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Modifiable determinants of fetal macrosomia

Role of life style related factors

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- Abstract: 232 words
- Article: 2137 words

Running Head:

Life style related factors and newborn macrosomia

Condensation

Besides BMI, weight gain and fasting plasma glucose, pre-gestational physical inactivity was found to be an independent determinant of fetal macrosomia

Abstract

Modifiable determinants of fetal macrosomia
Role of life style related factors

Background. Newborn macrosomia is associated with both short and long term health risks for the infant, and increases the prevalence of birth complications. Parity, maternal age and gender of the child are known variables that influence fetal growth. The purpose of the present investigation was to evaluate prospectively the contributions of modifiable maternal predictors of fetal macrosomia (≥4200g) which included life style related factors like nutritional intake, physical activity, and plasma glucose values, besides overweight and pregnancy weight gain.

Methods. Five hundred and fifty-three women were followed through pregnancy. Predictive variables were subjected to univariate and multiple logistic regression analysis. Among these were: body mass index (BMI), weight gain, maternal subcutaneous fat (mm), fasting and 2 hour plasma glucose, self reported physical activity before and during pregnancy, and nutritional intake of macronutrients. Gestational age, parity and gender were also included in the model. All continuous variables were dichotomized, using upper quartile as cut point in most cases.

Results. If physical activity was left out from the analyses, BMI, weight gain, plasma glucose and gestational age were independent determinants of macrosomia. After including low level of pre-gestational physical activity in the model, we found that this was now a significant determinant of delivering a macrosomic infant with an OR=2.9 (95% CI 1.9, 7.3).

Conclusion. The present study indicates that low level of physical activity pre-gestational adds to the modifiable determinants of newborn macrosomia.

Keywords:

Fetal macrosomia; Physical activity; Body Mass Index; Nutritional intake; Plasma glucose

Modifiable determinants of fetal macrosomia
Role of life style related factors

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INTRODUCTION

The incidence of macrosomic newborns is increasing in many parts of the world (1;2). In Norway the percentage of newborns weighing 4000 g or more has increased from 16 to 20% in less than three decades (3).

There is no generally accepted definition of newborn macrosomia. Irrespective of definitions, most studies show that being born large is associated with both short and long term health risks for the newborn.

The short term risks include intrapartal hypoxia, brachial plexus injuries, low Apgar score, asphyxia and hypoglycaemia (4). Being born large is associated with overweight, diabetes, metabolic syndrome and cancer later in life (5;6). Giving birth to macrosomic infants is associated with higher risk of maternal complications including prolonged labour, operative deliveries and perineal injuries (7;8).

Factors contributing to fetal macrosomia may be classified as modifiable and non-modifiable. Modifiable factors include maternal nutritional and anthropometric variables, levels of physical activity, diabetes, glucose intolerance and other features of metabolic syndrome (9-13). Non-modifiable factors consist of genetic factors and effects of parental imprinting (14;15).

Most studies on causes of fetal macrosomia are retrospective and the majority has evaluated the effect of maternal overweight, weight gain, diabetes and glucose intolerance (16;17). Only a few studies have included effects of maternal nutritional intake and physical activity (13). It remains unclear to which extent each of the modifiable factors independently contributes to fetal macrosomia. In the present study we have evaluated the contributions of a number of modifiable factors.

MATERIALS AND METHODS

The study followed a prospective cohort design and consists of 553 pregnant women and their newborns. The inclusion period was from 2002 to 2005. Newborn macrosomia was defined as birth weight ≥ 4200 g.

Characteristics of the cohort

Healthy women with single pregnancies of Scandinavian heritage booked for birth place at Rikshospitalet Medical Centre were invited to participate in the study. Approximately one third of the eligible women were invited to participate (figure 1). In order to evaluate the representativity of the cohort a comparison group was obtained consisting of 150 non-participating women delivering at the hospital during the same period.

The participants were subjected to a scheduled prospective follow up with four visits during pregnancy (table I). Visit one was conducted between gestational week 14 to16. Body mass index (BMI, kg/m^2) and maternal anthropometric measures were collected at each visit. Subcutaneous fat was estimated at the triceps, sub-scapular and iliac sites using a caliper (Holtain, Crymych, UK).

A standard oral glucose tolerance-test with 75 g glucose after 10-12 h fasting was performed twice (visit one and three). Plasma glucose was measured immediately in EDTA blood, venous, by Accu Chek Glucose Test strips (Roche Diagnostics, Basel, Switzerland). A previously validated self-administered quantitative food frequency questionnaire was filled

out at visit one and three(18). Intake of macronutrients was calculated as the mean of the values obtained at visit one and three.

In the current study physical activity was defined as one or more activity per week, each of at least 20 minutes duration. Physical activity was assessed by a questionnaire according to these definitions (19). The level of physical activity pre-gestationally and first and second trimester was obtained by the questionnaire at the third visit (week 30-32). Information about physical activity in third trimester was obtained at 36-38 weeks. By combining the answers of the questions 1) *How often do you exercise (times per week)* and 2) *For how long do you usually exercise (minutes)?,* information of the mean time spent on physical activity weekly was obtained. Women exercising less than one hour per week were defined as performing low level of physical activity. (13;20).

Statistical methods.

Differences and similarities of the study cohort and the comparison group were explored by two sample t-tests and Pearson's χ^2 tests. Analyses of possible predictors of giving birth to a macrosomic newborn were done by univariate and multiple logistic regression analyses.

The modifiable predictors of macrosomia chosen for the regression analyses included maternal BMI and maternal subcutaneous fat at visit one, weight gain in pregnancy, plasma glucose values (visit one and three), intake of energy and energy providing nutrients, smoking and level of physical activity before and during pregnancy. Also non modifiable predictors including gestational age, gender of child, parity and maternal age were included in univariate analyses. Potential predictors included categorical and continuous variables. A dichotomizing of all continuous variables was done, with the upper quartile as cut point.

In multiple analyses, both forward and backwards variable selection procedures were used to explore stability of the results. Backwards variable selection procedure was used as the final model. Gestational age is considered to be a major determinant of fetal weight.

Consequently an adjustment for gestational age was done in all multiple analyses. The only interaction term considered in the model was between BMI and physical activity.

All analyses were confirmed with imputed values for missing data on physical activity. The imputation was done by replacing missing values of physical activity with the mode (the most frequent answers) of the registrations. To explore stability of the results further, the analyses were also run with lower quartiles as cut points for nutrition, and with all continuous variables as continuous ones. All statistical models were thoroughly checked for possible violations of assumptions connected to the logistic model (21).

All analyses were done by the statistical software program SPSS 13.0 (SPSS Inc., Chicago, IL). P-values less than 0.05 were considered statistically significant.

Ethics

The study was approved by the Regional Ethic Committee and performed according to the Declaration of Helsinki and written informed consent obtained.

RESULTS

Characteristics of the women

Evaluations of the cohort and the comparison group revealed no significant differences in maternal height, age, parity, smoking habits, marital status educational level or percentage working outside home between the groups (data not shown). The mean weight before pregnancy in the study group was 67.2 kg (SD 11.1) versus 64.5 (SD 10.0) among the non-participants ($p<0.01$). This difference remained significant throughout pregnancy.

Demographic and anthropometric data and glucose values are shown in table II. Ten women (1.9%) had two-hour glucose values ≥ 7.8 mmol/l at the first visit and 56 (10.6%) at the third visit. The median was chosen as cut-off values for weight gain, while 25 (kg/m^2) was chosen for BMI, as this corresponds to the most frequent use for overweight. The other

variables were analyzed with upper quartiles versus the three lower quartiles (all cut-off values are shown in table III).

Mean intakes of energy and macronutrients are shown in table II. When using exercising less than one hour per week as a definition of low level of physical activity, the percentage of women with low level before pregnancy, at first, second and third trimester, were 7.1%, 19.7%, 24.4% and 27.7%, respectively (table II). The most frequent answers to the questions of physical activity were to spend 30-60 minutes on physical activity 2-3 times a week. .

Mean birth weight was 3619g (SD 570, range 1275g -5420g,). Fifteen percent of the children weighed 4200g or more and 4.9% weighed 4500g or more. These figures correspond to the birth weight distribution of the general Norwegian population (3).

Regression analysis

BMI and subcutaneous fat at the triceps at the inclusion, and weight gain during pregnancy were significantly associated with macrosomia in univariate analyses (table III).

The fasting plasma glucose levels at the first visit showed a borderline significant association with newborn macrosomia. At visit three, however, fasting plasma glucose values were significantly related to macrosomia (table III). Neither of the two-hour plasma glucose values showed significant association with macrosomia. Total intake of energy or macronutrients in mean percent was not associated with risk of delivering a macrosomic child (table III). Low level of physical activity before pregnancy was significantly associated with increased risk of macrosomia (table III) in the univariate analyses. The proportions giving birth to a macrosomic child were 0.33 among women exercising less than one hour per week, and 0.15 among women exercising more than one hour per week. This corresponds to an absolute risk difference of 0.19 (95% CI 0.02, 0.35). No relation between physical activity *during* pregnancy and risk of newborn macrosomia was found.

Gestational age had a strong impact on birth weight above 4200g. In addition, odds for macrosomic newborns showed significant associations with gender and parity. Maternal age or smoking was not associated with the risk of macrosomia (table III).

The multiple analysis showed that low level of pre-gestational physical activity (i.e. less than one hour a week) increased the risk of delivering a baby weighing 4200g or more with an OR of 2.9 (95% CI 1.2-7.3, p=0.01) (table III). No significant interaction between physical activity and BMI was found. If physical activity was left out from the multiple analyses, BMI, weight gain, fasting plasma glucose (at visit three) and gestational age were independent determinants of macrosomia (p-values 0.04, 0.04, 0.03, <0.01 respectively).

The known associations between birth weight and the non-modifiable predictors, gestational age, gender and parity were confirmed. None of these variables gave substantial alterations in the adjusted effects size, or in the p values of the modifiable variables (data not shown).

Due to a lower number of women reporting physical activity (467) we did several additional analyses to explore the results. The significant effect of low level of physical activity was confirmed in analysis with the imputed physical activity variable. As this analysis made it possible to include all women in the study, the power of the calculations increased (data not shown).

In addition, the analyses were repeated with macrosmia defined as birth weight at or above 4500 g. This analysis repeated the finding of a significant effect of low level of physical activity, also after mutual adjustment (data not shown).

DISCUSSION

Maternal BMI is a consistent determinant of fetal macrosomia (22). The present study indicates that being physically inactive before pregnancy is an additional independent risk

factor. We consider this observation of particular interest given the indications of reduced level of physical activity in many current societies (23).

We chose birth weight at or above 4200g mainly because the risk of clinically significant maternal and newborn birth complications increases when fetal weight reaches the range of 4000-4500g (7;8;24). Furthermore, birth weight of 4200 g corresponds approximately to the 90th percentile in the Norwegian population (3).

We did not obtain data on paternal weight and height. However, data on paternal high birth weight were available, which did not influence the overall risk of macrosomia (data not shown).

Moderate weight bearing activity started early in pregnancy does not seem to reduce average birth weight, whereas reducing the volume of activity half way into pregnancy seems to increase birth weight (25). We are not aware of similar studies on the risk of fetal macrosomia as endpoint.

In the current study the participants were asked if they performed a certain level of physical activity or not before and/or during pregnancy. By this definition less than 1 in 10 women reported low level of activity. It is likely that the questionnaire method has overestimated the proportion of physically active women. But we consider it unlikely that women carrying a fetus ending up with high birth weight should report their (pre)gestational physical activity differently from women with normal weight infants. The women who reported low level of physical activity may represent the most sedentary among the inactive ones.

The non-significant effect of BMI, plasma glucose values and gestational weight gain found in multiple regression analyses when including physical inactivity, may be due to type 2 error as indicated by the significant effect on these two predictors following analyses with

imputed data. Similarly, absence of effects of macronutrient intake and physical activity *during* pregnancy may be due to sample size (26).

The current study followed a prospective design except for data on physical activity which partly was retrospective. There was a low incidence of drop-outs from the study once included. The significant effect of low level of physical activity on the risk of fetal macrosomia was reproduced using several alternative analyses.

Fetal macrosomia has become a major obstetrical challenge during the last 20-30 years. In addition, the negative long term consequences of being born large or disproportionate in terms of body composition (fat mass to fat free mass ratio) are emerging (6;27-30). The current and several previous studies indicate that the maternal nutritional and metabolic status before pregnancy may play an important role in determining the risk of macrosomia or fat mass fat-free mass ratio of the newborn (26;31). During pregnancy maternal weight gain and last trimester plasma glucose are important modifiers of the risk (22).

In conclusion, the present study indicates that low level of physical activity pre-gestational adds to the modifiable determinants of newborn macrosomia. Many of the modifiable determinants are features of "westernized" lifestyle making them targets for intervention.

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Fig. 1: Flow chart

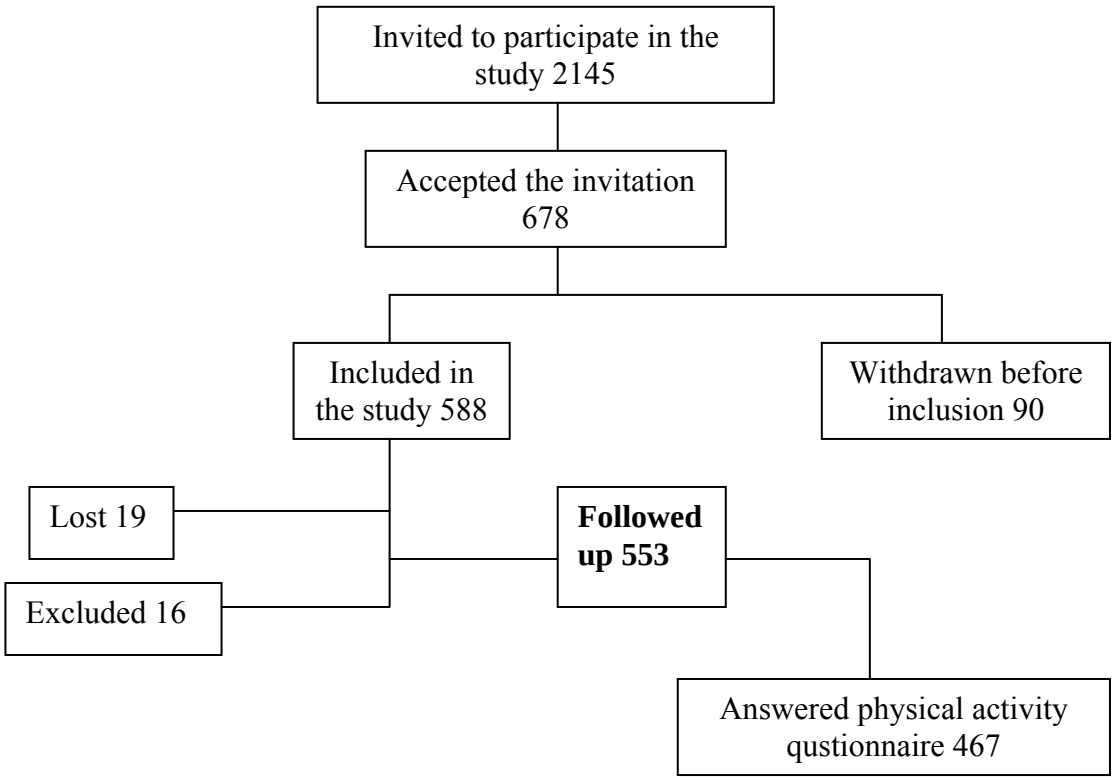

Figure legend.

figure 1. Flow chart

Table I: Design and follow up through pregnancy

	Weeks of gestation			
Investigation	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
	14 -16	**22 – 24**	**30– 32**	**36 - 38**
General follow up *	+	+	+	+
Glucose tolerance test	+		+	
Blood samples †	+	+	+	+
Food intake ‡	+		+	
Physical activity §	+	+	+	+

* Including blood pressure, weight, sub-scapular skin folds

† Serum EDTA, citrate plasma and buffy coat for immediate freezing at -70° C

‡ Food frequency questionnaire answered at visit one and three

§ Level of physical activity pre-gestational and at each visit was obtained by a questionnaire handed out at visit three.

Table II: Characteristics of the women and their newborns

	n	(%)	mean	range	SD
Demography n=553					
Education ≥ 12 yr	543	(98)			
Married or partnership	574	(99)			
Occupation 50% or more	543	(98)			
Daily smoking (yes)	22	(4)			
Para 0	292	(53)			
Maternal age (year)			31.2	19-42	4
Gestational age (weeks)			40	28.4-43.1	1.8
Anthropometry					
Height (cm)			168.5	150-183	5.6
Weight (kg) visit 1			70.8	44.6-123.1	12.1
Body mass index (m/kg^2) visit 1			24.9	17.5-44.0	4.1
Subcutaneous fat triceps (mm) visit 1			21.2	7.1-44.2	7.4
Weight (kg) visit 4			81.3	53.9-130.9	12.5
Weight gain (kg) (visit 1 – visit 4)			10.6	-1.2 – 29.4	3.8
Plasma glucose values					
Fasting plasma glucose (mmol/l) visit 1			4.2	2.6-5.6	0.5
Two-hour plasma glucose (mmol/l) visit 1			4.4	1.4-8.3	1.2
Fasting plasma glucose (mmol/l) visit 3			4.4	3.1-6.8	0.5
Two-hour plasma glucose (mmol/l) visit 3			6.1	2.8-10.8	1.4
Nutrients					
Energy (kJ)			8605	4041-14816	1855

Protein E% *		15.5	9.8-23.1	1.9
Fat E% *		31.5	18.4-46.1	4.6
Carbohydrate E% *		52.9	39.9-91.3	5.2
Physical activity n=467				
Pre-gestational (hour/week)		3.4	0.3 – 20 0	2.6
Low physical activity † pre-gestational	33 (7.1)			
1st trimester (hour/week)		2.4	0.3 – 10.5	1.9
Low physical activity †1st trimester	92 (19.7)			
2nd trimester (hour/week)		2.2	0.3 – 11.3	2
Low physical activity † 2nd trimester	114 (24.4)			
3rd trimester (hour/week)		1.7	0.3 – 10.5	1.6
Low physical activity† 3rd trimester	129 (27.6)			
The newborn n=553				
Birth weight		3619	1275-5420	570
Weight < 2500 g	18 (3.3)			
Weight 2500 – 4199 g	451 (81.6)			
Weight 4200 – 4499 g	57 (10.3)			
Weight ≥ 4500 g	27 (4.9)			

* Percent of total energy intake

† Less than one hour per week

Table III: Risk of delivering a macrosomic infant (≥4200g)

		Univariate analyses. Unadjusted OR. 95 % confidence intervals (CI) for OR and p-values			Multiple analyses Adjusted OR. 95 % confidence intervals (CI) for OR and p-values		
	Cut off	OR	95% CI	p-value	OR	95% CI	p-value
Anthropometry							
BMI visit 1	< 25	1.0			1.0		
	≥ 25	2.1	1.3-3.4	<0.01	1.8	1.0-3.4	0.07
Sub fat triceps (mm) visit 1†	< 26	1.0					
	≥ 26	2.0	1.2-3.3	<0.01			
Weight gain (kg)*	< 10.2	1.0			1.0		
	≥ 10.2	1.7	1.0-2.8	0.04	1.7	0.9-3.2	0.09
Plasma glucose values							
Fasting .glucose, (mmol/l) †							
Visit 1	< 4.5	1.0					
	≥ 4.5	1.7	1.0-2.8	0.05			
2-hour glucose, (mmol/l) †							
Visit 1	< 5.0	1.0					
	≥ 5.0	1.2	0.7-2.1	0.51			
Fasting glucose, (mmol/l) †					1.0		
Visit 3	< 4. 1	1.0					
	≥ 4. 1	2.0	1.2-3.3	0.01	1.9	0.9-3.7	0.08
2-hour glucose, (mmol/l) †							
Visit 3	< 6.9	1.0					
	≥ 6.9	1.3	0.8-2.3	0.28			

Nutrition							
Energy kJ †	< 9814	1.0					
	≥ 9814	1.4	0.9-3.4	0.18			
Protein † E%	< 16.7	1.0					
	≥ 16.7	0.7	0.4-1.2	0.17			
Fat † E%	< 34.5	1.0					
	≥ 34.5	1.1	0.6-1.8	0.79			
Carbohydrate † E%	< 55.7	1.0					
	≥ 55.7	1.1	0.6-1.8	0.79			
Physical Activity							
pre-gestational (hr /week)	≥ 1	1.0			1.0		
	< 1	2.9	1.3-6.4	0.01	2.9	1.2-7.3	0.01
1st trimester (hr /week)	≥ 1	1.0					
	< 1	1.6	0.9-3.0	0.15			
2nd trimester (hr /week)	≥ 1	1.0					
	< 1	1.3	0.7-2.4	0.45			
3rd trimester (hr /week)	≥ 1	1.0					
	< 1	1.2	0.6-2.3	0.57			
Gestational age (weeks)		2.7	1.6-4.4	<0.01	1.8	1.4-2.5	<0.01
Gender (boy vs. girl) ‡		2.2	1.3-3.6	<0.01			
Parity (0 vs. 1+) ‡		2.4	1.5-4.0	<0.01			
Maternal age		0.8	0.5-1.4	0.51			
Daily smoking (yes/no)		0.5	0.1-2.4	0.42			

*Cut off at median

† Cut off at upper quartile

‡ See statistical method