Upsala J Med Sci 105: 41–56, 2000

The Effect of Smoking on Glucose Homeostasis and Fetal Growth in Pregnant Women

Birgitta Zarén,[1] Gunilla Lindmark,[2] Lars Wibell[3] and Ivar Følling[4]

Department of Women's and Children's Health, [1]Section for Obstetrics and Gynaecology, and [2]Section for International Maternal and Child Health, and [3]Department of Medical Sciences, Internal Medicine, University Hospital, Uppsala, Sweden, and [4]Department of Endocrinology, Central Hospital of Akershus, Nordbyhagen, Norway

ABSTRACT

Objective: To examine the relationship between maternal blood glucose levels, cigarette smoking in pregnancy and fetal growth.

Design A prospective study of healthy parous women from early pregnancy and their infants.

Setting: Three Scandinavian university hospitals covering all deliveries from well defined geographical areas.

Subjects: Study groups of non-smoking (150), light smoking (131) and heavily smoking mothers (218), para 1 and 2 and with > 37 weeks of gestational length.

Main outcome measures: Oral glucose tolerance test performed in pregnancy week 37, glycated hemoglobin measured the 3rd day post partum and neonatal anthropometric parameters including skinfold measurements.

Results: Among heavily smoking mothers 12.4% displayed a 2-hour glucose value in the range of gestational diabetes (> 8.5 mmol/l) compared to 9.2% among light smokers and 6.0% among nonsmokers ($p < 0.05$). Heavily smoking mothers also had significantly ($p < 0.05$) higher glycated hemoglobin compared to nonsmokers, 5.01 v.s. 4.86. These changes in glucose parameters in smokers were not associated with higher birthweights.

Conclusions: Smoking in pregnancy affects parameters of glucose homeostasis in the direction of gestational diabetes. The retarding effect of smoking on fetal growth abolished any expected growth stimulation from the higher blood glucose levels seen in the smokers.

INTRODUCTION

A normal glucose metabolism in pregnancy is important for a normal development of the fetus. The adaptation in carbohydrate metabolism during the latter half of pregnancy is potentially diabetogenic and in some women an impaired glucose tolerance develops, causing gestational diabetes, a condition associated with exaggerated fetal growth. The importance of a normal glucose metabolism is underlined by the fact that hypoglycaemia during pregnancy is also a risk factor, related to fetal growth retardation [11, 12].

Maternal smoking in pregnancy has a documented negative effect on fetal growth and is related to various adverse outcomes of pregnancy [7]. The way in which it exerts its negative influence is not fully understood, and it may be inferred that part of the effect of smoking on birthweight is mediated by nutritional factors [9]. The possible interaction between smoking and other risk factors has not been much studied.

The present study deals with healthy smoking and non-smoking mothers and their term infants, and aims to investigate, prospectively, the mutual relationships between maternal blood glucose levels, smoking in pregnancy and fetal growth.

MATERIALS AND METHODS

The data on which this study was based were collected in connection with a Scandinavian multicenter investigation of risk factors for small for gestational age, the "SGA Scandinavian Study". The study population consisted of 5722 women, with one ore two previous children, booked for antenatal care January 1986 - March 1988, in the cities of Bergen, Trondheim and Uppsala. All women had their first visit before 17 weeks of pregnancy, and only women speaking Swedish or Norwegian were selected. The study protocol has been described elsewhere [4].

The present study uses data obtained from two subgroups of the SGA-study: 1) from a 10 % random sample of the whole population (n=561); 2) 50% of all smokers at conception (n=778) in the rest of the study population. As shown in Fig.1, these 1339 women were offered a simplified oral glucose tolerance test in week 37 of pregnancy. This extra visit to the hospital, with fasting over night, was accepted by 664 (49.6%) of the mothers. After exclusions of premature deliveries (n=64) and patients with inconsistent smoking behavior (n=101), 499 mothers remained for analysis. As outlined in Figure 1 the following three groups were obtained: 150 nonsmoking mothers, 131 light smokers and 218 heavy smokers (altogether 349 mothers smoking from conception and throughout pregnancy). All mothers were healthy and their pregnancies were normal or with only minor complications, going to term. Smoking mothers were slightly younger, otherwise they did not differ from non-smoking mothers, regarding BMI, prepregnancy weight or pregnancy weight gain.

Definitions

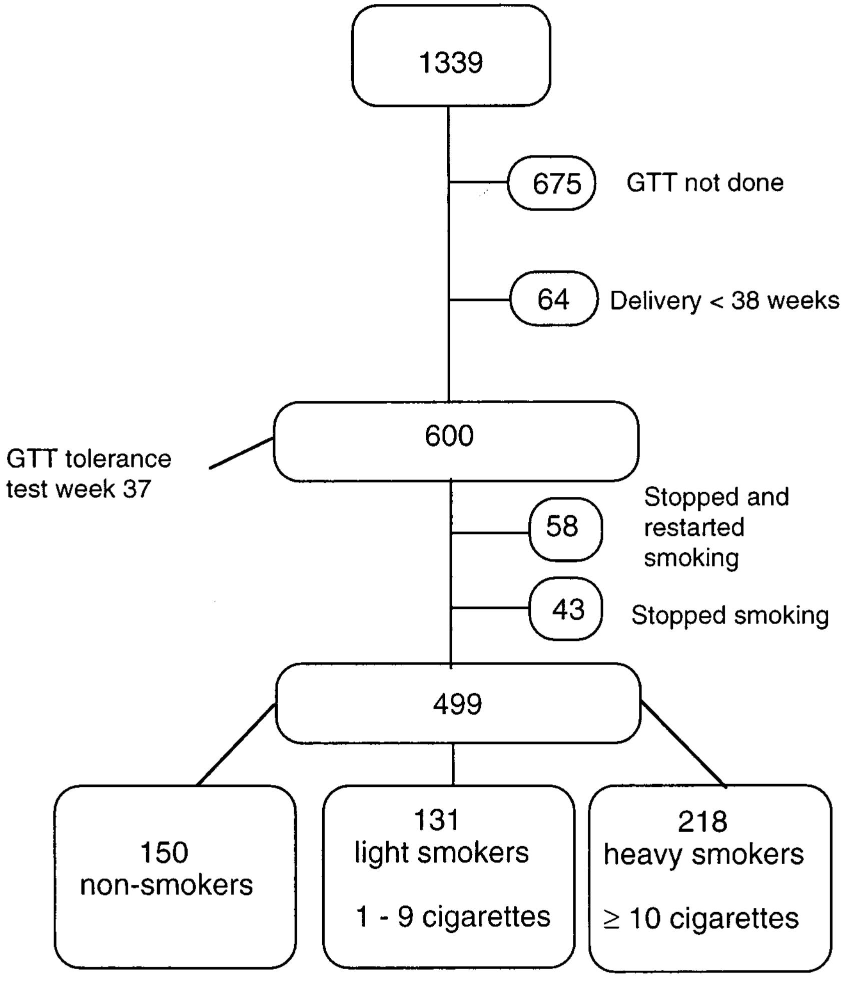
Maternal variables

Age was defined as age in years at the infant's birth and stratified into five year age groups.

Maternal smoking. Information about the number of cigarettes smoked per day was obtained from the mother on registration for antenatal care, regarding smoking at conception, and at interviews at weeks 17, 25, 33, 37 and at delivery.

The mothers were classified into non-smokers, light smokers (between 1 and 9 cigarettes per day), and heavy smokers (10 or more cigarettes per day) on the basis of the average amount reported.

Figure 1. Flow sheet of the study material.



The pre-pregnancy weight was reported by the mother on antenatal registration.

Height was registered at booking, the woman barefoot, on a wooden measuring scale to an accuracy of 0.1 cm.

The pregnancy weight gain was calculated from the pre-pregnancy weight and the weight recorded in late pregnancy (pregnancy weeks 36+0 to 38+6;mean gestational length 37+1).

Maternal Body Mass Index (BMI) was calculated as pre-pregnancy weight(kg)/height2(m).

Arm circumference in pregnancy week 17 was recorded as the largest circumference (to the nearest mm) of the left upper arm (approximately at the middle). A non-stretchable metric tape was used and the arm hanging straight.

Skinfold measurements, in week 17, were recorded with a Harpenden caliper with an accuracy to the nearest 0.1 mm. Triceps skinfold - at the midpoint of the upper arm with the arm hanging straight-, and subscapular skinfold - just below the tip of the inferior angle of the scapula - were measured three times and the mean of these measurements was taken.

Gestational age was primarily based on the date of the first day of the last menstrual period (LMP), if the date was known for certain to within 3 days. Each mother underwent an obstetric ultrasound examination at an estimated gestational length of 17 weeks. If the ultrasound-estimated gestational age differed more than 14 days from that estimated from LMP, the ultrasound estimation was used.

Serum ferritin samples were collected in week 33, and determined by radioimmunoassay (Magic Ferritin assay from Corning, Medfield, MA).

75 g oral glucose tolerance tests (OGTT) were performed in pregnancy week 37, in the morning after overnight fast. Fasting and 2-hour blood glucose were measured in capillary samples by use of an automated method (Grainer). When the present study was initiated, a 2-hour blood glucose of 8.0 mmol/l was suggested to be a useful cut off level for screening of gestational diabetes (WHO-criteria for impaired glucose tolerance at OGTT). Later, most centers have found it reasonable to change the cut off level to 9.0 mmol/l (recommended by an European study group). As only 5 non-smokers and 17 smokers in our material reached this higher diagnostic level, the intermediate level of 8.5 mmol/l was chosen for the analysis. However, the outcome for all the 3 levels are shown in Table 1.

Glycated hemoglobin (glyc.Hb) was measured the 3rd day post partum. Venous EDTA-blood was drawn in the fasting state and 50 µl mixed with 500 µl of reagent (Vortex mixer, stand for 5 min) before being stored at -20° C until analysis in duplo by affinity chromatography on boronic acid. This analysis detects all glycated derivates of hemoglobin, of which HbA1c is most abundant [1]. The samples were analysed continuously with mean storage time 3.7 month (SD 2.3 month, range 0-11 months).

Table 1. Prevalence of high 2-hours blood glucose values with different cut-off levels according to maternal smoking habits.

	> 8.0 mmol/l		>8.5 mmol/l		> 9.0 mmol/l	
	%	n	%	n	%	n
Non-smoking mothers	10.7	16	6.0	9	3.3	5
Smoking mothers, 1-9 cig/day	13.7	18	9.2	12	5.3	7
Smoking mothers, ≥ 10 cig/day	17.4 ▲	38	12.4 ■	27	7.8 △	17
	▲ $p = 0.072$		■ $p < 0.05$		△ $p = 0.076$	

Infant outcome variables

Birthweight was recorded on an electronic scale with an accuracy of ± 10 grams.

Length was obtained with the infant placed supine with both legs extended, using a measuring board with a movable foot-piece with an accuracy of 0.1 cm.

The circumference of the head (HC) was recorded with a disposable paper tape to the nearest mm and with the infant supine. HC (maximal occipito-frontal circumference) was measured three times, the largest measure was used in the analyses.

Subscapular and triceps skinfolds were measured to the nearest 0.1 mm with the child prone, using a Harpenden caliper. When measuring the subscapular skinfold thickness, a vertical fold was grasped and pulled in the sagittal plane. The measure was recorded at exactly 15 seconds with use of a stop-watch. The left side was measured. Triceps skinfold was measured on the left arm in the middle between the posterior aspect of the tip of the acromion and the olecranon and parallel with the long axis of the arm, at exactly 15 seconds. Apart from the weight, which was recorded immediately after birth, the measurements were generally performed on the second or third day after birth (at a mean age of 50 ±27(SD) hours), by one of the project pediatricians.

Statistical analysis

The Statistical Analysis System (SAS) program package was used [20]. Descriptive statistics of each parameter were calculated, and intergroup differences were determined with one-way analysis of variance (Anova T tests (LSD) alfa=0.05). For intergroup comparisons of distributions the chi square method was used. The group of non-smoking mothers was used as reference group. To explore the differences in birth weight and glyc.Hb, linear regression analyses were used. A significance level of $p < 0.05$ was chosen.

RESULTS

Table 2 shows some of the characteristics of the three investigated groups: non- smoking mothers, light smokers and heavy smokers. Smoking mothers were found to be somewhat younger. The individual anthropometric measurements (skinfold) were not significantly different between the groups and the mean BMI values were also similar between smokers and non-smokers. As regards glucose homeostasis, the heavy smokers were found to have a higher mean glyc.Hb. The mean fasting blood glucose values in the two smoking groups were not significantly higher, when separately compared with non smokers, however.

The characteristics of mothers who had not performed the OGTT (n=675) and their infants, did not show any differences from the tested group as regards maternal age, pre-pregnancy weight, height, pregnancy weight increase, proportion of smoking mothers, gestational length or birthweight (not shown).

Table 2. Maternal characteristics for the study groups of smokers and non-smokers, mean values and SD.

	Non-smoking mothers N = 150		Smoking mothers 1-9 cigarettes per day N = 131		Smoking mothers ≥10 cigarettes per day N = 218	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age (year)	30.1	(3.85)	28.4 ***	(3.96)	28.0 ***	(3.93)
BMI	21.9	(2.67)	21.3	(2.64) *	21.8	(3.2)
Pre-pregnancy weight (kg)	60.7	(8.6)	59.0	(9.5)	60.7	(9.8)
Height (cm)	167	(5.7)	166	(6.3)	167	(5.9)
Pregnancy weight gain (kg)	13.7	(3.7)	13.9	(4.4)	13.8	(4.7)
Fasting glucose (mmol/l)	4.54	(0.58)	4.66	(0.57)	4.65	(0.59)
2-hours glucose (mmol/l)	6.77	(1.27)	6.69	(1.43)	6.79	(1.43)
Glyc Hb (%)	4.86	(0.51)	4.87	(0.49)	5.01 ***	(0.47)
Serum ferritin, week 33 (μg/l)	12.5	(12.7)	13.2	(19.5)	11.6	(12.4)
Hb week 37 g/l	11.8	(0.98)	11.7	(0.93)	11.7	(0.90)
Gestational length (days)	281	(7.6)	280	(9.2)	282	(8.5)
Arm circumference (cm)	28.1	(2.91)	28.0	(2.7)	28.3	(3.4)
Triceps skinfold (mm)	17.2	(5.51)	16.5	(4.7)	16.7	(6.2)
Subscapular skinfold (mm)	16.3	(6.64)	15.5	(6.4)	15.9	(6.8)
* = $p < 0.05$						

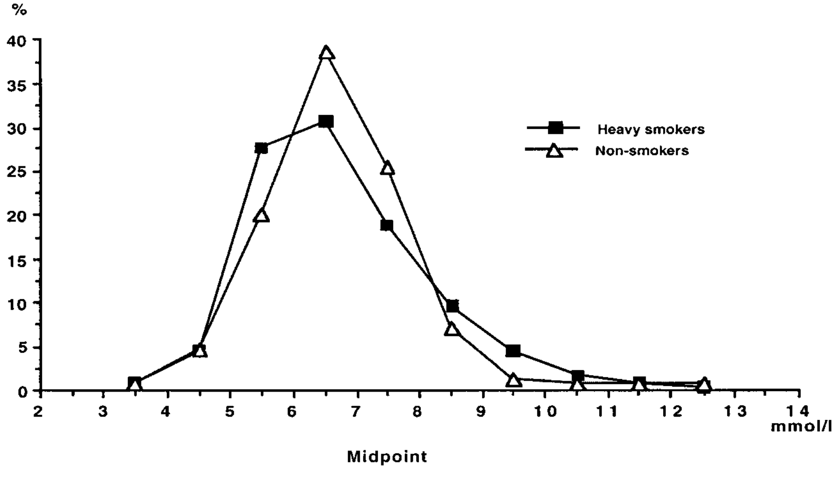
Table 3 shows anthropometric characteristics of the newborn infants. As expected, the infants delivered by smoking mothers were smaller than infants of non-smoking women.

Table 1 it is shown that smoking was associated with a higher frequency of raised 2-hour blood glucose values (in the range of cut off values for gestational diabetes). Figure 2 pictures the distribution of 2-hour values for heavily smoking mothers in comparison with nonsmoking.

Table 3. Anthropometric characteristics of infants to smoking and non-smoking mothers, mean values and SD.

	Non-smoking mothers N = 150		Smoking mothers 1-9 cigarettes per day N = 131			Smoking mothers ≥10 cigarettes per day N = 218		
	Mean	(SD)	Mean		(SD)	Mean		(SD)
Birthweight (g)	3802	(499)	3531	***	(496)	3558	***	(417)
Length (cm)	51.3	(1.93)	50.1	***	(2.4)	50.5	***	(2.1)
Head circumference (cm)	35.6	(1.2)	35.1	***	(1.3)	35.2	***	1.1
Chest circumference (cm)	34.4	(1.8)	33.7	***	(1.7)	33.7	***	(1.7)
Abdomen circumference (cm)	33.0	(2.0)	32.1	***	(2.1)	32.3	***	(1.9)
Arm circumference (cm)	11.2	(0.9)	10.8	***	(1.0)	10.8	***	(0.9)
Femur length (cm)	10.3	(1.1)	10.0	***	(1.1)	10.0	***	(1.1)
Triceps skinfold (mm)	4.94	(1.1)	4.72		(1.0)	4.74		(0.9)
Subscapular skinfold (mm)	5.07	(1.2)	4.67	***	(1.2)	4.61	***	(1.0)
** = p < 0.005 *** = p < 0.001								

Figure 2. 2-hours blood glucose levels in non-smoking and heavy smoking mothers.



Tables 4a and 4b describes in detail the mothers with a 2-hour glucose > 8.5 mmol/l (chosen as the median cut-off value of the three levels shown in Table 3) and their newborns. Between smokers and non-smokers there were neither significant differences in any anthropometric characteristic of mother or infant, nor in glucose metabolism parameters of the mothers. Compared to mothers with normal glucose levels (the whole population shown in Table 2), both smoking and nonsmoking, the mothers with high 2-hour glucose were thinner and shorter, and so were, somewhat unexpectedly, their newborns. Also fasting glucose and glyc.Hb tended to be higher, corroborating that high 2-hour blood glucose was signalling a somewhat impaired glucose tolerance.

Table 4a. Maternal characteristics for smoking and non-smoking mothers with 2-hours glucose ≥8.5 mmol/l.

Characteristic	Non-smoking mothers N = 9		Smoking mothers 1-9 cigarettes per day N = 12		Smoking mothers ≥10 cigarettes per day N = 27	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age (years)	28.6	(2.4)	27.6	(2.5)	28.7	(3.6)
BMI	20.5	(2.3)	22.2	(5.1)	21.6	(2.6)
Pre-pregnancy weight (kg)	54.1	(8.0)	59.2	(15.2)	59.1	(7.7)
Height (cm)	162	(6.3)	163	(6.1)	166	(7.1)
Pregnancy weight gain	13.2	(3.5)	11.9	(5.3)	14.4	(4.8)
Fasting glucose (mmol/l)	4.86	(0.5)	5.2	(0.9)	4.86	(0.5)
2-hours glucose (mmol/l)	9.89	(1.6)	9.78	(1.3)	9.58	(1.0)
Hb week 37 (g/l)	11.9	(0.66)	11.7	(0.82)	11.6	(1.0)
Glyc Hb (%)	5.1	(0.5)	5.0	(0.5)	5.2	(0.5)
Serum ferritin 3 (μg/l)	5.4	(6.2)	21.2	(43.0)	13.3	(18.9)
Hb week 37 (g/l)	11.9	(0.66)	11.7	(0.82)	11.6	(1.0)
Gestational length (days)	280	(7.2)	277	(10.6)	281	(10.9)
Arm circum-ference (cm)	26.4	(2.8)	28.9	(4.4)	27.8	(3.3)
Triceps skinfold (mm)	15.2	(4.8)	17.1	(6.0)	17.0	(6.3)
Subscapular skinfold (mm)	14.5	(6.6)	18.6	(9.4)	18.0	(7.8)

Table 4b. Infant characteristics for smoking and non-smoking mothers with 2-hours glucose ≥ 8.5 mmol/l.

Characteristic	Non-smoking mothers N = 9		Smoking mothers 1-9 cigarettes per day N = 12		Smoking mothers ≥10 cigarettes per day N = 27	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Birthweight (g)	3631	(417)	3615	(581)	3499	(409)
Length (cm	51.4	(2.6)	49.8	(3.3)	50.6	(2.0)
Head circumference (cm)	35.7	(1.0)	35.1	(1.5)	35.1	(1.2)
Chest circumference (cm)	33.7	(1.3)	33.6	(2.1)	33.6	(1.8)
Abdomen circumference (cm)	32.1	(2.6)	31.7	(1.9)	32.0	(1.9)
Arm circumference (cm)	10.9	(0.8)	11.1	(0.8)	10.7	(0.9)
Femur length (cm)	10.0	(0.9)	10.0	(1.4)	9.8	(1.2)
Triceps skinfold (mm)	4.50	(0.7)	5.40	(0.68)	4.70	(1.0)
Subscapular skinfold (mm)	4.11	(0.7)	5.38	(1.2)	4.56	(1.0)

Table 5 shows a linear regression analysis with birthweight as dependent variable, controlling for prepregnancy weight, height, pregnancy weight gain, smoking and 2-hour blood glucose. All those variables except a low 2-hour glucose seemed to have an independent influence on the birth weight. Glucose was divided in low < 6.0 (< 25th percentile), normal > 6.0 - 7.5 < (> 25 - < 75 percentile), and relatively high ≥ 7.5 mmol/L (> 75th percentile) by use of the distribution of values in the non-smoking reference group.

The linear regression analysis in Table 6 shows the influence on blood glucose levels measured as effect on glyc.Hb, in the three groups of mothers. Age, smoking, 2-hour glucose and prepregnancy weight were independently related to glyc.Hb.

Table 5. Linear regression. Dependent variable: birth weight. Independent variables: gestational age, pre-pregnancy weight, height, pregnancy weight gain, smoking and 2-hours glucose. N = 499

	Estimated birth weight	SE	TPn H:O	Prob > T
Intercept	3709	51.8	71.7	0.0001
Gestational age				
< 270 days	-127	64.2	-2.0	0.0492
> 283 days	235	38.2	6.2	0.0001
Pre-pregnancy weight				
≤ 55 kg	-199	46.0	-4.3	0.0001
≥ 67 kg	118	47.5	2.5	0.0127
Height				
≤ 162 cm	-16	48.8	-0.3	0.7384
≥ 171 cm	99	46.0	2.1	0.0322
Pregnancy weight gain				
≤ 11 kg	-168	42.6	-4.0	0.0001
≥ 17 kg	160	46.4	3.5	0.0006
Smoking				
1-9 cig/day	-218	48.9	-4.5	0.0001
≥ 10 cig/day	-247	42.8	-5.8	0.0001
2-hours glucose				
< 25 percentile (≤ 6.0 mmol/l)	-22	44.6	-0.5	0.6187
> 75 percentile (≥ 7.5 mmol/l)	117	47.8	2.5	0.0146

Intercept (normal pregnancy): gestational age 271-282 days; 2-hours glucose between 6.1-7.4 mmol/l, no smoking, pre-pregnancy weight 55-66 kg, height 163-170 cm, pregnancy weight gain 12-16 kg.

Table 6. Linear regression. Dependent variable: Glyc Hb. Independent variables: age, pre-pregnancy weight, smoking, 2-hours glucose. N = 499

	Estimated Hblac	SE	TPn H:O	Prob > T
Intercept	4.75	0.06	85.4	0.0001
Age				
≤ 24	-0.07	0.07	-1.0	0.3160
30-34	0.13	0.05	2.5	0.0118
≥35	0.20	0.08	2.4	0.0177
Pre-pregnancy weight				
≤ 55 kg	-0.01	0.05	-0.1	0.8848
≥ 67 kg	0.12	0.06	2.2	0.0265
Smoking				
1-9 cig/day	0.10	0.06	1.8	0.0696
≥ 10 cig/day	0.17	0.05	3.1	0.0016
2-hours glucose				
≤ 25 percentile	-0.13	0.05	-2.6	0.0096
> 75 percentile	0.18	0.05	3.2	0.0013

Intercept (normal pregnancy): Age 25-29 years, no smoking, pre-pregnancy weight 55-66 kg, 2-hours glucose 6.1-7.4 mmol/l.

DISCUSSION

Studies in habitual smokers have most often been carried out in middle-aged men. Differences to non-smokers have been found both in glucose parameters and for other nutrients. Smokers seem to be relatively insulin resistant, hyperinsulinemic and dyslipidemic, and be at an increased risk of later developing Type 2 diabetes [2, 3, 19]. In patients with an already established insulin dependent diabetes mellitus the smokers have higher insulin requirements [15]. Whether young women, if they continue smoking during pregnancy, also show an increased insulin resistance in comparison to non-smoking controls is not established.

In this study of pregnant women a slightly higher mean 2-hour glucose value at OGGT in 37th week of pregnancy, and a slightly higher glyc.Hb at term, were found in heavily smoking individuals. Further, in this study no accelerating effect of higher blood glucose values on fetal growth could be seen. Smoking has been reported to give chronic metabolic derangements in the form of insulin resistance, hyperlipidaemia and hyperinsulinemia in men [6]. It is conceivable that it may also have negative effects on the developing fetus, mediated by similar effects on maternal glucose metabolism, should smoking be continued throughout pregnancy.

The acute effect of smoking on glucose metabolism may be expected to be a transient increase in blood glucose, probably from increased levels of catecholamines [21], causing increased hepatic glycogenolys and glyconeogenesis, and decreasing pancreatic insulin secretion. The chronic effects of smoking - dyslipidemia, hyperinsulinemia and insulin resistance [5] - are similar to the physiologic changes in the glucose metabolism during a normal pregnancy. As pregnancy continues, the increasing insulin resistance, at least partly due to hormones acting as insulin antagonists, is putting strain on the pancreatic insulin secretion. The metabolic adaptation during pregnancy, with higher postprandial blood glucose in the mother but a lower fasting blood glucose, promotes the nutritional supply to the fetus, not only of glucose, but of other fuels.

Both in the pregnant and nonpregnant state the insulin sensitivity is important for normal glucose disposal, without an undue stress load on the beta-cell, and also to permit lipids and proteins to be used as fuels. However, glucose metabolism parameters vary considerably between individuals. Even in nonobese normal individuals one might find an increased insulin resistance equal to that of Type 2 diabetes patients in 25% [18]. Still, the maximal secretion capacity of the beta cells would usually be sufficient to compensate for the raised demand of insulin during the later part of pregnancy. However, in some individuals glucose intolerance, i.e. gestational diabetes, occurs. In the present study 6% of non-smoking and 12.4% of smoking mothers had a 2h blood glucose value > 8.5 mmol/l. To the extent smoking causes an increased insulin resistance, this should contribute to the burden on glucose homeostasis, already caused by pregnancy per se. This is a plausible explanation for smoking mothers more often than non-smokers to display raised 2-hour glucose values after an oral glucose load.The smoking mothers did not differ from non-smokers concerning other factors known to influence insulin resistance (general health, medication, age, weight or subcutaneous fat).

The results in previous studies on the effect of smoking on blood glucose level must be evaluated with consideration of various patient categories and methodology. Attvall et al., using the normoglycemic clamp technique in a group of healthy habitual smokers, found that smoking acutely impaired insulin action, mainly due to an impaired glucose uptake by peripheral organs [2]. These results were not quite in accordance with previous data [24].

One research group reported smokers to have a more pronounced early blood glucose rise after an oral glucose load (OGTT), while the 2-hour value remained lower than in non-smokers [10]. An accelerated gastric emptying was suggested to explain this pattern, at least partly [8]. These studies were performed in middle-aged men, abstaining from smoking for at least 10 hours. However, also a delayed stomach emptying has been reported as a more "acute" effect of smoking [17]. In the present study the smoking mothers show a fairly wide distribution of 2-hour glucose values in Figure 2, possibly indicating both lower 2-hour values in some and higher values in others of the smokers. A possible reason would be that a somewhat impaired beta-cell function is needed for smoking to cause an elevated 2h blood glucose level during pregnancy, the insulin resistance otherwise being overruled. In one study with intravenous glucose tolerance tests performed in late pregnancy, the smokers were found to have an exaggerated insulin response with shorter glucose half-times [13]. In that study of selected healthy subjects, it seemed that smoking could lead to somewhat lower mean blood glucose values, perhaps contributing to the lower birth weights usually seen in smoking mothers.

The smoking mothers were required to abstain before and during the oral tolerance tests. It is difficult to exclude that a few of them did not fully comply. Stress, due to nicotine abstinence would be another hypothetical source of spurious results. However, the observed tendency towards somewhat raised glucose values among smokers in this study presumably reflects a less efficient glucose metabolism due to chronic smoking during pregnancy. The higher glyc.Hb values, reflecting mean blood glucose during the last weeks, seen among heavily smoking mothers, compared to non-smokers, support this conclusion. A raised hemoglobin A1c level among smokers has previously mainly been reported in middle aged men, also a group likely to contain individuals with a latent impaired glucose tolerance [23].

By linear regression glyc.Hb was independently somewhat influenced by age and by prepregnancy weight (to a lesser extent), but more definitely associated to heavy smoking and a 2-hour glucose > 7.5 mmol/l as seen in Table 6. Smoking and non-smoking mothers were not different in age, pre-pregnancy body weight, pregnancy weight gain, late gestational serum ferritin or hemoglobin levels (indicative of iron deficiency anemia), potentially confounding variables regarding glyc.Hb.

Gestational diabetes is a known cause of high birth weights with increased subcutaneous fat. When glucose tolerance is normal a correlation has also been demonstrated between birth weight and glucose metabolism (both IVGTT k-values and indices of insulin response) [14, 22]. This was not possible to show in newborns to the mothers with high 2-hour blood glucose in the present study. However, the heavily smoking mothers had newborns which were expectedly slightly smaller than the newborns to nonsmoking mothers with the same blood glucose. The retarding effect of smoking on the fetal growth thus overruled any accelerating effect of higher blood glucose levels, as illustrated by the regression analysis in Table 5.

Maternal body habitus must always be considered a possible confounder in the relationship between glucose tolerance and fetal growth. Fetal overgrowth may partly be attributed to maternal overweight [16]. In our group of non-smoking mothers, the nine mothers with 2-hour glucose >8.5 mmol/l were unusually thin and short compared to the rest of the non-smokers. This could have influenced on the neonatal anthropometric measurements.

CONCLUSIONS

Infants delivered by smoking mothers are, as previously shown, smaller than infants of non-smoking mothers. In this study all anthropometric parameters were negatively affected, suggesting that smoking reduces fetal growth in a general and non-selective way, giving a symmetric growth retardation. Heavily smoking mothers also more often displayed 2-hour glucose values close to the diagnostic range for gestational diabetes and they also had a higher glyc.Hb. Any glycemic effect, expected to accelerate fetal growth, was overruled by the retarding effect of smoking.

There are good reasons for pregnant women to stop smoking. The hazard of a disturbed glucose metabolism should also be considered and deserve further studies. As the effect of smoking on glucose tolerance most often has been studied in middle-aged, male populations, more research in pregnant women seems warranted.

ACKNOWLEDGEMENT

This study used data from the SGA - Scandinavia study supported by NIH, Bethesda, Washington, USA. The research was supported by funds from the Gillbergska Foundation and the medical foundation "Förenade Liv".

REFERENCES

1. Abraham, E. C. & Stallings, M.: Application of affinity chromatography for separation and quantification of glycosylated haemoglobins. J Lab Clin Med 102: 187-197, 1983.
2. Attvall, S., Fowelin, J., Lager, I., Von-Schenck, H. & Smith, U.: Smoking induces insulin resistance--a potential link with the insulin resistance syndrome. J Intern Med 233: 327-332, 1993.
3. Axelsen, M., Eliasson, B., Joheim, E., Lenner, R. A., Taskinen, M. R. & Smith, U.: Lipid intolerance in smokers [see comments]. J Intern Med 237: 449-455, 1995.
4. Bakketeig, L. S., Jacobsen, G., Hoffman, H. J., Lindmark, G., Bergsjoe, P., Molne, K. & Roedsten, J.: Pre-pregnancy risk factors of small-for-gestational age births among parous women in Scandinavia. Acta Obstet Gynecol Scand 72: 273-279, 1993.
5. Eliasson, B., Attvall, S., Taskinen, M. R. & Smith, U.: The insulin resistance syndrome in smokers is related to smoking habits. Arterioscler Thromb 14; 1946-1950, 1994.
6. Facchini, F. S., Hollenbeck, C. B., Jeppesen, J., Chen, Y. D. & Reaven, G. M.: Insulin resistance and cigarette smoking [published erratum appears in Lancet 1992 Jun 13;339(8807):1492] [see comments]. Lancet 339: 1128-1130, 1992.

7. Floyd, R. L., Zahniser, S. C., Gunter, E. P. & Kendrick, J. S.: Smoking during pregnancy: prevalence, effects, and intervention strategies.Birth 18, 48-53 1991.
8. Hanson, M. & Lilja, B.: Gastric emptying in smokers. Scand J Gastroenterol 22: 1102-1104, 1987.
9. Haste, F. M., Brooke, O. G., Anderson, H. R. & Bland, J. M.: The effect of nutritional intake on outcome of pregnancy in smokers and non-smokers. Br J Nutr 65: 347-354, 1991.
10. Janzon, L., Berntorp, K., Hanson, M., Lindell, S. E. & Trell, E.: Glucose tolerance and smoking: a population study of oral and intravenous glucose tolerance tests in middle-aged men. Diabetologia 25: 86-88, 1983.
11. Khouzami, V. A., Ginsburg, D. S., Daikoku, N. H. & Johnson, J. W.: The glucose tolerance test as a means of identifying intrauterine growth retardation. Am J Obstet Gynecol 139: 42342-6, 1981.
12. Langer, O., Damus, K., Maiman, M., Divon, M., Levy, J. & Bauman, W.: A link between relative hypoglycemia-hypoinsulinemia during oral glucose tolerance tests and intrauterine growth retardation. Am J Obstet Gynecol 155: 711-716, 1986.
13. Langhoff-Roos, J., Wibell, L., Gebre-Medhin, M. & Lindmark, G.: Effect of smoking on maternal glucose metabolism. Gynecol Obstet Invest 36: 8-11, 1993.
14. Langhoff-Roos, J., Wibell, L., Gebre-Medhin, M. & Lindmark, G.: Maternal glucose metabolism and infant birth weight: a study in healthy pregnant women. Diabetes Res 8: 165-170, 1988.
15. Madsbad, S., McNair, P., Christensen, M. S., Christiansen, C., Faber, O. K., Binder, C. & Transbol, I.: Influence of smoking on insulin requirement and metbolic status in diabetes mellitus. Diabetes Care 3: 41-43, 1980.
16. Maresh, M., Beard, R. W., Bray, C. S., Elkeles, R. S. & Wadsworth, J.: Factors predisposing to and outcome of gestational diabetes. Obstet Gynecol 74: 342-346, 1989.
17. Nowak, A., Jonderko, K., Kaczor, R., Nowak, S. & Skrzypek, D.: Effect of cigarette smoking on gastric emptying in patients with an active duodenal ulcer. Scand J Gastroenterol 22: 1105-1108, 1987.
18. Reaven, G. M.: Role of Insulin Resistance in Human Disease. Diab. 37: 1595-1606, 1988.
19. Rimm, E. B., Manson, J. E., Stampfer, M. J., Colditz, G. A., Willett, W. C., Rosner, B., Hennekens, C. H. & Speizer, F. E.: Cigarette smoking and the risk of diabetes in women. Am J Public Health 83: 211-214, 1993.
20. SAS (NC: SAS Institute, Cary) 1985.
21. Surgeon & General (1979) Smoking and health.
22. Tallarigo, L., Giampietro, O. & Penno, G.: Relation of glucose tolerance to complications of pregnancy in nondiabetic women. N Engl J Med 315: 989-992, 1986.

23. Urberg, M., Shammas, R. & Rajdev, K.: The effects of cigarette smoking on glycosylated hemoglobin in nondiabetic individuals [see comments]. J Fam Pract 28: 529-531, 1989.
24. Walsh, C. H., Wright, A. D., Allbutt, E. & Pollock, A.: The effect of cigarette smoking on blood sugar, serum insulin and non esterified fatty acids in diabetic and non diabetic subjects. Diabetologia 13: 491-494, 1977.

Corresponding address:
Dr Birgitta Zarén
Department of Women's and Children's Health
Section for Obstetrics and Gynaecology
University Hospital
SE-751 85 UPPSALA
Sweden
phone: +46 18 66 30 00
fax: +46 18 55 97 75