Journal of the Medical Research Institute
Vol. 23 No. 2 (2002)

DIABETES IN PREGNANCY: INFLUENCE ON FETAL DEVELOPMENT

Samia A. El-Dardiry, Nagwa M. Assem, Khalid O. Aboulnaja*, Anas M. El-Marzouki, and Ahmed Abou Freikha**

Dept. of Biochemistry, Faculty of Medicine, Tanta University, Medical Research Institute, Alexandria University, Faculty of Science, King Abdulaziz University, Dept. of Obstetrics and Gynecology, Faculty of Medicine, King Abdulaziz University and Tanta University**.*

Summary

Multiple metabolic and endocrine mechanisms include progressive adaptation of maternal metabolism through the mechanisms associated with adiposity, glycemic status, hormonal milieu and oxidative stress. Assessed influence of glycemic and hormonal status in coordination with magnitude of oxidative stress in diabetic versus non-diabetic pregnant women elaborated significant increase in the circulating levels of human placental lactogen (hPL), free estriol (E3), total estradiol (E2), fructosamine, glycated albumin, leptin, fasting insulin versus decreased antioxidant defense mechanisms and involved relative increase in maternal weight, body mass index (BMI), both fetal birth weight and neonatal leptin level. Maternal and neonatal thyroid functions presented, in diabetic relative to non-diabetic pregnancies, a significant increase in serum levels of thyroglobulin (TG), thyroid stimulating hormone (TSH), thyroid binding globulin (TBG) versus decreased level of free thyroxine ((FT4). The data verified the impact of glycemic status and obesity on free radical mechanisms influencing hormonal milieu, thyroid economy and antioxidant defense mechanisms with a subsequent outcome on fetal growth and maternal insult.

Introduction

References indicated that control of glycemic status could delay the onset of ischemic changes (1). During pregnancy, emerging challenges point to the fact that maternal glucoregulation influences the metabolic environment during intrauterine development which may impact adversely on fetal outcome (2). Hence, a disorder of multiple fuels and many nutrients besides glucose are disturbed in event to mildest forms of diabetes in pregnancy (3).

Thyroid disorders are particularly frequent in women and, second to diabetes are the most common endocrine disease during pregnancy (4). On the other hand, poorly compensated diabetes mellitus may cause alterations in the production and metabolism of thyroid hormones (4). Changes in maternal thyroid economy have been reported to occur during gestation in normal cases and furthermore in cases delivering small for gestational age babies (5).

Obesity in pregnancy is characterized by insulin resistance with advanced gestation (6,7). A close association between

hyperinsulinemia and hyperleptinemia suggests that *(ob)* gene expression may be mediated by insulin (8). The diabetic status is associated with antioxidant capacity and with oxidative stress (9,10). Fructosamine and glycated albumin have been used as parameters of the long term glycemic status in diabetes mellitus and reflect maternal glucose metabolism during pregnancy (2). On this basis, the present study aims to evaluate the relationship between diabetes in pregnancy and the influence of obesity, glycemic, thyroidal, and hormonal status and oxidative stress on fetal development.

Material and Methods

The investigation was composed of a selected group of twenty diabetic and twenty non-diabetic pregnant women. Their gestational age range was 37-40 weeks and their age range was 18-28 years. None of these cases had suffered prior to pregnancy from hypertensive or cardiac manifestations. They had normal liver and kidney function tests. All cases were subjected to the following analyses: anthropometric indices [maternal weight, body mass index (BMI) (13), fetal birth weight, gestational age at birth] and maternal and neonatal leptin levels (14).

Blood samples were withdrawn after overnight fasting and sera were separated by centrifugation. The following biochemical parameters were assessed: human placental lactogen (hPL) by radioimmunoassay (RIA) (13) using commercial kits from Diagnostic Products Corporation (DPC), Los Angles, California, USA; free estriol (E3), total estradiol (E2) (14); fructosamine (15,16), glycated albumin (17); insulin (18); and maternal and neonatal thyroid hormonal parameters including thyroglobulin (TG) which was assessed by double antibody RIA (19) using commercial kits provided by Techland, Liege, Belgium; thyroid stimulating hormone (TSH) (20); free thyroxine (FT4) (21); thyroid binding globulin (TBG) that was monitored according to Glinoer et al., 1978 (22) using conventional RIA (Baxter Cambridge MA, USA), and TBG saturation was calculated from individual T4 and TBG determinations as the molar T4/TBG ratio (23). Antioxidant status was monitored by the determination of enzyme activity of superoxide dismutase (24); plasma thiols, lysate thiols (25); and ceruloplasmin (26).

Results

Anthropometric indices (Table I) showed that in diabetic pregnancy (GII) a statistically significant increase in maternal weight and body mass index (BMI) ($P<0.05$) and a more significant increment in fetal birth weight and maternal and neonatal serum leptin levels ($P<0.01$) when compared to normal gestation levels (GI).

Glycemic status and hormonal levels (Table II) indicated in diabetic pregnancy (GII) statistically significant higher levels of hPL, E3, E2 and fasting insulin ($P<0.05$) and a more significant values ($P<0.01$) of fructosamine and glycated albumin in comparison to GI.

Measurement of maternal thyroid hormones (Table III) revealed in diabetic pregnancy (GII) a statistically significant increase in levels of TG, TSH, TBG and TBG saturation versus a significant decline in levels of FT4 ($P<0.01$). The same pattern of results was monitored in levels of neonatal thyroid hormones but with less

Table (I): Anthropometric Indices in Maternal and Neonates in Selected Cases. Data are Mean ± SD.

Parameter	Normal Gestation GI (n=20)	Diabetic Pregnancy GII (n=20)
Maternal Weight (Kg)	79.1±19.2	91.8±23.2*
Body Mass Index (BMI) (Kg/m^2)	27.8±7.9	34.7±9.8*
Fetal Birth Weight (kg)	2.82±0.88	3.91±1.2**
Fetal BMI (kg/m^2)	13.4±3.3	16.5±4.6*
Gestational Age at Birth (Weeks)	39.3±11.2	38.6±11.0
Maternal Serum Leptin (ng/mL)	23.8±6.6	33.7±10.8**
Neonatal Serum, Leptin (ng/mL)	4.12±1.2	5.83±1.8**

Statistically Significant Values at * (P<0.05) and **(P<0.01).

Table (II): Glycemic Status and Hormonal levels in Selected Cases. Data are Mean ± SD.

Parameter	Normal Gestation GI (n=20)	Diabetic Pregnancy GII (n=20)
Human Placental Lactogen (hPL) (mg/L)	6.32±1.8	8.21±2.8*
Free Estriol (E3) (n mol/L)	26.4±7.8	34.1±10.2*
Total Estradiol (E2) (n mol/L)	75.1±16.9	89.7±23.6*
Fructosamine (µ mol/L)	282±44.3	259±59.1**
Glycated Albumin(%)	14.1±3.9	18.8±4.6**
Fasting Serum Insulin (IU/mL)	8.93±2.4	11.2±3.3*

Statistically Significant Values at * (P<0.05) and **(P<0.01).

Table (III): Maternal and Neonatal Thyroid Function in Selected Cases. Data are Mean ± SD.

Parameter	Normal Gestation GI (n=20)	Diabetic Pregnancy GII (n=20)
A) Maternal Thyroid Hormones		
Serum Thyroglobulin (TG) (µg/L)	32.4±9.0	44.7±14.6**
Thyroid Stimulating Hormone (TSH) (mU/L)		
Free Thyroxine (FT4) (pmol/L)	2.32±0.72	3.34±1.10**
Thyroid-binding Globulin (TBG) (mg/L)	17.1±4.8	12.3±3.9
TBG Saturation(%)	26.3±8.1	36.9±10.6**
B) Neonatal Thyroid Hormones	33.8±8.7	45.2±12.6**
TG (µg/L)	72.4±18.7	60.1±13.9*
TSH (mU/L)	6.24±1.9	8.12±2.6*
FT4 (pmol/L)	21.7±6.7	16.8±4.9*

Statistically Significant Values at * (P<0.05) and **(P<0.01).

Table (IV): Indices of Oxidative Stress in Selected Cases. Data are Mean ± SD.

Parameter	Normal Gestation GI (n=20)	Diabetic Pregnancy GII (n=20)
Superoxide Dismutase (SOD) (µg/mL)	51.7±13.4	38.5±10.9**
Plasma Thiol (U/L)	316±87.4	236±66.7**
Lysate Thiol (U/L)	451±98.5	347±86.9**
Ceruloplasmin (Cp) (mg/dL)	23.9±6.9	32.7±9.1**

Statistically Significant Values at **(P<0.01).

significant differences (P<0.05) between GI and GII.

Indices of oxidative stress (Table IV) illustrated in diabetic pregnancy (GII) a statistically significant reduction (P<0.01) in values of superoxide dismutase (SOD), plasma thiol and lysate thiol versus a significant increment in values of ceruloplasmin (P<0.01).

Discussion

The present data coincide with the emerging awareness that all aspects of intrauterine development are exequisitively sensitive to even the most minor abnormalities of ambient fuels. It would comply with implications that diabetes with pregnancy has an impact on the long-range anthropometric, metabolic, and perhaps even cognitive development of the offspring (3).

The assessed increments herein of fructosamine levels in diabetic gestation reflect the recent glycemic state of abnormal glucose tolerance. Moreover, the monitored increments of glycated albumin provides additional information for the detection and control of abnormal glucose tolerance (2). Hence, protein glycation reflects the non-enzymatic reaction between glucose and an amino acid group in protein which may be altered in a manner dependent on the level of the glycemic control (27). This has been hypothesized to contribute to the genesis of neural and vascular complications as well as permeability factors (28).

From another perspective, women who gain more weight during pregnancy were noted to pertain higher leptin levels (29). Such a profile reflects the hypostatic role of leptin as an afferent signal in a feedback loop regulating fat mass (30). Evidently, this signal could be defective in obese individuals (31,32). In consistence, hyperleptinemia and intrauterine growth retardation may be inter-related (33). Reports also noted in obese women who have developed gestational diabetes, lower ambilical artery flow which influences the pattern of fetal growth (34).

On the other hand, it was noted that increased basal and glucose-stimulated levels of plasma insulin with advancing gestation is paralleled with a progressive increase in progesterone, estrogen, and human placental lactogen (hPL) which may affect the expression of *(ob)* gene (35). However, the close association between hyperinsulinemia and hyperleptinemia

appears to be more complex in obese states (36). Previous findings illustrated the administration of antidiabetics not only improves insulin sensitivity and glucose homeostasis, but also down regulates the *(ob)* gene expression (37).

In alignment, the impact of glycemic and thyroidal status on fetal development herein is verified by the variations in maternal hormonal levels that were monitored with the diabetic gestational state. Hence, the incremental levels of hPL, E2, and TSH was paralleled with decreased T3 and T4 maternal and neonatal values reflecting mild thyroid abnormalities. Moreover, the lower birth weights confirm such relationships to the state of biochemical hypothyroidism evidenced herein and reported elsewhere (23,38).

In fact, due to physiological changes of thyroid hormone economy in the child bearing period, thyroid dysfunction may affect carbohydrate metabolism and worsen glucose control in diabetic state. As well, poorly compensated diabetes may cause alterations in the production and metabolism of thyroid hormones (39).

On the other hand, increased serum TBG coincides with the assessed hyper-estrogenic state potentiated by the diabetic impact. This could be associated with a decreased peripheral TBG degradation as noted elsewhere (40). Nonetheless, reports also identified an estrogen-induced mechanism influencing a reduced clearance rate of TBG with increased sialation (41,42).

The reduction of FT4 in maternal diabetic states may develop due to TBG desaturation within the pattern of thyroidal adjustment in diabetes within the 3rd trimester of pregnancy. Subsequently, fetal development of mild hypothyroidism viz lower levels of TG and FT4 versus higher TSH was assessed herewith in newborns. Reports indicated that hypothyroidism apparent during fetal and early postnatal life not only affects postnatal growth but also brain development which could influence physical and cognitive capabilities (43).

It is evident from the data that maternal thyroid economy presents a higher degree of glandular stimulation verified by higher T3/T4 ratio, TSH and TG relative to TBG desaturation. This represents hypo-thyroxinemia as higher setting of pituitary thyrostat. Consistently, maternal thyroid economy influences fetal birth weight and TSH in the overall pattern verified elsewhere in small for gestational age babies (43,44).

Conceivably, fetal birth weight herein is influenced by the impact of obesity, glycemic status, and oxidative stress viz decrements in plasma thiol, lysate thiol and superoxide dismutase. Hence, they coordinated with hyperleptinemia, hyperinsulinemia, increments of fructosamine, glycated albumin and ceruloplasmin. Subsequently, alterations in cord blood levels of ascorbic acid and ceruloplasmin versus reduced total free radical trapping ability of cord blood (45), and neonatal oxygen radical toxicity may event as noted elsewhere (46,47). It would delineate that these babies are more susceptible to tissue injury owing to imbalanced prooxidant/oxidant mechanisms initiating formation of hydroxyl radicals playing a role in cellular damage as reported in premature babies (48,49). The maternal inefficient antioxidant capacity implements liability to

participate in pathogenic mechanisms involving retinal microvascular vessels leading to the evolution of retinopathy(50).

In conclusion, the glycemic impact on thyroid economy could perpetuate a hypothyroid status which, on the long term, may affect intellectual capabilities of the newborn. The influence of oxidative stress may delineate the initiation of hydroxyl radical formation with its sequelae of events resulting in tissue injury and cellular damage.

References

1. Kesler A, Kaneti H, Kidron D. Transient cortical blindness in pre-eclampsia with indication of generalized vascular endothelial damage. J Neuroophthalmol 1998; 18 (3): 163-5.
2. Kurishita M, Nakashima K, Kozu H. Glycated hemoglobin of fractionated erythrocytes, glycated albumin, and plasma fructosamine during pregnancy. Chem Pharm Bull (Tokyo) 1992; 40(2): 387-91.
3. Freinkel N, Metzger BE. Emerging challenges in diabetic pregnancy: diabetic embryopathy and gestational diabetes. The Diabetes Annual 1988; 179-95.
4. Glinoer D, De Nayer P, Lemone N, Robyn C, Van Steirteghem A, Kinthaert J, Lejeune B. Regulation of maternal thyroid during pregnancy. J Clin Endocrinol Metab 1990; 71: 276-80.
5. Aboulnaja KO, El-Dardiry SA, Abduljabbar HS. Pre-eclampsia: Sustained effects by hepatic predisposition. J Med Res Inst 1997; 18 (2): 13-25.
6. Zuniga-Gonzalez SA. Diabetes and pregnancy. Ginecol Obstet Mex 1998; 66: 221-6.
7. Schindler AE. Obesity and pregnancy. Zentralbl Gynakol 1998; 120 (5): 241-4.
8. Cusin I, Sainsburg A, Doyle P, Rohner-Jeanrenaud F, Jeanrenaud B. The ob gene and insulin. A relationship leading to clues to the understanding of obesity. Diabetes 1995; 44: 1467-70.
9. Bloomgarden Z. Antioxidants and diabetes. Diabetes 1997; 20 (4): 671-4.
10. Giugliano D, Corriello A. Oxidative stress and diabetic vascular complications. Diabetes Care 1996; 19 (3): 257-67.
11. Keys A, Fidanaza F, Karvonen MJ. Indices of relative weight and obesity. J Chronic Dis 1972; 25: 329.
12. Ma ZA, Gingerich RL, Santiago JV, Klein S, Smith HC, Landt M. Radioimmunoassay of leptin in human plasma. Clin Chem 1996;42: 942-6.
13. Tanaka T, Shiu R, Gout P. A new sensitive and specific assay for lactogenic hormones: Measurement of prolactin and growth hormones in human serum. J Clin Endocrinol Metab 1980; 51: 1058-63.
14. Gronowski M, Landau-Levine M. Reproductive endocrine function. In: Burtis CA & Ashwood ER (eds.). Tietz Textbook of Clinical Chemistry. 3rd ed, Philadelphia, USA. W.B. Saunders Company, 1999: 1601-41.
15. Johnson RN, Metcalf PA, Baker JR. Fructosamine: A new approach to the estimation of serum glycosylprotein. An index of diabetic control. Clin Chim Acta 1983; 127: 87-95.
16. Schleicher ED, Vogt BW. Standardization of serum fructosamine assays. Clin Chem 1990; 36: 136-9.
17. Dolhofer R, Wieland OH. Increased glycosylation of serum albumin in diabetes mellitus. Diabetes 1980; 29:417-22.
18. Haffner SM, Stern MP, Hazuda HP. Pugh JA, Patterson JK. Hyperinsulinemia in a population at a high risk for non-insulin dependent diabetes mellitus. N Engl J Med 1986; 315: 220-4.
19. Caldwell G. A new strategy for thyroid function testing. Lancet 1985; 1: 1117.
20. Penary A, Hersham JM, Parlow AF. A sensitive and precise radioimmunoassay for human thyroid stimulating hormone. J Clin Endocrin 1975; 41: 676.
21. Franklyn JA, Sheppard MC, Ramsden DB. Serum free thyroxine and free triiodothyronine concentration in pregnancy. Br Med J 1983; 287: 394.

22. Glinoer D, Frenandez-Deville M, Ermans AM. Use of direct thyroxine-binding globulin measurement in the evaluation of thyroid function. J Endocrinol Invest 1978; 1: 329.
23. Lao TT, Chin RKH, Swaminathan R, Lam YM. Maternal thyroid hormones and outcome of pre-eclamptic pregnancies. Br J Obstet Gynecol 1990; 97: 71-4.
24. Misra HP, Fridovich I. Superoxide dismutase, a photochemical augmentation assay. Arch Biochem Biophys 1977; 181: 308.
25. Ellman GL. Tissue sulphhydryl groups. In: Davis H. (ed.). Therapy of liver disease. London, Balliere Tindall 1979: 1-20.
26. Mancini G, Vaernman J, Carbonara A, Hermans J. A single radioimmunodiffusion method for the immunological quantitation of proteins. Immunochem 1965; 2: 235.
27. Brownlee M, Vlassara H, Cerami A. Non-enzymatic glycosylation and the pathogenesis of diabetic complications. Ann Intern Med 1984; 101:527-37
28. Daniels BS, Hauser EB. Glycation of albumin, not glomerular basement membrane, alters permeability in an in vitro model. Diabetes 1992; 41: 1415-21.
29. Stock SM, Bremme KA. Elevation of plasma leptin levels during pregnancy in normal and diabetic women. Metabolism 1998; 47(7): 840-3.
30. Sattar N, Greer IA, Pirwani I, Gibson J, Wallace AM. Leptin levels in pregnancy: marker for fat accumulation and mobilization. Acta Obstet Gynecol Scand 1998; 77 (3): 278-83.
31. Wolfe H. High pre-pregnancy body mass index: A maternal-fetal risk factor. N Engl J Med 1998; 15: 338 (3): 147-52.
32. Levin BE, Govek E. Gestational obesity accentuates obesity in obesity-prone progeny. Am J Physiol 1998; 274 (4 pt 2):
33. Shekhawat PS, Garland JS, Shipuri C, Mick GJ, Sasidharan P, Pelz CJ, McCormick KL. Neonatal cord blood leptin, its relationship to birth weight, body mass index, maternal diabetes, and steroids. Pediatr Res 1998; 43 (3): 338-43.
34. Santoloya J, Kahn D, Nobles D, Ramakrishnan V, Warsof SL. Ultrasonographic growth and Doppler hemodynamic evaluation of fetus of obese women. J Reprod Med 1994; 39 (9): 690-4.
35. Butte V, Hopkinson JM, Nicolson MA. Leptin in human reproduction. Serum leptin levels in pregnant and lactating women. J Clin Endocrinol Metab 1997; 82: 585-9.
36. Considine RV, Sinha MK, Heiman ML. Serum immunoreactive leptin concentrations in normal-weight and obese humans. N Engl J Med 1996; 334: 292-5.
37. Zhang B, Graziano MP, Doebber TW. Down-regulation of the expression of the obese gene by an antidiabetic thiazolidinedione in zucker diabetic fatty rats and ob/ob mice. J Biol Chem 1996; 271: 9455-9.
38. Glinoer D, Sato FM, Bourdoux P, Lejeune B, Delagne F, Lemone M, Kinthaert J, Robijn C, Grun JP, De Nayer P. Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. J Clin Endocrinol Metab 1991; 73: 421-5.
39. Tolino A, de Concilis B, Montemageno U. Thyroid hormones in the human pregnancy. Acta Obstet Gynecol Scand 1985; 64: 557.
40. Katz FH, Kappas A. The effects of estradiol and estriol on plasma levels of cortisol and thyroid hormone-binding globulin and on aldosterone and cortisol secretion rates in man. J Clin Invest 1967; 46; 1768.
41. Ain KB, Mori Y, Refetoff S. Reduced clearance rate of thyroxine-binding globulin (TBG) with increased sialylation: a mechanism for estrogen-induced elevation of serum TBG concentration. J Clin Endocrinol Metab 1987; 65: 686-91.
42. Yoshikawa N, Nishikawa M, Horimoto M. Thyroid stimulating activity in serum of normal pregnant women. J Clin Endocrinol Metab 1989;69:891-6
43. El-Dardiry SA, Abdel Motteleb S, El-Dardiry N,Nosseir M, Abo Al Azm A, Bayoumi ML. Pregnancy-induced hypertension in patients with past history of schistosomiasis vs maternal and neonatal thyroid activities. J Med Res Inst 1993; 14 (3): 1-7.

44. Delagne F. Neonatal hypothyroidism: recent developments. In Balliere's Clin Endocrinol Metab 1988; 2 (3): 637-52.
45. Lindeman JHN, Van Zoeren-Grobben D, Shriver J, Speck AJ, Poorthuis B JHM, Berger HM. The total free radical trapping ability of cord blood plasma in preterm and term babies. Pediatr Res 1989; 26: 20-4.
46. Saugstad OD. Oxygen toxicity in the neonatal period. Acta Pediatr Scand 1988; 79: 881-2.
47. Gutteridge GMC. Plasma ascorbate levels and inhibition of the antioxidant activity of ceruloplasmin. Clin Sci 1994; 81: 413-17.
48. Silvers KM, Gibson AT, Powers HJ. High plasma vitamin C concentration at birth associated with low antioxidant status and poor outcome in premature infants. Arch Dis Child 1994; 71: 40-4.
49. Powers HJ, Loban A, Silvers KM, Gibson AT. Vitamin C concentrations observed in premature babies inhibit the ferroxidase activity of ceruloplasmin. Free Rad Res 1995; 22: 57-65.
50. Megahed MA, Youssef SS, Mohamed IA, Ahmed OZ, Hassan HH. Plasma antioxidant activity in relation to vitamin C concentration in premature infants. J Med Res Inst 1998; 19 (2): 31-40.