METABOLIC ADJUSTMENTS IN PREGNANCY

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INTRODUCTION

Physiologically, the mother becomes almost a new person during the nine months of pregnancy. Virtually every system undergoes some change. In this respect, the pregnant woman is a natural laboratory in which to observe the effects of pregnancy hormones and nutritional demands of the fetus. Moreover, understanding the maternal adaptations to fetal growth has an important practical aspect in the management of the abnormal pregnancy. The question may be posed whether the fetus acts solely as a parasite draining fuels from the mother or whether the mother adapts to augment the supply of energy fuels to the fetus.

The Maltese woman is characterised by a high incidence of abnormal glucose metabolism during pregnancy when compared to other populations. Gestational impaired glucose tolerance, defined by the W.H.O. criteria, has been shown to affect about 14% of pregnant Maltese women[1]. Women with gestational impaired glucose tolerance have been shown to exhibit specific metabolic adaptations during their pregnancy[2]. This study attempts to identify the metabolic alterations which occur during the last trimester of pregnancy in this high risk population.

MATERIAL AND METHODS

One hundred and forty pregnant women booking for antenatal care at Karen Grech Hospital (Malta) were selected randomly, excluding only patients known to be diabetic. Karin Grech Hospital accounts for about 90% of all the deliveries which occur in the Maltese Islands. The study population thus constituted about 2.5% of the total population in Malta during the year of the study. Blood was taken in the fasting state from all the subjects who subsequently underwent a 75-gram glucose load for oral glucose tolerance testing at 24 and 34 weeks of pregnancy. One mother was found to have diabetes mellitus and was excluded from the study. The non-pregnant population included the data of the 645 non-diabetic women aged 15-44 years who participated in the National Diabetes Programme in Malta[3], besides data from other studies measuring haemoglobin levels in 1008 women of childbearing age[4]. The data were statistically tested using the standard error of the means, with significance being accepted at a probability value of less than 0.05.

RESULTS

Some maternal adaptations in metabolic functions can be understood from the pattern of weight gain in pregnancy. The last trimester is the time when nutritional demands by the conceptus on maternal fuel supplies are greatest and the main contribution to maternal weight is the growth of the conceptus. In the first trimester there appeared to be a gain in mean body weight of approximately 8.3% from 60.32 kg in the non-pregnant female to 65.31 kg at 24 weeks of pregnancy. As the pregnancy proceeded in the third trimester, there appeared to be a gain in body weight of 3.55 kg, a 5.4% rise over the mean body weight at 24 weeks. This increase was not solely contributed to by conceptual growth, since a 12.4% gain in fat area could be demonstrated (Table 1). The regulation of fuel metabolism in general is dependant on the relationship of insulin with other regulatory hormones.

Table 1: Body Weight Accumulation (mean ± s.d.)

	24 weeks	*34 weeks*	*% change*	*p value*
Maternal weight (kg)	65.31±13.66	68.86±13.55	+5.4	p<0.05
Skinfold thickness				
midarm triceps	20.30±5.89	24.04±6.86	±18.4	p<0.001
suprailiac	23.66±7.0	27.79±7.75	±17.5	p<0.001
Fat Area	193.52	217.42	±12.4	–

The mean fasting blood glucose levels at 24 weeks appeared to be at a lower level than the mean value in the non-pregnant female. The level subsequently rose by a significant proportion (12.4%) by 34 weeks. The blood glucose level two hour post-glucose load was markedly higher (28.5%) at 24 weeks than pre-pregnancy levels. The level at 34 weeks showed a non-significant drop. The basal insulin at 24 weeks showed a marked drop of 53.2% from pre-pregnancy levels, but by 34 weeks rose to 70.4% of the pre-pregnancy level. The mean fasting plasma C-peptide at 24 weeks showed a 22.9% rise from the pre-pregnancy level and subsequently showed a further 12.5% rise from the pre-pregnancy level throughout the third trimester. Glycosyated haemoglobin levels showed similar trends with a fall in mean levels in the first trimester and a rise during the third trimester (Table 3). As gestation proceeded from 24 to 34 weeks there appeared to be an increase in the stimulated insulin secretory responses in association with an increase in the basal insulin and glucose concentrations. Thus there appeared to be a 45.0 and a 103.9% rise in the early 30 minute and the 2 hour insulin secretory response to a 75g oral glucose load respectively. The response to the glucose load suggests a delay in insulin response at 34 weeks with higher 30 minute blood glucose and insulin levels. There was however a discordant response at 2 hours with no significant change in glucose load in the presence of elevated insulin levels (Table 2).

The cholesterol and triglyceride levels rose persistently throughout gestation from the pre-pregnancy levels with the rise being more marked in the triglyceride levels. The serum albumin concentration on the other hand showed a significant fall of about 10.5% with advancing gestation while the haemoglobin level rose after a 15% fall from the pre-pregnancy level. The products of metabolism in the form of blood urea and serum creatinine showed a fall in the mean values at 24 weeks from pre-pregnancy levels but increased subsequently in the third trimester. No significant change was noted during pregnancy in the urine nitrogen excretion calculated from the appropriate formula involving the urine urea nitrogen (Table 3), though increasing degrees of body weight seemed to be associated with higher levels of urine nitrogen excretion so that whereas in lean women there was a -1.5% change, in the obese woman the change was +9.3% (Table 4). These differences were however not statistically significant.

Table 2: Response to 75g Oral Glucose Load (mean ± s.d.)

	24 weeks	*34 weeks*	*p value*
Blood Glucose mmol/l			
Fasting	4.05±1.61	4.55±1.35	p<0.01
30 min	5.97±1.81	6.62±1.68	p<0.01
2 hrs	6.04±1.86	5.69±1.72	p>0.1
Serum Insulin uIU/ml			
Fasting	10.74±10.00	16.18±13.38	p<0.001
30 min	55.88±43.82	87.50±57.65	p<0.001
2 hrs	45.88±42.50	64.27±51.18	p<0.01
Insulin Secretory Response			
Early 30 minute	22.64	32.83	–
Late 2 hours	16.38	33.39	–

Table 3: Changes in Blood Biochemistry (mean ± s.d.)
[* based on Katona et al, 1983; ** Fenech, 1968]

	Pre-pregnancy	*24 weeks*	*34 weeks*	*p value (24vs34wks)*
Body weight kg	60.32*	65.31±13.66	68.86±13.55	p<0.05
Insulin uIU/ml	23.0*	10.74±10.00	16.18±13.38	p<0.001
C-peptide nmol/l	0.48*	0.59±0.33	0.65±0.10	p<0.05
Fasting Glucose nmol/l	4.3*	4.05±1.61	4.55±1.35	p<0.01
2-hour Glucose nmol/l	4.7*	6.04±1.86	5.69±1.72	p>0.10
HbA glyc %	6.7*	5.75±2.56	6.67±2.81	p<0.01
Cholesterol nmol/l	4.81*	6.60±1.45	7.72±1.65	p<0.001
Triglycerides nmol/l	1.14*	1.85±0.71	3.87±1.56	p<0.001
Albumin g/l	–	31.57±4.84	28.26±5.20	p<0.001
Haemoglobin g/dl	13.6**	11.56±3.91	12.93±3.62	p<0.01
Urea mg/dl	30.4*	24.10±12.16	30.21±11.84	p<0.001
Creatinine umol/l	47.71*	30.21±13.18	33.55±14.23	p<0.05
Urine N_2 excretion	–	7.08±5.32	7.43±5.15	p>0.5

Table 4: Urine Nitrogen Excretion (mean ± s.d.)

	24 weeks	*34 weeks*	*% change*	*p value*
Lean	7.16±4.6	7.05±4.6	-1.5	p>0.5
Overweight	7.24±5.2	7.62±5.8	+5.3	p>0.5
Obese	7.86±6.3	8.59±6.8	+9.3	p>0.5

DISCUSSION

Pregnancy is characterised by major physiological adjustments affecting every system of the body. The changes are frequently on a scale otherwise unknown in healthy adult life and have led to diagnostic confusions. The altered conditions characteristic of pregnancy allow maximum efficiency of fetal growth and metabolism, and are initiated and controlled by the various placental hormones. The changes noted to occur in body fat storage, and insulin secretion and action suggest that there is both a maternal "push" as well as a fetal "pull" with respect to nutrient flow across the placenta.

The average healthy pregnant woman, eating to appetite, has been reported to gain about 12.5 kg of bodyweight, considerably more than can be accounted for by the product of conception, the growth of the uterus and breasts and the expansion of the blood volume. Approximately half this weight gain is accounted for during the first two trimesters, while a further third is accumulated from 24 to 34 weeks of pregnancy[5]. With a total mean weight grain of 8.5 kg, the Maltese pregnant woman appeared to follow a similar pattern but with a slight decrease in the overall weight gain. This weight gain is significantly contributed to by an increase in the fat area. The discrepancy to reported averages may be accounted for by the fact that a significant proportion (55.8%) of women participating in the study were overweight or obese. It has been shown that previously overweight women gain less adipose tissue mass overall in pregnancy, possibly because the hypothalamic appetite centre becomes somehow "awakened" to the degree of maternal adiposity[5]. It appears therefore that the main stimulus to fat storage in the pregnant woman is not simply through the appetite-satiety centres driving the mother to eat more but by a more fundamental change in the control of energy balance. There is animal evidence to suggest that the total quantity of body fat is controlled by some central "lipostat" which is set higher during pregnancy by the influence of progesterone. The new level of body fat is achieved by eating more and expending less energy[6].

Insulin is central to adipose tissue metabolism as well as the regulation of fuel metabolism in general. The fasting blood glucose level fell in the first two trimesters by about 5.8%, while the fasting insulin level fell by 53%. During the third trimester both the fasting glucose and insulin levels rose significantly to approximate pre-pregnancy levels. During the glucose tolerance test, it appears that as pregnancy proceeds, there is a mild deterioration in blood glucose levels in spite of the increased secretion of insulin, thus resulting in a rise in both the early and late insulin secretory response. The changes demonstrated in the Maltese pregnant women are similar to those described in other populations, reflecting the recognised balance between the "accelerated catabolism" in the fasted state and the "facilitated anabolism" of the fed state[7,8]. The apparent paradox of decreased glucose tolerance of pregnancy in the face of a greatly raised level of circulating insulin suggest a "resistance" to insulin action. The nature of the insulin resistance in pregnancy is not yet fully elucidated, but appears to be related to changes in the insulin receptors which occurs during pregnancy. This insulin resistance serves to maintain glucose concentrations within a reasonable range and reduce maternal glucose utilisation, thereby maintaining an adequate plasma glucose supply for the fetus. In this manner, glucose in the circulation is "pushed" to the fetus in addition to the passive "pull" of nutrients by the fetus from the mother[9]. Other hormonal alterations during pregnancy affect carbohydrate metabolism. Free cortisol concentrations are increased in pregnancy and have been associated with reductions in insulin effectiveness. Growth hormone reduces insulin binding to receptors, while the analogous placental hormone – human chorionic somatomammotropin – could also reduce insulin receptor concentrations. Hyperprolactinaemia has been shown to produce a hyperglycaemic hyperinsulinaemic state similar to that seen in late pregnancy. Glucose intolerance and insulin resistance could also be mediated in pregnancy through increased secretion of pancreatic glucagon or increased insensitivity of the liver to glucagon effects[10].

Lipoprotein composition undergoes interesting changes during pregnancy. The triglyceride and cholesterol content of all three lipoprotein fractions is increased. The

endogenous hyperlipidaemia of pregnancy is a progressive one resulting primarily by an increased endogenous tri-glyceride entry into the circulation[11]. The changes noted in the Maltese population followed the previously reported trends. The albumin level on the other hand has been shown to decline as pregnancy advances. It has been suggested that this fall in serum albumin con-centration is principally a haemodilutional effect, but may also be contributed to by a fall in the total circulating albumin mass[12]. Haemoglobin con-centration, in contrast to previously reported trends, rose significantly during the third trimester. This rise was probably due to the routine iron supplementation the women received during pregnancy.

The biochemical parameters of waste-end products in the form of blood urea and serum creatinine showed a significant drop from the pre-pregnancy values by 24 weeks of pregnancy, the values later rising in the third trimester in contradistinction to the generally expected trends. The urine nitrogen excretion similarly rose in the third trimester. These waste-end product parameters are however not accurate markers for metabolic function since they are closely dependant of renal function, which is rather unsatisfactory to study during pregnancy because of the confounding influence of a number of factors.

It appears therefore that the "parasitic" fetus alters significantly the homeostatic mechanisms of its host so that it produces an internal milieu which allows maximum efficiency for its growth and metabolism. Many of these physiological changes occur and reach their full development in early pregnancy when the metabolic demands of the fetus are presumably negligible. Thus the physiological adjustments of pregnancy anticipate possible needs, unlike most other physiological responses which occur after a need has arisen. The pregnant woman is physiologically almost a different species.

REFERENCES

1. Schranz AG. and Savona-Ventura C.: Gestational impaired glucose tolerance in Malta. Bulletin Medit. Group for the Study of Diabetes. 1991, 4(2):9-14.
2. Schranz AG. and Savona-Ventura C.: Metabolic alternations in gestational IGT. Diabet Croatica. 1993, 22-3:55-59.
3. Katona G., Aganovic I., Vuskan V., and Skrabalo Z.: National Diabetes Programme in Malta – Final Report Phase I-II. W.H.O., Geneva, 1983, +115p.
4. Fenech, FF.: Haemoglobin levels in maltese women of childbearing age. St Luke's Hosp Gaz, 1958, 3(2):79-82.
5. Hytten FE., Thomson AM., and Taggart N.: Total body water in normal pregnancy. Obstet Gynaecol Br Commonw, 1966, 73:553.
6. Knopp RH.: Fuel metabolism in pregnancy. Contemp Ob/Gyn, 1978, 12:83.
7. Freinkel N.: Of Pregnancy and progeny: Banting Lecture 1980. Diabetes, 1980, 29:1023-1035.
8. Hollingsworth DR.: Types of carbohydrate intolerance in pregnancy. In Pregnancy, Diabetes and Birth (ed. Hollingsworth DR.), Williams & Wilkins, Baltimore, 1984, 2:2-16.
9. Knopp RH., Montes A., Childs M, Li JR., and Mabuchi H.: Metabolic adjustments in normal and diabetic pregnancy. Clinical Obstet Gynecol, 1981, 24:21-49.
10. Kalkhoff RH., Kissebah AH., and Kim HJ.: Carbohydrate and lipid metabolism during pregnancy: relationship to gestational hormone action. Semin Perinatol, 1978, 2:291.
11. Hollingworth DR.: Metabolic changes in Pregnancy. In Pregnancy in Pregnancy Diabetes and Birth (ed. Hollingworth DR.), Williams & Wilkins, Baltimore, 1984, 4:21-38.
12. Studd, J.: The plasma proteins in pregnancy. Clinics Obstet Gynaecol, 1975, 2:285-300.