 2 – 5% and 5.7%, respectively. GDM rate in Malaysia (8 – 11%) [12,13] is much higher than those reported for most Asian populations (2 – 7%) [9–11]. As the rate of obesity increases among women, a parallel rise in GDM rate is inevitable. The National Health and Morbidity Survey (NHMS) reported that the prevalence of obesity in Malaysian women aged 18 years old and above increased from 5.7% in 1996 to 17.6% in 2011 [14,15]. As more women in reproductive age become overweight or obese prior to pregnancy, they will be at greater risk of maternal hyperglycemia.

At present, limited data are available on determinants and outcomes of hyperglycemia during pregnancy in Malaysia [13,16]. This study will provide important insights on lifestyle factors and weight gain patterns during pregnancy as determinants as well as birth and early child growth data as short and long-term outcomes of maternal glycemia. In light of increasing rates of child and adult obesity, GDM and diabetes mellitus and persistence of child under-nutrition in Malaysia, such information on intergenerational transmission of risk of obesity and non-communicable diseases are pertinent for planning effective strategies that best meet the needs and resources to achieve a future healthy generation.

Materials and methods

Study design

SECOST is an on-going prospective cohort study in which pregnant women and their infants are followed-up through 2 years postnatal. Women in the first trimester (< 10th weeks of gestation) of pregnancy are recruited from three [3] Maternal and Child Health (MCH) clinics in Seremban District, Negeri Sembilan, Malaysia. There are 7 follow-up visits for mothers (3 pregnancy and 4 postnatal visits) and 4 follow-up visits for infants at an interval of 6 months after birth (Table 1).

Participants

Pregnant women attending MCH clinics for antenatal booking are eligible to participate in the study upon screening based on study criteria:

Inclusion criteria:

Malaysian women (age more than 18 years) with singleton pregnancy, BMI ≥ 18.5 – < 40.0, normal glycemia at study enrolment (FPG 3.0 – 6.0 mmol/l) and free from any medical illness or obstetrics complications

Exclusion criteria:

Women with multiple pregnancies, became pregnant with assistance of advanced reproductive technology, unable to complete OGTT within 24 – 32nd weeks of gestation, pre-existing diabetes mellitus (FPG > 7.0 mmol/l), diagnosis of diabetes during this pregnancy, abnormal glycemia (FPG < 3.0 mmol/L or FPG > 6.0 mmol) at study enrolment, previous diagnosis of diabetes requiring treatment with medication outside of pregnancy, BMI > 40.0, other medical problems (e.g. HIV positive, Hepatitis B/C, hypertension, renal disease, anemia, thalassemia) at study enrolment.

Recruitment

Study information leaflet is given to all pregnant women attending the 3 MCH clinics for antenatal booking by nurses. Pregnant women who meet the selection criteria are invited to participate in the study. Study participation is on a voluntary basis and participants can withdraw from the study at any time during the study period. A study manual that outlines the details of study visits and measurements are given to participants. The period of recruitment is from 2013 – 2016.

Sample size

Sample size is estimated using a statistical formula for a proportion by Scheaffer, Mendenhall, Ott, & Gerow (2011). Based on 18.3% of pregnant women in Malaysia had abnormal OGTT [18], 95% confidence level and 5% probability of missing a true difference, a minimum of 230

pregnant women are required as study participants. To account for an attrition rate of 50%, the sample is increased to a minimum of 345 pregnant women.

Measurements

The schedule of measurements for mothers and infants at study enrolment and follow-up visits are summarized in Table 1.

Table 1. Schedule of measurements

Measurements	Study enrolment	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit	7th visit
	As early as possible (< 10 weeks)	10-13 weeks of gestation	24-32 weeks of gestation	34-38 weeks of gestation	6 months postpartum	12 months postpartum	18 months postpartum	24 months postpartum
Mother								
Socio-demographic	x							
Obstetrical information	x							
Anthropometric measurements								
Waist	x				x	x	x	x
Height	x							
Weight	x	x	x	x	x	x	x	x
Blood pressure	x	x	x	x	x	x	x	x
Biochemical								
Hemoglobin	x	x	x	x				
Fasting glucose	x				x			
Lipid profile	x				x			
Vitamin D	x				x			
OGTT			x					
Dietary intake								
FFQ	x	x	x	x				
24 dietary recall	x	x	x	x	x			
Physical activity	x	x	x	x	x			
Smoking		x						
Food insecurity			x					
Depression				x	x			
Birth information					x			

Table 1: Schedule of measurements (continue)

Measurements	Study enrolment	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit	7th visit
	As early as possible (< 10 weeks)	10-13th weeks of gestation	24-32nd weeks of gestation	34-38th weeks of gestation	6 months postpartum	12 months postpartum	18 months postpartum	24 months postpartum
Infant								
Anthropometric measurements								
Weight					x	x	x	x
Length					x	x	x	x
Head circumference					x	x	x	x
Waist circumference					x	x	x	x
Skinfold thickness					x	x	x	x
Arm circumference								
Postnatal environment								
Dietary intake					x	x	x	x
Infant feeding practices					x	x	x	x
Diet diversity					x	x	x	x

Mothers

Socio-demographics

The socio-demographic information obtained include current age, years of education, ethnicity, marital status, occupation, income, spouse's years of education, spouse's occupation, spouse's income and household income.

Dietary intake

Dietary intake is assessed using one day 24-hours diet recall and Food Frequency Questionnaire (FFQ).

1. Energy and nutrient intakes

A 24-hour diet recall is used to obtain dietary information. Standard household measuring cups, glasses, bowls and spoons are used to assist respondents to estimate food portion size. Dietary data are analysed using Nutritionist Pro Diet Analysis software [19] and comparison of energy and nutrient intakes is made to the Malaysian Recommended Nutrient Intake [20] to determine intake adequacy. Intakes of grains, meat, fish, legumes, fruits, vegetables and dairy product (gram/day) are calculated as number of servings and compared to the Malaysian Dietary Guidelines [21].

2. Alcohol use

The frequency of drinking alcohol and amount of alcohol (glass) are obtained.

3. Energy density

Energy density is calculated by dividing each subject's daily energy intakes (in kilocalories) by the reported weight of all foods consumed (in grams) [22].

4. Dietary pattern

Food Frequency Questionnaire (FFQ) is utilized to assess food consumption patterns. There are 12 main food groups with 50 sub-food groups which include cereals, meat and meat products, fish and seafood, eggs, fruits, vegetables, legumes and nuts, milk and dairy products, fat and oil, sugar and sugary food, flavouring and beverages [23]. Dietary patterns are determined based on standard procedures [24,25].

5. Dietary glycemic index and glycemic load

Dietary glycemic index (GI) and glycemic load (GL) are calculated from Food Frequency Questionnaire and 24-hour dietary recall. The GI values will be categorized into low GI: ≤55, medium GI: 56 – 70 and high GI: >70. The formulae to calculate dietary GI and GL as used are [26–28]:

Dietary glycemic index = [Glycemic index value of the food x Frequency of servings of the food per day (g) x carbohydrate content of the food (%)] / Total daily carbohydrate (g)

Dietary glycemic load = [Glycemic index value of the food x Frequency of servings of the food per day (g) x carbohydrate content of the food (%)]

Physical activity

Pregnancy Physical Activity Questionnaire (PPAQ) is used to determine physical activity of pregnant women [29]. The PPAQ is a semi quantitative questionnaire that requires participants to report the time spent participating in 32 activities including household/care giving (13 activities), occupational (5 activities), sports/exercise (8 activities), transportation (3 activities), and inactivity (3 activities).

Anthropometry

Weight, height and waist circumference are measured at study enrolment (antenatal booking) using standard instrument (SECA digital weighing scale, SECA body meter and SECA measuring tape). Pre-pregnancy body weight (current pregnancy) and weight at the beginning of first pregnancy are obtained from medical record. Pre-pregnancy BMI is calculated as pre-pregnancy weight (kg) divided by recommendation of World Health Organization [30]. Inter-pregnancy weight change is defined as the difference between weight at the beginning of the first and current pregnancies. Postpartum weight retention is calculated as the absolute difference between weight measured at each of 4th and 5th visit and pre-pregnancy weight. Total gestational weight gain is defined as the difference between measured weight at last prenatal visit and pre-pregnancy weight. Rate of weight gain in first, second or third trimester is defined as the average weekly weight gain in that trimester.

Biochemical

A standard 75g OGTT is performed at 2 time points. The first OGTT is performed for all participants at 10 – 13th weeks of gestation. The second OGTT is performed between 24th and 32nd weeks of gestation (2nd visit) and as close to 28th weeks of gestation as possible. A 2ml fasting venous blood is drawn prior to ingestion of a standard glucose solution. Another 2 ml of venous blood is drawn at 2-hours after ingestion of standard glucose solution. All blood samples are sent for analysis on the same day to determine fasting glucose, 2-hr plasma glucose concentration. Additional blood (3ml) is obtained for analysis of total cholesterol, HDL-cholesterol, triglycerides and vitamin D. Normal fasting plasma glucose for pregnant women is

defined according to the Ministry of Health (MOH) (3.0 mmol/l to < 6.0 mmol/l). The cut off values for serum lipid is according to the National Cholesterol Education Program Adult Treatment Panel III [31] guidelines. Vitamin D cut offs for severe deficiency, mild deficiency, insufficiency and sufficiency are < 25 nmol/L, 25 – <50 nmol/L, 50 – <75 nmol/L and ≥ 75 nmol/L, respectively [32].

Blood pressure

Right arm systolic blood pressure (SBP) and diastolic blood pressure (DBP) is measured using OMRON SEM-1 Automatic Blood Pressure Monitor by trained nurses.

Smoking habit

The status of smoking, frequency of smoking and number of cigarettes smoked are obtained.

Food insecurity

A 10 items questionnaire is use to assess women food insecurity. All items are rated on a 3 response point ranging from always, sometimes or never [33]

Depression

Depression during pregnancy and postpartum depression is assessed using a self-administered 10 question Edinburg Postnatal Depression Scale (EPDS) [34]

Maternal birth information

1. Delivery

Mode of birth (normal vaginal birth, assisted breech delivery, instrumental delivery or caesarean section) and gestational age at birth are obtained from medical record. Premature birth is defined as childbirth occurring at less than 37 completed weeks of gestation or 259 days of gestation [35].

2. Birth information of infants

Birth data are obtained from medical record. Birth weight is categorized according to the recommendation of United Nations Children's Fund (UNICEF) and World Health Organization [36]. SGA is defined as an infant weighing less than 10th percentile of birth weight. An infant with >90th percentile of birth weight was classified as large-for-gestational age (LGA), while an infant with the 10th-90th percentile of birth weight as appropriate-for-gestational-age (AGA) [37].

Infants

1. Anthropometry

All infants are measured for weight (to the nearest 0.1 kg), length (to the nearest 0.1 cm), head circumference and mid arm circumference (to the nearest 0.1 cm) using TANITA digital baby weighing scale with recumbent length meter and SECA fibreglass measuring tape, respectively. Infants are measured using standard procedures as described by Gibson, (2005) [38]. Growth data are analyzed using Anthro Plus software that utilizes World Health Organization growth standard [39]. Five growth indicators (weight-for-age, weight-for-height, height-for-age, head circumference-for-age and BMI-age) will be determined. In order to assess subcutaneous fat,

triceps and subscapular are measured using Harpenden Skinfold Caliper and recorded to the nearest 0.1mm [40].

2. Dietary intake

A 24-hour diet recall is used to obtain dietary information of infants from parents / guardians with the aid of standard household measurements. Dietary data are then analysed for adequacy of energy and nutrients [19, 20] as well as dietary diversity [41]. Parents are also interviewed on infant feeding practices (e.g. milk feeding, complementary feeding).

Data collection

All enumerators are given an intensive briefing and field training before data collection. Study visits are scheduled on the same day of appointments at MCH clinics. A day before each visit, enumerators are required to remind participants of their clinic appointments through telephone calls. During the visits, participants are interviewed or measured for relevant data. For participants who are not able to be interviewed at the clinics, home visits or telephone interviews are carried out by enumerators.

Data Analysis

Data will be analyzed using IBM SPSS Statistic 22. Descriptive statistics (mean, standard deviation, median, frequency) will be used to describe the data. Multiple logistic regression will be used to determine the relationship between predictors and maternal glycemia, as well as the relationship between maternal glycemia with pregnancy outcomes controlling for confounding variables. Significant level for all statistical analysis will be set at $p<0.05$.

Discussion

Globally, the prevalence of overweight and obesity is increasing among women, particularly during reproductive years. A study on trends of obesity in the United States (US) showed that the prevalence of obesity (BMI ≥ 30 kg/m^2) in US women aged 20 – 39 years increased from 28.4% in 1999 to 34.0% in 2007 [42]. In the Malaysian National Health and Morbidity Survey 1996 (NHMS II), women showed a significantly higher prevalence of obesity (BMI ≥ 30kg/m^2) (17.5%) than man (10.2%). In the period between the NHMS II (1996) and the NHMS (2011), there was an 11.9% increase in the prevalence of obesity (BMI ≥ 30kg/m^2) among females aged ≥18 years old. With increasing prevalence of obesity among women of childbearing age, the risk of having higher pre-pregnancy BMI and excessive gestational weight gain are inevitable [43,44]. These conditions could further increase the risk of pregnant women to have higher blood glucose level and subsequently poor pregnancy outcomes.

Studies have shown that women with hyperglycemia during pregnancy are at higher risk for poor pregnancy outcomes, such as caesarean delivery, pregnancy induced hypertension and preeclampsia [18,45,46]. Apart from that, mothers with hyperglycemia during pregnancy tend to have large-for-gestational-age (LGA) infants and infants with asphyxia and hypoglycemia [46–48]. These conditions can lead to other long-term child health problems such as obesity, type II diabetes, cancer and cardiovascular disease in later life. For the mothers with hyperglycemia, they are at higher risk of developing cardiovascular disease and overt diabetes, mainly type 2 diabetes in later life [49–51]. However, there is no clear threshold above which women are at high risk and below which they are at low risk. Moreover, the impact of maternal hyperglycemia,

which is characterized by value of glucose tolerance intermediate between normal and gestational diabetes on outcomes of pregnancy remains unclear.

Dietary intake and physical activity are important modifiable risk factors for the development of type 2 diabetes, as well as gestational hyperglycemia. While higher total fat and lower carbohydrate intakes during second trimester of pregnancy were associated with maternal hyperglycemia [52], pregnant women in the high quartile of moderate intensity activity and occupational activity during early pregnancy had about 50% decreased risk of abnormal glucose tolerance [53]. A lower energy intake and higher physical activity are known to improve insulin sensitivity and reduce glucose levels, however, there is less information on dietary nutrients intakes, particularly fat types, vitamin D and iron related to maternal hyperglycemia, as well as the optimal distribution of macronutrient intakes during pregnancy to prevent maternal hyperglycemia. Therefore, there is a need for a better understanding of the role of lifestyle factors, especially energy and nutrient intakes, physical activity and sedentary behavior in the development of maternal hyperglycemia.

SECOST is the first prospective study in Malaysia to provide a better understanding of weight gain and lifestyle patterns from early pregnancy until 1 year postpartum and to quantitate the relationship between maternal glucose levels and pregnancy outcomes. As GDM impacts maternal and fetal health, detailed information on lifestyle factors, biochemical parameters and weight gain patterns during pregnancy can provide insight on determinants of maternal glycemia. Data on early child growth and development obtained periodically will not only provide information on short and long-term outcomes of maternal glycemia but also indicate the role of

environment (e.g. infant feeding, diet, parent-infant interaction, home environment) that could potentially impact child growth and development. Despite the modest sample size, this pregnancy cohort study provides an opportunity for many hypotheses related to maternal and infant health and nutrition to be tested or confirmed. SECOST is expected to provide valuable data that can be used not only for strengthening existing strategies but also formulating new strategies that are in accordance with promoting maternal and child health.

Ethics and dissemination

This study is approved by the Medical Research Ethics Committee (MREC), Universiti Putra Malaysia (UPM/FPSK/100-9/2-MJKEtika) and the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (KKM/NIHSEC/08/0804/P12-613). Permission to conduct this study is also obtained from the Head of Seremban District Health Office. All participants are required to provide written informed consent prior to data collection. The research findings will be disseminated through publications and conference presentations. Data sharing is available upon request.

Acknowledgements

The authors would like to thank all women and infants who took part in this study and all nurses, and staff in MCH clinics of Seremban district, Negeri Sembilan for their assistance during data collection.

Author's contributions

ZMS – conceptualized and designed the study; contributed to the development of study protocol; supervise data collection; read, revised and approved the final draft of manuscript

YHY – conceptualized and designed the study; contributed to the development of study protocol; involve in data collection; drafted the manuscript

ZR and BNMY – contributed to the development of study protocol; read and approved the manuscript

FY and LP – involve in data collection

Study funding

Funding is provided by Danone Dumex (Malaysia) Shd. Bhd.

Competing interests

Although SECOST is funded by the Danone Dumex (Malaysia) Shd. Bhd, the company does not influence the study protocol and preparation of this manuscript. As the nature of this study is more of exploratory and does not involve any testing of company product, the researchers are free to report any findings of this study in future publications. All authors declare that they have no competing interests.

References

1. Perkins JM, Dunn JP, Jagasia SM. Perspectives in Gestational Diabetes Mellitus: A Review of Screening, Diagnosis, and Treatment. Vol. 25, Clinical Diabetes. 2007. p. 57–62.
2. Panel IA of D and PSGC. International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. Diabetes Care [Internet]. 2010 Mar 1;33(3):676–82. Available from: http://care.diabetesjournals.org/content/33/3/676.short
3. Cundy T, Ackermann E, Ryan E a. Gestational diabetes : new criteria may triple the prevalence but effect on outcomes is unclear. Bmj [Internet]. 2014;1567(March):1–5. Available from: http://dx.doi.org/doi:10.1136/bmj.g1567
4. Blackwell SC. Enough evidence to treat? The American College of Obstetricians and Gynecologists Guidelines. Clin Chem. 2012;58(7):1098–100.
5. Coustan DR. Medical Management of Pregnancy Complicated by Diabetes [Internet]. Coustan DR, editor. American Diabetes Association; 2013. 188 pages. Available from: https://books.google.com.my/books?id=NDbQlAEACAAJ
6. Langer O, Umans JG, Miodovnik M. Perspectives on the proposed gestational diabetes mellitus diagnostic criteria. Obstet Gynecol. 2013 Jan;121(1):177–82.
7. Hillier TA, Vesco KK, Pedula KL, Beil TL, Whitlock EP, Pettitt DJ. Screening for gestational diabetes mellitus: A systematic review for the U.S. preventive services task force. Vol. 148, Annals of Internal Medicine. 2008. p. 766–75.
8. Buckley BS, Harreiter J, Damm P, Corcoy R, Chico A, Simmons D, et al. Gestational diabetes mellitus in Europe: Prevalence, current screening practice and barriers to

screening. A review. Vol. 29, Diabetic Medicine. 2012. p. 844–54.

9. Zhang Y, Peck K, Spalding M, Xu T, Ragain M. A study to examine the attitudes, knowledge, and utilization of CAM by primary care professional in West Texas. Complement Ther Med. 2010;18:227–32.

10. Jang HC. Gestational diabetes in Korea: incidence and risk factors of diabetes in women with previous gestational diabetes. Diabetes Metab J [Internet]. 2011;35(1):1–7. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3080571&tool=pmcentrez&rendertype=abstract

11. Sumeksri P, Wongyai S, Aimpun P. Prevalence of gestational diabetes mellitus (GDM) in pregnant women aged 30 to 34 years old at Phramongkutklao Hospital. J Med Assoc Thai. 2006;89(Suppl 4):S94-9.

12. Kwapisz J, Bodaghi M. Preliminary Report of National Obstetrics Registry, Jan-December 2010. Jeganathan R, Karalasingam SD, editors. Kuala Lumpur, Malaysia, Malaysia: Jointly published by the National Obstetrics Registry and the Clinical Research Centre (CRC), Ministry of Health Malaysia.; 2013. 1-24 p.

13. Tan PC, Ling LP, Omar SZ. Screening for gestational diabetes at antenatal booking in a Malaysian university hospital: The role of risk factors and threshold value for the 50-g glucose challenge test. Aust New Zeal J Obstet Gynaecol. 2007;47:191–7.

14. IPH. National Health and Morbidity Survey 2011 (NHMS 2011). Ministry of Health Malaysia. Kuala Lumpur.: Institute for Public Health. Ministry of Health, Malaysia; 2011. 258 pages.

15. IPH. The Second National Health and Morbidity Study (NHMS 2). Ministry of Health

Malaysia. Kuala Lumpur.: Institute for Public Health. Ministry of Health, Malaysia; 1996.

16. Kampan N, Azman H, Hafiz I, Mohammad H, Yee CS, Azurah N, et al. Outcome of pregnancy among Malaysian women with diabetes mellitus - A single centre experience. Malaysian J Public Heal Med. 2013;13(2):1–10.

17. Scheaffer R, Mendenhall W, Ott R, Gerow K. Elementary Survey Sampling [Internet]. 7th ed. Cengage Learning; 2011. 480 pages. (Advanced series). Available from: https://books.google.com.my/books?id=TbSjtoy4p-8C

18. Nordin NM, Wei JWH, Naing NN, Symonds EM. Comparison of maternal-fetal outcomes in gestational diabetes and lesser degrees of glucose intolerance. J Obstet Gynaecol Res. 2006 Feb;32(1):107–14.

19. Axxya Systems LLC. Nutritionist Pro Diet Analysis [Internet]. 2011. Available from: http://www.axxya.com/products.html.

20. National Coordinating Committee on Food and Nutrition. Recommended Nutrient Intakes for Malaysia. A Report of the Technical Working Group on Nutritional Guidelines. Ministry of Health Malaysia, Putrajaya.; 2005.

21. National Coordinating Committee on Food and Nutrition. Malaysian Dietary Guidelines 2010. A Report of the Technical Working Group on Nutritional Guidelines. [Internet]. Vol. 1. Ministry of Health Malaysia, Putrajaya.; 2010. Available from: http://www.moh.gov.my/images/gallery/Garispanduan/diet/introduction.pdf

22. Ledikwe JH, Blanck HM, Kettel Khan L, Serdula MK, Seymour JD, Tohill BC, et al. Dietary energy density is associated with energy intake and weight status in US adults. Am J Clin Nutr. 2006 Jun;83(6):1362–8.

23. Ministry of Health Malaysia. The Malaysian Adults Nutrition Survey (MANS)-Findings

Report 2003. Nutrition Section Family Health Development Division, Putrajaya: Ministry of Health Malaysia, Malaysia; 2007.

24. Randall E, Marshall JR, Graham S, Brasure J. Patterns in food use and their associations with nutrient intakes. Am J Clin Nutr [Internet]. 1990 Oct 1;52(4):739–45. Available from: http://ajcn.nutrition.org/content/52/4/739.abstract

25. Nicklas TA, Webber LS, Thompson B, Berenson GS. A multivariate model for assessing eating patterns and their relationship to cardiovascular risk factors: the Bogalusa Heart Study. Am J Clin Nutr. 1989 Jun;49(6):1320–7.

26. Sieri S, Krogh V, Berrino F, Evangelista A, Agnoli C, Brighenti F, et al. Dietary glycemic load and index and risk of coronary heart disease in a large italian cohort: the EPICOR study. Arch Intern Med. 2010 Apr;170(7):640–7.

27. Villegas R, Liu S, Gao Y-T, Yang G, Li H, Zheng W, et al. Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2 diabetes mellitus in middle-aged Chinese women. Arch Intern Med. 2007 Nov;167(21):2310–6.

28. Liu S, Willett W. Dietary glycemic load and atherothrombotic risk. Curr Atheroscler Rep [Internet]. 2002;4(6):454–61. Available from: http://dx.doi.org/10.1007/s11883-002-0050-2

29. Chasan-Taber L, Schmidt MD, Roberts DE, Hosmer D, Markenson G, Freedson PS. Development and validation of a Pregnancy Physical Activity Questionnaire. Med Sci Sports Exerc. 2004 Oct;36(10):1750–60.

30. WHO. Physical status: The Use and Interpretation of Anthropometry. Report of a WHO Expert Committee. World Health Organization, editor. Geneva: WHO Technical Report Series No. 854.; 1995.

31. NCEP. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002 Dec;106(25):3143–421.

32. Hamid Jan, Mohamed, Angela R, Bertram F, Loy SL. Maternal serum and breast milk vitamin D levels: findings from the Universiti Sains Malaysia Pregnancy Cohort Study. PLoS One. 2014;9(7):e100705.

33. Radimer KL, Olson CM, Campbell CC. Development of indicators to assess hunger. J Nutr. 1990 Nov;120 Suppl(December 1989):1544–8.

34. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987 Jun;150:782–6.

35. WHO. International classification of diseases and related health problems. 10th ed. World Health Organization, editor. Geneva.; 1992.

36. UNCF/WHO. Low Birthweight: Country, regional and global estimates. UNICEF, New York. United Nations Children's Fund and World Health Organization, editor. UNICEF, New York; 2004.

37. Bukowski R, Hansen NI, Willinger M, Reddy UM, Parker CB, Pinar H, et al. Fetal Growth and Risk of Stillbirth: A Population-Based Case–Control Study. Fisk NM, editor. PLoS Med [Internet]. 2014 Apr 22;11(4):e1001633. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3995658/

38. Gibson RS. Principles of Nutritional Assessment [Internet]. Oxford University Press; 2005. 908 pages. Available from: https://books.google.com.my/books?id=lBlu7UKI3aQC

39. WHO. Training Course on Child Growth Assessment. [Internet]. World Health Oraganization, editor. Geneva, WHO; 2008. Available from:

http://www.who.int/childgrowth/software/en/

40. Dauncey MJ, Gandy G, Gairdner D. Assessment of total body fat in infancy from skinfold thickness measurements. Arch Dis Child. 1977;52(August 1976):223–7.

41. Food and Agriculture Organization and Food and Nutrition Technical Assistance Project. Guidelines for measuring household and individual dietary diversity. Rome, Italy; 2013.

42. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among us adults, 1999-2008. JAMA [Internet]. 2010;303(3):235–41. Available from: http://dx.doi.org/10.1001/jama.2009.2014

43. Gunderson EP. Childbearing and Obesity in Women: Weight Before, During, and After Pregnancy. Vol. 36, Obstetrics and Gynecology Clinics of North America. 2009. p. 317–32.

44. Li N, Liu E, Guo J, Pan L, Li B, Wang P, et al. Maternal prepregnancy body mass index and gestational weight gain on pregnancy outcomes. PLoS One [Internet]. 2013 Dec 20;8(12):e82310. Available from: http://dx.doi.org/10.1371%252Fjournal.pone.0082310

45. Catalano PM, Tyzbir ED, Wolfe RR, Calles J, Roman NM, Amini SB, et al. Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. Am J Physiol [Internet]. 1993;264(1 Pt 1):E60–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8430789

46. Lowe LP, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TRJ, et al. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: Associations of maternal A1C and glucose with pregnancy outcomes. Diabetes Care [Internet]. 2012 Mar 10;35(3):574–80. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3322718/

47. Leary J, Pettitt DJ, Jovanovič L. Gestational diabetes guidelines in a HAPO world. Vol. 24, Best Practice and Research: Clinical Endocrinology and Metabolism. 2010. p. 673–85.

48. Polin RA, Fox WW, Abman SH. Fetal and Neonatal Physiology [Internet]. Elsevier Health Sciences; 2011. Available from: https://books.google.com.my/books?id=38X8Kc_YMMUC

49. Gilmartin A "Bird" H, Ural SH, Repke JT. Gestational Diabetes Mellitus. Rev Obstet Gynecol [Internet]. 2008;1(3):129–34. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2582643/

50. Negrato C, Gomes M. Historical facts of screening and diagnosing diabetes in pregnancy. Diabetol Metab Syndr [Internet]. 2013;5(1):22. Available from: http://www.dmsjournal.com/content/5/1/22

51. Carr DB, Utzschneider KM, Hull RL, Tong J, Wallace TM, Kodama K, et al. Gestational Diabetes Mellitus Increases the Risk of Cardiovascular Disease in Women With a Family History of Type 2 Diabetes. Diabetes Care [Internet]. 2006 Sep 1;29(9):2078–83. Available from: http://care.diabetesjournals.org/content/29/9/2078.abstract

52. Ley SH, Hanley AJ, Retnakaran R, Sermer M, Zinman B, O'Connor DL. Effect of macronutrient intake during the second trimester on glucose metabolism later in pregnancy. Am J Clin Nutr [Internet]. 2011 Nov 1;94(5):1232–40. Available from: http://ajcn.nutrition.org/content/94/5/1232.abstract

53. Chasan-Taber L, Silveira M, Lynch KE, Pekow P, Braun B, Manson JE, et al. Physical activity before and during pregnancy and risk of abnormal glucose tolerance among Hispanic women. Diabetes Metab [Internet]. 2014 Feb;40(1):67–75. Available from: http://www.sciencedirect.com/science/article/pii/S126236361300178X

BMJ Open

Seremban Cohort Study (SECOST): A prospective study of determinants and pregnancy outcomes of maternal glycemia in Malaysia

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018321.R2
Article Type:	Protocol
Date Submitted by the Author:	17-Nov-2017
Complete List of Authors:	yong, heng yaw; University Putra Malaysia, Nutrition and Dietetics MOHD SHARIFF, ZALILAH; University Putra Malaysia, Nutrition and Dietetics Rejali, Zulida; University Putra Malaysia, Department of Obstetrics and Gynaecology Mohd Yusof, Barakatun Nisak ; University Putra Malaysia, Nutrition and Dietetics Yasmin, Farah; University Putra Malaysia, Nutrition and Dietetics Palaniveloo, Lalitha; Institute for Public Health Malaysia, Center for Nutrition Epidemiology Research
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Nutrition and metabolism, Diabetes and endocrinology
Keywords:	DIABETES & ENDOCRINOLOGY, NUTRITION & DIETETICS, OBSTETRICS, PRIMARY CARE, PUBLIC HEALTH

Study protocol

Seremban Cohort Study (SECOST): A prospective study of determinants and pregnancy outcomes of maternal glycemia in Malaysia

Yong Heng Yaw[1], Zalilah Mohd Shariff[1]*, Zulida Rejali[2], Barakatun Nisak Mohd Yusof[1], Farah Yasmin[1], Lalitha Palaniveloo[3]

[1]Department of Nutrition and Dietetics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia

[2]Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia

[3]Center for Nutrition Epidemiology Research, Institute for Public Health, Ministry of Health Malaysia

* Corresponding author

Email: zalilahms@upm.edu.my

Abstract

Introduction: Both gestational diabetes mellitus (GDM) and hyperglycemia less severe than GDM are associated with risk of adverse pregnancy outcomes. We describe the study design of a prospective cohort of pregnant women recruited in early pregnancy with follow-ups of mothers and infants up to 2 years after birth. The primary aim of the study was to identify the determinants and outcomes of maternal glycemia.

Methods and analysis: Seremban Cohort Study (SECOST) is an on-going prospective cohort study in which eligible pregnant women in first trimester (< 10th weeks of gestation) are recruited from Maternal and Child Health (MCH) clinics in Seremban District, Negeri Sembilan with 7 follow-ups during pregnancy through 2 years postnatal. Infants are followed-up every 6 months after birth until 2 years old. A standard 75g Oral Glucose Tolerance Test (OGTT) is performed between 24th and 32nd of weeks of gestation and as close to 28th weeks of gestation. Pregnancy and birth information are obtained from medical records. Socio-demographic, anthropometric, biochemical, dietary, physical activity, smoking, depression, child feeding, and other data of mothers and infants are obtained at follow-ups.

Ethics and dissemination: This study is approved by the Medical Research Ethics Committee (MREC), Universiti Putra Malaysia (UPM/FPSK/100-9/2-MJKEtika) and the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (KKM/NIHSEC/08/0804/P12-613). Permission to conduct this study is also obtained from the Head of Seremban District Health Office. The research findings will be disseminated at journals and conference presentations.

Strengths and limitations of this study:

1. SECOST is the first prospective study in Malaysia to provide data on determinants and pregnancy outcomes of maternal glycemia.
2. Information on lifestyle factors and weight gain patterns during pregnancy will provide insight on determinants of maternal glycemia.
3. Data on birth and early child growth patterns will inform on the short and long-term outcomes of maternal glycemia.
4. The cohort of pregnant women and their off-springs may not represent the general population of pregnant women and infants in Malaysia due to the location of subject recruitment and study selection criteria.
5. High attrition rate of subjects during pregnancy and infancy is expected.

Introduction

During pregnancy, substantial changes occur in glucose, lipid and protein metabolism as to meet the increasing demands of the fetus. In a normal pregnancy, an increase in insulin resistance will reduce glucose uptake into maternal tissues as to make glucose more readily available for fetal growth. This hyperglycemic state is mainly due to the increased production of placental growth hormones that may interfere with insulin receptor's action and inhibit glucose uptake as pregnancy progresses [1]. Pregnant women will develop elevated blood glucose level (hyperglycemia) or gestational diabetes mellitus (GDM) if the mother's beta cells are unable to increase insulin secretion to compensate for the insulin resistance in pregnancy.

The international multicenter Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study reported that maternal fasting and stimulated glucose levels showed linear associations with risks of increased size at birth, caesarian delivery, neonatal hypoglycemia and fetal hyperinsulinemia (Metzger et al., 2008). On the basis of this landmark study, the International Association of Diabetes in Pregnancy Study Groups (IADPSG) and the American Diabetes Association (ADA) have recommended new lower diagnostic criteria for GDM (2). However, the use of these new criteria has resulted in a dramatic increase in the number of women diagnosed with GDM [3–5]. Increased health care cost and lack of improvement in maternal and infant outcomes are other concerns related to the new diagnostic criteria [6]. Thus, the optimal diagnostic threshold of GDM during pregnancy remains controversial.

Globally, the prevalence of GDM ranging from 1 to 14% of all pregnancies, depends on the population and diagnostic criteria of GDM [5]. In the United States, GDM affected 7% of all pregnancies annually [7]. In Europe, a 2 - 6% prevalence of GDM was reported with a lower prevalence in the Northern Europe (less than 4%) than in the Southern Europe (higher than 6%) [8]. Similarly, in Asian countries, the prevalence of GDM in China [9], Korea [10] and Thailand [11] were 6.8%, 2 – 5% and 5.7%, respectively. GDM rate in Malaysia (8 – 11%) [12,13] is much higher than those reported for most Asian populations (2 – 7%) [9–11]. As the rate of obesity increases among women, a parallel rise in GDM rate is inevitable. The National Health and Morbidity Survey (NHMS) reported that the prevalence of obesity in Malaysian women aged 18 years old and above increased from 5.7% in 1996 to 17.6% in 2011 [14,15]. As more women in reproductive age become overweight or obese prior to pregnancy, they will be at greater risk of maternal hyperglycemia.

At present, limited data are available on determinants and outcomes of hyperglycemia during pregnancy in Malaysia [13,16]. This study will provide important insights on lifestyle factors and weight gain patterns during pregnancy as determinants as well as birth and early child growth data as short and long-term outcomes of maternal glycemia. In light of increasing rates of child and adult obesity, GDM and diabetes mellitus and persistence of child under-nutrition in Malaysia, such information on intergenerational transmission of risk of obesity and non-communicable diseases are pertinent for planning effective strategies that best meet the needs and resources to achieve a future healthy generation.

Materials and methods

Study design

SECOST is an on-going prospective cohort study in which pregnant women and their infants are followed-up through 2 years postnatal. Women in the first trimester (< 10th weeks of gestation) of pregnancy are recruited from three [3] Maternal and Child Health (MCH) clinics in Seremban District, Negeri Sembilan, Malaysia. There are 7 follow-up visits for mothers (3 pregnancy and 4 postnatal visits) and 4 follow-up visits for infants at an interval of 6 months after birth (Table 1).

Participants

Pregnant women attending MCH clinics for antenatal booking are eligible to participate in the study upon screening based on study criteria:

Inclusion criteria:

Malaysian women (age more than 18 years) with singleton pregnancy, BMI ≥ 18.5 – < 40.0, normal glycemia at study enrolment (FPG 3.0 – 6.0 mmol/l) and free from any medical illness or obstetrics complications

Exclusion criteria:

Women with multiple pregnancies, became pregnant with assistance of advanced reproductive technology, unable to complete OGTT within 24 – 32nd weeks of gestation, pre-existing diabetes mellitus (FPG > 7.0 mmol/l), diagnosis of diabetes during this pregnancy, abnormal glycemia (FPG < 3.0 mmol/L or FPG > 6.0 mmol) at study enrolment, previous diagnosis of diabetes requiring treatment with medication outside of pregnancy, BMI > 40.0, other medical problems (e.g. HIV positive, Hepatitis B/C, hypertension, renal disease, anemia, thalassemia) at study enrolment.

Recruitment

Study information leaflet is given to all pregnant women attending the 3 MCH clinics for antenatal booking by nurses. Pregnant women who meet the selection criteria are invited to participate in the study. Study participation is on a voluntary basis and participants can withdraw from the study at any time during the study period. A study manual that outlines the details of study visits and measurements are given to participants. The period of recruitment is from 2013 – 2016.

Sample size

Sample size is estimated using a statistical formula for a proportion by Scheaffer, Mendenhall, Ott, & Gerow (2011) [17]. Based on 18.3% of pregnant women in Malaysia had abnormal OGTT [18], 95% confidence level and 5% probability of missing a true difference, a minimum of 230

pregnant women are required as study participants. To account for an attrition rate of 50%, the sample is increased to a minimum of 345 pregnant women.

Measurements

The schedule of measurements for mothers and infants at study enrolment and follow-up visits are summarized in Table 1.

Table 1. Schedule of measurements

Measurements	Study enrolment	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit	7th visit
	As early as possible (< 10 weeks)	10-13 weeks of gestation	24-32 weeks of gestation	34-38 weeks of gestation	6 months postpartum	12 months postpartum	18 months postpartum	24 months postpartum
Mother								
Socio-demographic	x							
Obstetrical information	x							
Anthropometric measurements								
Waist	x				x	x	x	x
Height	x							
Weight	x	x	x	x	x	x	x	x
Blood pressure	x	x	x	x	x	x	x	x
Biochemical								
Hemoglobin	x	x	x	x				
Fasting glucose	x				x			
Lipid profile	x				x			
Vitamin D	x				x			
OGTT			x					
Dietary intake								
FFQ	x	x	x	x				
24 dietary recall	x	x	x	x	x			
Physical activity	x	x	x	x	x			
Smoking		x						
Food insecurity			x					
Depression				x	x			
Birth information					x			

Table 1: Schedule of measurements (continue)

Measurements	Study enrolment	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit	7th visit
	As early as possible (< 10 weeks)	10-13th weeks of gestation	24-32nd weeks of gestation	34-38th weeks of gestation	6 months postpartum	12 months postpartum	18 months postpartum	24 months postpartum
Infant								
Anthropometric measurements								
Weight					x	x	x	x
Length					x	x	x	x
Head circumference					x	x	x	x
Waist circumference					x	x	x	x
Skinfold thickness					x	x	x	x
Arm circumference								
Postnatal environment								
Dietary intake					x	x	x	x
Infant feeding practices					x	x	x	x
Diet diversity					x	x	x	x

Mothers

Socio-demographics

The socio-demographic information obtained include current age, years of education, ethnicity, marital status, occupation, income, spouse's years of education, spouse's occupation, spouse's income and household income.

Dietary intake

Dietary intake is assessed using one day 24-hours diet recall and Food Frequency Questionnaire (FFQ).

1. Energy and nutrient intakes

A 24-hour diet recall is used to obtain dietary information. Standard household measuring cups, glasses, bowls and spoons are used to assist respondents to estimate food portion size. Dietary data are analysed using Nutritionist Pro Diet Analysis software [19] and comparison of energy and nutrient intakes is made to the Malaysian Recommended Nutrient Intake [20] to determine intake adequacy. Intakes of grains, meat, fish, legumes, fruits, vegetables and dairy product (gram/day) are calculated as number of servings and compared to the Malaysian Dietary Guidelines [21].

2. Alcohol use

The frequency of drinking alcohol and amount of alcohol (glass) are obtained.

3. Energy density

Energy density is calculated by dividing each subject's daily energy intakes (in kilocalories) by the reported weight of all foods consumed (in grams) [22].

4. Dietary pattern

Food Frequency Questionnaire (FFQ) is utilized to assess food consumption patterns. There are 12 main food groups with 50 sub-food groups which include cereals, meat and meat products, fish and seafood, eggs, fruits, vegetables, legumes and nuts, milk and dairy products, fat and oil, sugar and sugary food, flavouring and beverages [23]. Dietary patterns are determined based on standard procedures [24,25].

5. Dietary glycemic index and glycemic load

Dietary glycemic index (GI) and glycemic load (GL) are calculated from Food Frequency Questionnaire and 24-hour dietary recall. The GI values will be categorized into low GI: ≤55, medium GI: 56 – 70 and high GI: >70. The formulae to calculate dietary GI and GL as used are [26–28]:

Dietary glycemic index = [Glycemic index value of the food x Frequency of servings of the food per day (g) x carbohydrate content of the food (%)] / Total daily carbohydrate (g)

Dietary glycemic load = [Glycemic index value of the food x Frequency of servings of the food per day (g) x carbohydrate content of the food (%)]

Physical activity

Pregnancy Physical Activity Questionnaire (PPAQ) is used to determine physical activity of pregnant women [29]. The PPAQ is a semi quantitative questionnaire that requires participants to report the time spent participating in 32 activities including household/care giving (13 activities), occupational (5 activities), sports/exercise (8 activities), transportation (3 activities), and inactivity (3 activities).

Anthropometry

Weight, height and waist circumference are measured at study enrolment (antenatal booking) using standard instrument (SECA digital weighing scale, SECA body meter and SECA measuring tape). Pre-pregnancy body weight (current pregnancy) and weight at the beginning of first pregnancy are obtained from medical record. Pre-pregnancy BMI is calculated as pre-pregnancy weight (kg) divided by recommendation of World Health Organization [30]. Inter-pregnancy weight change is defined as the difference between weight at the beginning of the first and current pregnancies. Postpartum weight retention is calculated as the absolute difference between weight measured at each of 4th and 5th visit and pre-pregnancy weight. Total gestational weight gain is defined as the difference between measured weight at last prenatal visit and pre-pregnancy weight. Rate of weight gain in first, second or third trimester is defined as the average weekly weight gain in that trimester.

Biochemical

A standard 75g OGTT is performed at 2 time points. The first OGTT is performed for all participants at 10 – 13th weeks of gestation. The second OGTT is performed between 24th and 32nd weeks of gestation (2nd visit) and as close to 28th weeks of gestation as possible. A 2ml fasting venous blood is drawn prior to ingestion of a standard glucose solution. Another 2 ml of venous blood is drawn at 2-hours after ingestion of standard glucose solution. All blood samples are sent for analysis on the same day to determine fasting glucose, 2-hr plasma glucose concentration. Additional blood (3ml) is obtained for analysis of total cholesterol, HDL-cholesterol, triglycerides and vitamin D. Normal fasting plasma glucose for pregnant women is

defined according to the Ministry of Health (MOH) (3.0 mmol/l to < 6.0 mmol/l). The cut off values for serum lipid is according to the National Cholesterol Education Program Adult Treatment Panel III [31] guidelines. Vitamin D cut offs for severe deficiency, mild deficiency, insufficiency and sufficiency are < 25 nmol/L, 25 – <50 nmol/L, 50 – <75 nmol/L and ≥ 75 nmol/L, respectively [32].

Blood pressure

Right arm systolic blood pressure (SBP) and diastolic blood pressure (DBP) is measured using OMRON SEM-1 Automatic Blood Pressure Monitor by trained nurses.

Smoking habit

The status of smoking, frequency of smoking and number of cigarettes smoked are obtained.

Food insecurity

A 10 items questionnaire is use to assess women food insecurity. All items are rated on a 3 response point ranging from always, sometimes or never [33]

Depression

Depression during pregnancy and postpartum depression is assessed using a self-administered 10 question Edinburg Postnatal Depression Scale (EPDS) [34]

Maternal birth information

1. Delivery

Mode of birth (normal vaginal birth, assisted breech delivery, instrumental delivery or caesarean section) and gestational age at birth are obtained from medical record. Premature birth is defined as childbirth occurring at less than 37 completed weeks of gestation or 259 days of gestation [35].

2. Birth information of infants

Birth data are obtained from medical record. Birth weight is categorized according to the recommendation of United Nations Children's Fund (UNICEF) and World Health Organization [36]. SGA is defined as an infant weighing less than 10th percentile of birth weight. An infant with >90th percentile of birth weight was classified as large-for-gestational age (LGA), while an infant with the 10th-90th percentile of birth weight as appropriate-for-gestational-age (AGA) [37].

Infants

1. Anthropometry

All infants are measured for weight (to the nearest 0.1 kg), length (to the nearest 0.1 cm), head circumference and mid arm circumference (to the nearest 0.1 cm) using TANITA digital baby weighing scale with recumbent length meter and SECA fibreglass measuring tape, respectively. Infants are measured using standard procedures as described by Gibson, (2005) [38]. Growth data are analyzed using Anthro Plus software that utilizes World Health Organization growth standard [39]. Five growth indicators (weight-for-age, weight-for-height, height-for-age, head circumference-for-age and BMI-age) will be determined. In order to assess subcutaneous fat,

triceps and subscapular are measured using Harpenden Skinfold Caliper and recorded to the nearest 0.1mm [40].

2. Dietary intake

A 24-hour diet recall is used to obtain dietary information of infants from parents / guardians with the aid of standard household measurements. Dietary data are then analysed for adequacy of energy and nutrients [19, 20] as well as dietary diversity [41]. Parents are also interviewed on infant feeding practices (e.g. milk feeding, complementary feeding).

Data collection

All enumerators are given an intensive briefing and field training before data collection. Study visits are scheduled on the same day of appointments at MCH clinics. A day before each visit, enumerators are required to remind participants of their clinic appointments through telephone calls. During the visits, participants are interviewed or measured for relevant data. For participants who are not able to be interviewed at the clinics, home visits or telephone interviews are carried out by enumerators.

Data Analysis

Data will be analyzed using IBM SPSS Statistic 22. Descriptive statistics (mean, standard deviation, median, frequency) will be used to describe the data. Multiple logistic regression will be used to determine the relationship between predictors and maternal glycemia, as well as the relationship between maternal glycemia with pregnancy outcomes controlling for confounding variables. Significant level for all statistical analysis will be set at $p<0.05$.

Discussion

Globally, the prevalence of overweight and obesity is increasing among women, particularly during reproductive years. A study on trends of obesity in the United States (US) showed that the prevalence of obesity (BMI ≥ 30 kg/m^2) in US women aged 20 – 39 years increased from 28.4% in 1999 to 34.0% in 2007 [42]. In the Malaysian National Health and Morbidity Survey 1996 (NHMS II), women showed a significantly higher prevalence of obesity (BMI ≥ 30kg/m^2) (17.5%) than man (10.2%). In the period between the NHMS II (1996) and the NHMS (2011), there was an 11.9% increase in the prevalence of obesity (BMI ≥ 30kg/m^2) among females aged ≥18 years old. With increasing prevalence of obesity among women of childbearing age, the risk of having higher pre-pregnancy BMI and excessive gestational weight gain are inevitable [43,44]. These conditions could further increase the risk of pregnant women to have higher blood glucose level and subsequently poor pregnancy outcomes.

Studies have shown that women with hyperglycemia during pregnancy are at higher risk for poor pregnancy outcomes, such as caesarean delivery, pregnancy induced hypertension and preeclampsia [18,45,46]. Apart from that, mothers with hyperglycemia during pregnancy tend to have large-for-gestational-age (LGA) infants and infants with asphyxia and hypoglycemia [46–48]. These conditions can lead to other long-term child health problems such as obesity, type II diabetes, cancer and cardiovascular disease in later life. For the mothers with hyperglycemia, they are at higher risk of developing cardiovascular disease and overt diabetes, mainly type 2 diabetes in later life [49–51]. However, there is no clear threshold above which women are at high risk and below which they are at low risk. Moreover, the impact of maternal hyperglycemia,

which is characterized by value of glucose tolerance intermediate between normal and gestational diabetes on outcomes of pregnancy remains unclear.

Dietary intake and physical activity are important modifiable risk factors for the development of type 2 diabetes, as well as gestational hyperglycemia. While higher total fat and lower carbohydrate intakes during second trimester of pregnancy were associated with maternal hyperglycemia [52], pregnant women in the high quartile of moderate intensity activity and occupational activity during early pregnancy had about 50% decreased risk of abnormal glucose tolerance [53]. A lower energy intake and higher physical activity are known to improve insulin sensitivity and reduce glucose levels, however, there is less information on dietary nutrients intakes, particularly fat types, vitamin D and iron related to maternal hyperglycemia, as well as the optimal distribution of macronutrient intakes during pregnancy to prevent maternal hyperglycemia. Therefore, there is a need for a better understanding of the role of lifestyle factors, especially energy and nutrient intakes, physical activity and sedentary behavior in the development of maternal hyperglycemia.

SECOST is the first prospective study in Malaysia to provide a better understanding of weight gain and lifestyle patterns from early pregnancy until 1 year postpartum and to quantitate the relationship between maternal glucose levels and pregnancy outcomes. As GDM impacts maternal and fetal health, detailed information on lifestyle factors, biochemical parameters and weight gain patterns during pregnancy can provide insight on determinants of maternal glycemia. Data on early child growth and development obtained periodically will not only provide information on short and long-term outcomes of maternal glycemia but also indicate the role of

environment (e.g. infant feeding, diet, parent-infant interaction, home environment) that could potentially impact child growth and development. Despite the modest sample size, this pregnancy cohort study provides an opportunity for many hypotheses related to maternal and infant health and nutrition to be tested or confirmed. SECOST is expected to provide valuable data that can be used not only for strengthening existing strategies but also formulating new strategies that are in accordance with promoting maternal and child health.

Ethics and dissemination

This study is approved by the Medical Research Ethics Committee (MREC), Universiti Putra Malaysia (UPM/FPSK/100-9/2-MJKEtika) and the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (KKM/NIHSEC/08/0804/P12-613). Permission to conduct this study is also obtained from the Head of Seremban District Health Office. All participants are required to provide written informed consent prior to data collection. The research findings will be disseminated through publications and conference presentations. Data sharing is available upon request.

Acknowledgements

The authors would like to thank all women and infants who took part in this study and all nurses, and staff in MCH clinics of Seremban district, Negeri Sembilan for their assistance during data collection.

Author's contributions

ZMS – conceptualized and designed the study; contributed to the development of study protocol; supervise data collection; read, revised and approved the final draft of manuscript

YHY – conceptualized and designed the study; contributed to the development of study protocol; involve in data collection; drafted the manuscript

ZR and BNMY – contributed to the development of study protocol; read and approved the manuscript

FY and LP – involve in data collection

Study funding

Funding is provided by Danone Dumex (Malaysia) Shd. Bhd.

Competing interests

Although SECOST is funded by the Danone Dumex (Malaysia) Shd. Bhd, the company does not influence the study protocol and preparation of this manuscript. As the nature of this study is more of exploratory and does not involve any testing of company product, the researchers are free to report any findings of this study in future publications. All authors declare that they have no competing interests.

References

1. Perkins JM, Dunn JP, Jagasia SM. Perspectives in Gestational Diabetes Mellitus: A Review of Screening, Diagnosis, and Treatment. Vol. 25, Clinical Diabetes. 2007. p. 57–62.
2. Panel IA of D and PSGC. International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. Diabetes Care [Internet]. 2010 Mar 1;33(3):676–82. Available from: http://care.diabetesjournals.org/content/33/3/676.short
3. Cundy T, Ackermann E, Ryan E a. Gestational diabetes : new criteria may triple the prevalence but effect on outcomes is unclear. Bmj [Internet]. 2014;1567(March):1–5. Available from: http://dx.doi.org/doi:10.1136/bmj.g1567
4. Blackwell SC. Enough evidence to treat? The American College of Obstetricians and Gynecologists Guidelines. Clin Chem. 2012;58(7):1098–100.
5. Coustan DR. Medical Management of Pregnancy Complicated by Diabetes [Internet]. Coustan DR, editor. American Diabetes Association; 2013. 188 pages. Available from: https://books.google.com.my/books?id=NDbQlAEACAAJ
6. Langer O, Umans JG, Miodovnik M. Perspectives on the proposed gestational diabetes mellitus diagnostic criteria. Obstet Gynecol. 2013 Jan;121(1):177–82.
7. Hillier TA, Vesco KK, Pedula KL, Beil TL, Whitlock EP, Pettitt DJ. Screening for gestational diabetes mellitus: A systematic review for the U.S. preventive services task force. Vol. 148, Annals of Internal Medicine. 2008. p. 766–75.
8. Buckley BS, Harreiter J, Damm P, Corcoy R, Chico A, Simmons D, et al. Gestational diabetes mellitus in Europe: Prevalence, current screening practice and barriers to

screening. A review. Vol. 29, Diabetic Medicine. 2012. p. 844–54.

9. Zhang Y, Peck K, Spalding M, Xu T, Ragain M. A study to examine the attitudes, knowledge, and utilization of CAM by primary care professional in West Texas. Complement Ther Med. 2010;18:227–32.

10. Jang HC. Gestational diabetes in Korea: incidence and risk factors of diabetes in women with previous gestational diabetes. Diabetes Metab J [Internet]. 2011;35(1):1–7. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3080571&tool=pmcentrez&rendertype=abstract

11. Sumeksri P, Wongyai S, Aimpun P. Prevalence of gestational diabetes mellitus (GDM) in pregnant women aged 30 to 34 years old at Phramongkutklao Hospital. J Med Assoc Thai. 2006;89(Suppl 4):S94-9.

12. Kwapisz J, Bodaghi M. Preliminary Report of National Obstetrics Registry, Jan-December 2010. Jeganathan R, Karalasingam SD, editors. Kuala Lumpur, Malaysia, Malaysia: Jointly published by the National Obstetrics Registry and the Clinical Research Centre (CRC), Ministry of Health Malaysia.; 2013. 1-24 p.

13. Tan PC, Ling LP, Omar SZ. Screening for gestational diabetes at antenatal booking in a Malaysian university hospital: The role of risk factors and threshold value for the 50-g glucose challenge test. Aust New Zeal J Obstet Gynaecol. 2007;47:191–7.

14. IPH. National Health and Morbidity Survey 2011 (NHMS 2011). Ministry of Health Malaysia. Kuala Lumpur.: Institute for Public Health. Ministry of Health, Malaysia; 2011. 258 pages.

15. IPH. The Second National Health and Morbidity Study (NHMS 2). Ministry of Health

Malaysia. Kuala Lumpur.: Institute for Public Health. Ministry of Health, Malaysia; 1996.

16. Kampan N, Azman H, Hafiz I, Mohammad H, Yee CS, Azurah N, et al. Outcome of pregnancy among Malaysian women with diabetes mellitus - A single centre experience. Malaysian J Public Heal Med. 2013;13(2):1–10.

17. Scheaffer R, Mendenhall W, Ott R, Gerow K. Elementary Survey Sampling [Internet]. 7th ed. Cengage Learning; 2011. 480 pages. (Advanced series). Available from: https://books.google.com.my/books?id=TbSjtoy4p-8C

18. Nordin NM, Wei JWH, Naing NN, Symonds EM. Comparison of maternal-fetal outcomes in gestational diabetes and lesser degrees of glucose intolerance. J Obstet Gynaecol Res. 2006 Feb;32(1):107–14.

19. Axxya Systems LLC. Nutritionist Pro Diet Analysis [Internet]. 2011. Available from: http://www.axxya.com/products.html.

20. National Coordinating Committee on Food and Nutrition. Recommended Nutrient Intakes for Malaysia. A Report of the Technical Working Group on Nutritional Guidelines. Ministry of Health Malaysia, Putrajaya.; 2005.

21. National Coordinating Committee on Food and Nutrition. Malaysian Dietary Guidelines 2010. A Report of the Technical Working Group on Nutritional Guidelines. [Internet]. Vol. 1. Ministry of Health Malaysia, Putrajaya.; 2010. Available from: http://www.moh.gov.my/images/gallery/Garispanduan/diet/introduction.pdf

22. Ledikwe JH, Blanck HM, Kettel Khan L, Serdula MK, Seymour JD, Tohill BC, et al. Dietary energy density is associated with energy intake and weight status in US adults. Am J Clin Nutr. 2006 Jun;83(6):1362–8.

23. Ministry of Health Malaysia. The Malaysian Adults Nutrition Survey (MANS)-Findings

Report 2003. Nutrition Section Family Health Development Division, Putrajaya: Ministry of Health Malaysia, Malaysia; 2007.

24. Randall E, Marshall JR, Graham S, Brasure J. Patterns in food use and their associations with nutrient intakes. Am J Clin Nutr [Internet]. 1990 Oct 1;52(4):739–45. Available from: http://ajcn.nutrition.org/content/52/4/739.abstract

25. Nicklas TA, Webber LS, Thompson B, Berenson GS. A multivariate model for assessing eating patterns and their relationship to cardiovascular risk factors: the Bogalusa Heart Study. Am J Clin Nutr. 1989 Jun;49(6):1320–7.

26. Sieri S, Krogh V, Berrino F, Evangelista A, Agnoli C, Brighenti F, et al. Dietary glycemic load and index and risk of coronary heart disease in a large italian cohort: the EPICOR study. Arch Intern Med. 2010 Apr;170(7):640–7.

27. Villegas R, Liu S, Gao Y-T, Yang G, Li H, Zheng W, et al. Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2 diabetes mellitus in middle-aged Chinese women. Arch Intern Med. 2007 Nov;167(21):2310–6.

28. Liu S, Willett W. Dietary glycemic load and atherothrombotic risk. Curr Atheroscler Rep [Internet]. 2002;4(6):454–61. Available from: http://dx.doi.org/10.1007/s11883-002-0050-2

29. Chasan-Taber L, Schmidt MD, Roberts DE, Hosmer D, Markenson G, Freedson PS. Development and validation of a Pregnancy Physical Activity Questionnaire. Med Sci Sports Exerc. 2004 Oct;36(10):1750–60.

30. WHO. Physical status: The Use and Interpretation of Anthropometry. Report of a WHO Expert Committee. World Health Organization, editor. Geneva: WHO Technical Report Series No. 854.; 1995.

31. NCEP. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002 Dec;106(25):3143–421.

32. Hamid Jan, Mohamed, Angela R, Bertram F, Loy SL. Maternal serum and breast milk vitamin D levels: findings from the Universiti Sains Malaysia Pregnancy Cohort Study. PLoS One. 2014;9(7):e100705.

33. Radimer KL, Olson CM, Campbell CC. Development of indicators to assess hunger. J Nutr. 1990 Nov;120 Suppl(December 1989):1544–8.

34. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987 Jun;150:782–6.

35. WHO. International classification of diseases and related health problems. 10th ed. World Health Organization, editor. Geneva.; 1992.

36. UNCF/WHO. Low Birthweight: Country, regional and global estimates. UNICEF, New York. United Nations Children's Fund and World Health Organization, editor. UNICEF, New York; 2004.

37. Bukowski R, Hansen NI, Willinger M, Reddy UM, Parker CB, Pinar H, et al. Fetal Growth and Risk of Stillbirth: A Population-Based Case–Control Study. Fisk NM, editor. PLoS Med [Internet]. 2014 Apr 22;11(4):e1001633. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3995658/

38. Gibson RS. Principles of Nutritional Assessment [Internet]. Oxford University Press; 2005. 908 pages. Available from: https://books.google.com.my/books?id=lBlu7UKI3aQC

39. WHO. Training Course on Child Growth Assessment. [Internet]. World Health Oraganization, editor. Geneva, WHO; 2008. Available from:

http://www.who.int/childgrowth/software/en/

40. Dauncey MJ, Gandy G, Gairdner D. Assessment of total body fat in infancy from skinfold thickness measurements. Arch Dis Child. 1977;52(August 1976):223–7.

41. Food and Agriculture Organization and Food and Nutrition Technical Assistance Project. Guidelines for measuring household and individual dietary diversity. Rome, Italy; 2013.

42. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among us adults, 1999-2008. JAMA [Internet]. 2010;303(3):235–41. Available from: http://dx.doi.org/10.1001/jama.2009.2014

43. Gunderson EP. Childbearing and Obesity in Women: Weight Before, During, and After Pregnancy. Vol. 36, Obstetrics and Gynecology Clinics of North America. 2009. p. 317–32.

44. Li N, Liu E, Guo J, Pan L, Li B, Wang P, et al. Maternal prepregnancy body mass index and gestational weight gain on pregnancy outcomes. PLoS One [Internet]. 2013 Dec 20;8(12):e82310. Available from: http://dx.doi.org/10.1371%252Fjournal.pone.0082310

45. Catalano PM, Tyzbir ED, Wolfe RR, Calles J, Roman NM, Amini SB, et al. Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. Am J Physiol [Internet]. 1993;264(1 Pt 1):E60–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8430789

46. Lowe LP, Metzger BE, Dyer AR, Lowe J, McCance DR, Lappin TRJ, et al. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: Associations of maternal A1C and glucose with pregnancy outcomes. Diabetes Care [Internet]. 2012 Mar 10;35(3):574–80. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3322718/

47. Leary J, Pettitt DJ, Jovanovič L. Gestational diabetes guidelines in a HAPO world. Vol. 24, Best Practice and Research: Clinical Endocrinology and Metabolism. 2010. p. 673–85.

48. Polin RA, Fox WW, Abman SH. Fetal and Neonatal Physiology [Internet]. Elsevier Health Sciences; 2011. Available from: https://books.google.com.my/books?id=38X8Kc_YMMUC

49. Gilmartin A "Bird" H, Ural SH, Repke JT. Gestational Diabetes Mellitus. Rev Obstet Gynecol [Internet]. 2008;1(3):129–34. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2582643/

50. Negrato C, Gomes M. Historical facts of screening and diagnosing diabetes in pregnancy. Diabetol Metab Syndr [Internet]. 2013;5(1):22. Available from: http://www.dmsjournal.com/content/5/1/22

51. Carr DB, Utzschneider KM, Hull RL, Tong J, Wallace TM, Kodama K, et al. Gestational Diabetes Mellitus Increases the Risk of Cardiovascular Disease in Women With a Family History of Type 2 Diabetes. Diabetes Care [Internet]. 2006 Sep 1;29(9):2078–83. Available from: http://care.diabetesjournals.org/content/29/9/2078.abstract

52. Ley SH, Hanley AJ, Retnakaran R, Sermer M, Zinman B, O'Connor DL. Effect of macronutrient intake during the second trimester on glucose metabolism later in pregnancy. Am J Clin Nutr [Internet]. 2011 Nov 1;94(5):1232–40. Available from: http://ajcn.nutrition.org/content/94/5/1232.abstract

53. Chasan-Taber L, Silveira M, Lynch KE, Pekow P, Braun B, Manson JE, et al. Physical activity before and during pregnancy and risk of abnormal glucose tolerance among Hispanic women. Diabetes Metab [Internet]. 2014 Feb;40(1):67–75. Available from: http://www.sciencedirect.com/science/article/pii/S126236361300178X