Pregnancy complicated by diabetic nephropathy

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1 Introduction

Diabetes mellitus is a high risk complication of pregnancy. When long standing diabetes is complicated by diabetic nephropathy, the management of pregnancy is even more complicated.

Chronic renal disease is generally associated with menstrual irregularity, infertility and fetal wastage [16]. In the past the successful outcome of these pregnancies was universally accepted to be poor [11, 17], and pregnancy was contraindicated in such patients mainly due to accelerated deterioration of renal function, high perinatal mortality rates, as well as a higher incidence of congenital malformations, and poor prognosis for the newborn [23]. In view of recent stress on maternal normoglycemia all during pregnancy and in the preconceptional period, improved outcome of diabetic pregnancies has been secured [8, 10, 18, 22]. Nevertheless, when the woman in whom diabetes is complicated by diabetic nephropathy desires children, the situation must be seriously evaluated. Absolute contraindications based on renal function, degree of hypertension, additional vasculopathies, intervention policies when problems arise, and maintenance of normoglycemia, are all issues that should be considered [12].

The purpose of this study was to reexamine the management of the pregnant diabetic with

Curriculum vitae

Dov Dicker, M.D. was born in 1951. He was graduated from Tel-Aviv University Medical School in 1976. Subsequently he has been training in the Department of Obstetrics and Gynecology at the Golda Meir Medical Center (Chief Prof. J. Goldman) Petah-Tikva, Israel.

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nephropathy on the basis of our findings, and reevaluate the fetal and neonatal prognosis.

2 Material and methods

Between the years 1981 — 1984, 71 pregnant insulin-dependent-diabetic (IDD) women were treated at the High-Risk Unit of the Golda Meir Medical Center, in association with the Institute of Pediatric and Adolescent Endocrinology, Division of Juvenile Diabetes Beilinson Medical Center, in Israel. In 5 patients 7.0 percent diabetic nephropathy (White's class F) was diagnosed on the basis of persistent proteinuria ($> 400_{mg}/24$ h).

Proteinuria was detected prior to pregnancy in 3 patients (60%), and at an early stage of pregnancy in the others. Renal biopsies were not performed to confirm the diagnosis of diabetic glomerulopathy. Spontaneous abortion occurred in one women and no elective abortions were performed.

The strategy of our diabetic pregnancy program has been reported in detail [2]. All patients were maintained with normoglycemia prior to and throughout the period of organogenesis. In three patients blood glucose normalization was achieved by optimized conventional mixed insulin therapy with NPH and regular insulin injections, twice daily, with additional administration of regular insulin according to need and strict diet. The other two patients were treated with continuous insulin infusion (Autosyringe AS-6C) as well as strict diet resulting in excellent diabetic control.

Since class F diabetic patients have a greater chance of developing uterine vascular disease, frequent periods of bed rest, (in the lateral position), were recommended after twenty weeks' gestation in order to increase cardiac output and uterine blood flow. Renal function was assessed by routine laboratory methods, and followed up to 12 months after pregnancy.

Hypertension (blood pressure > 140/90 mm Hg) was treated with hydralazine or methyldopa. Patients with substantially impaired renal function, persistent hypertension or suspected fetal jeopardy were hospitalized at 24—33 weeks' gestation, whereas, patients without these complications were hospitalized routinely at 34—37 weeks.

Evaluation of fetal well-being included monthly serial ultrasound imaging for fetal growth or anomalies starting at 8—10 weeks' gestation. Daily fetal movements count (DFMC) [25] after 20—22 weeks' gestation, non-stress-test (NST) twice a week during the early third trimester period (28—33 weeks' gestation), and four times a week during the late third trimester (34—37 weeks' gestation). Patients with suspicious NST were followed by contraction stress test (CST). Moreover, fetal condition was assessed weekly by the fetal biophysical profile [15]; lung maturity was evaluated by means of lung profile [14] and amniotic fluid mircoviscosity [1]. Timing of delivery was individualized on the basis of balanced evaluation of maternal condition considering renal function and hypertension, as well as signs of fetal jeopardy manifested by diminution of daily fetal movements count, pathological NST, positive CST, low biophysical score, severe intrauterine-growth-retardation, (IUGR) and fetal pulmonary maturity. The route of delivery was individualized according to maternal and fetal condition.

3 Results

Clinical data, mean blood pressure values, renal function and pregnancy outcome are summarized in tables I — III.

Table I. General information concerning gestants with diabetic nephropathy.

Patient No.	Age (yr)	Parity	Duration of diabetes (yr)	Glycemic control	Maternal complication
1	28	1	18	NPH + RI	Superimposed PET
2	30	2	20	SCII	Superimposed PET
3	27	1	19	SCII	Superimposed PET
4	26	2	20	NPH + RI	Polyhydramnios
5	25	1	19	NPH + RI	

Abbreviations used: RI = Regular Insulin; PET = Preeclamptic Toxemia; SCII = Subcutaneous Continuous Insulin Infusion.

The preconceptional range of creatinine clearance in our patients was 48–82 ml/min. It remained stable throughout pregnancy, and did not demonstrate the expected progressive increase for pregnancy. Proteinuria increased dramatically in the third trimester while the creatinine clearance had the expected inverse relationship to proteinuria and to serum creatinine concentration. Serum creatinine re-

mained below the value of 1.0 mg/dl in the third trimester in two women, and was elevated to 1.4–1.8 mg/dl in two other patients.

Of the four women who began pregnancy with normal blood pressure two developed superimposed hypertension in the second half of the second and third trimester of pregnancy. One woman started pregnancy with elevated blood

Table II. Blood pressure and renal function in 5 women with diabetic nephropathy.

(a) Prepregnancy

Patient No.	Mean blood pressure (mmHg)	Urine protein (gm/day)	Creat. clearance (ml/min)	Serum creat/BUN (mg/dl)
1	130/80	1.5	70	1.2/22
2	140/90	1.8	48	1.4/22
3	110/80	1.0	71	0.9/18
4	120/80	0.3	82	0.9/18
5	120/70	0.4	68	1.0/17

(b) First trimester

1	120/80	1.5	71	1.3/24
2	140/90	1.7	49	1.4/22
3	120/80	1.1	77	0.9/19
4	120/80	0.8	84	0.8/16
5	120/70	0.5	77	0.9/17

(c) Second trimester

1	140/90	2.2	69	1.4/20
2	140/100	3.0	50	1.7/38
3	120/80	1.4	76	1.0/18
4	130/80	0.8	82	0.9/21
5	–	–	–	–

(d) Third trimester

1	150/100	6.8	61	1.4/23
2	160/110	7.0	47	1.8/24
3	150/100	3.8	72	0.9/22
4	130/80	1.0	75	0.9/16
5	–	–	–	–

(e) End of follow up (6–12) months post partum)

1	150/90	1.3	72	1.4/20
2	150/100	2.5	53	1.8/24
3	140/80	1.7	64	0.9/24
4	110/70	0.4	85	0.7/16
5	120/70	0.4	82	0.9/18

Table III. Fetal condition and outcome of pregnancy.

No.	DFMC	NST	CST	Bioph. Profile	Lung Maturity	Gest. age (wk)	Route of delivery	Birth weight	Apgar Score 1' 5'	RDS	Malf.	Hypo-glyce-mia	Hypo-calce-mia	Jaun-dice
1	Preserved	Normal		10	+	35	C.S.	2800	8 10	–	–	–	–	–
2	Diminution	Suspicious	+	4	–	34	C.S.	2550	8 7	+	–	+	+	+
3	Preserved	Normal		8	+	35	C.S.	2640	7 8	+	–	–	–	+
4	Preserved	Normal		10	+	36	Sp. Vag delivery	3610 (LGA)	9 10	–	–	+	+	+
5	Aborted spontaneously at 9 weeks' gestation.													

Abbreviations used: DFMC = Daily fetal movements count; NST = Non stress test; CST = Contraction stress test; Bioph = Biophysical; Gest = Gestational; RDS = Respiratory distress syndrome; C.S. = Cesarean section; LGA = Large for gestational age; Malf = Malformations; Sp. Vag = Spontaneous vaginal.

pressure of 140/90 mm Hg with superimposed malignant hypertension of 160/110 mm Hg during the third trimester. Despite antihypertensive treatment these women had more severe proteinuria and lower creatinine clearance than the normotensive patients.

The mean increase in insulin requirement during pregnancy was 28 ± 12 units, (range 10 to 46 units), and the control of hyperglycemia was no more difficult than in our diabetic patients with normal kidney function.

Proliferative retinopathy was diagnosed and treated prior to pregnancy by laser photocoagulation in two of the patients.

All patients were available for clinical studies of renal function 6–12 months after pregnancy (table II e). Proteinuria decreased more than 50 percent from the elevated levels of the third trimester in all patients: whereas, creatinine clearance levels and serum creatinine remained about the same.

Diastolic hypertension persisted after pregnancy in two patients and resolved in one patient. Two normotensive patients retained normal values after pregnancy. In three women pregnancy was complicated by severe hypertension and all underwent delivery by cesarean section at 34–35 weeks' gestation; the infants were appropriate for gestational age. Antepartum fetal distress suspected on the basis of diminution of fetal movements, suspicious NST and positive CST in one patient at 34 weeks' gestation (Case No. 2) were one more indication for premature abdominal delivery. Delivery was vaginal in one patient with polyhydramnions and overdistended uterus, who developed spontaneous labor at 36 weeks' gestation, and delivered a large for gestational age infant. Birth weight, adjusted for gestational age, was inversely relatet to maternal diastolic pressure and creatinine clearance in the third trimester. Two infants, delivered at 34 and 35 weeks' gestation, developed respiratory distress syndrome (RDS), one of them despite maternal dexamethasone treatment. There was no evidence for congenital malformations, and all infants survived.

4 Comment

The responsibility of parenthood must be presented to the couple considering pregnancy, especially if proteinuria is found in the patient. Both the mother and infant may be adversely affected by the pregnancy. According to the literature, once continuous proteinuria develops, end-stage kidney disease follows. Furthermore, the fact that proteinuria is an ominous sign was put forth by JONES' study [7] in which less than 28 percent of diabetic patients lived longer than ten years.

MOGENSEN et al [20] calculated that even when the patient had a normal creatinine clearance at the onset of proteinuria, she would lose average of 11 ml/min/year. Consequently, the husband must be advised that he may be a single parent and must determine if this outlook would change his mind about becoming a father.

The data on improvement of kidney function with improvement of glucose levels in the patient with diabetes mellitus is controversial [3, 6] and no promises on longevity can be given to the couple. The establishment of normoglycemia must be part of the prepregnancy counseling; it cannot be used as a guarantee for prolonged life, but only an absolute prerequisite for pregnancy planning.

Recently, excellent maternal glucose control has been linked to the absence of congenital malformations in offspring of IDD mothers. MILLER et al [19] noted a 30 percent increase in congenital malformations in infants born of women with elevated glycosylated hemoglobin levels at the time of organogenesis (the first 8 − 10 weeks of pregnancy). FUHRMANN and coworkers [4] reported no increased incidence of congenital anomalies over that seen in the nondiabetic control group, when diabetic women achieved strict normoglycemia prior to and throughout the period of organogenesis. The older literature [24] relates a prevalence of congenital anomalies in the infant of the diabetic mother to White's classification. The higher the White group, the greater the risk of producing a malformed infant.

Therefore, a woman with diabetic nephropathy, considered by most a "high White class" who is not normoglycemic at the time of organogenesis, would have the highest risk of any diabetic woman.

The second concern for the infant of the diabetic mother is the size and metabolic status of the infant. Most of the earlier literature claims that patients with diabetic nephropathy have growth-retarded infants [26]. The hypothesis was that maternal hypertension and vasculopathy produced an ischemic, small placenta, and thus a growth retarded fetus. As programs of normoglycemia have been the accepted norm for pregnancies complicated by diabetes, the observation that maternal glycemic levels affect fetal size has emerged. In JOVANOVIC's series [9] of 22 vascularly compromised women, (patients with retinopathy and nephropathy), the infant birth weight correlated well with the third trimester glycosylated hemoglobin levels; the smaller babies were born of women with lower glycosylated hemoglobin levels while the bigger babies were born of women with higher levels. The metabolic status of the infant at birth is also related to blood sugar levels of the mother; in fact, the latter's levels in the last days prior to delivery affect fetal glucose homeostasis the most [21]. Thus pre-delivery glucose control is as important as that achieved during the entire nine months.

In our experience, a creatinine clearance as low as 40 ml/min does not affect the 24-hour insulin requirement. We still see a first trimester insulin requirement of 0.7 units/kg/24 hours and the steady insulin increase throughout pregnancy of 0.8 units/kg/24 hours at 26 weeks, 0.9 units/kg/24 hours at 32 weeks, and 1.0 unit/kg/24 hours after the 35th week of gestation. Similar to our diabetic patients with normal kidney function, the insulin dose is best divided into two-thirds in the morning, one-sixth before dinner and one sixth before bed. The two-thirds in the morning is 2:1 NPH to regular; the one-sixth before dinner is regular and one-sixth before bed consists of NPH. Home blood-glucose-monitoring before and one hour after each

meal guides the insulin adjustment to keep up with the ever increasing insulin requirements of pregnancy [8].

It is a well-known fact that the coexistence of severe renal disease and pregnancy is usually associated with a high rate of fetal wastage. Moreover, a normal gestational course is described as rare when preconception serum creatinine is higher than 3.0 mg/dl and/or the BUN is greater than 30 mg/dl [16]. KITZMILLER et al [12] has emphasized the issue of perinatal outcome in pregnancies complicated by diabetic nephropathy. In a series of 36 patients with nephropathy, spontaneous abortion occurred in four, elective abortions in five, while the rest delivered live infants after 27 weeks of gestation. Of the 26 live births all survived the perinatal period.

Examination of our series of women with diabetic nephropathy, all of whom had prepregnancy normal glucose values and were sustained with normoglycemia throughout pregnancy, allowed us to note a number of clinical findings: first, normoglycemia removes the additional risks and improves the outcome in these pregnancies in which superimposed hypertension is not a concomitant risk factor. Second, our findings suggest that creatinine clearance is not worsened by the course of pregnancy in the majority of women with diabetic nephropathy and that proteinuria per se does not add additional risk to the pregnancy or outcome. Moreover, the usual trend of renal status improvment retained post partum (table II). Nevertheless, hypertension serves as a major pathogenic factor in these pregnancies since it is related to increased proteinuria, decreased creatinine clearance and decreased fetal growth.

Three of our patients, one with inital hypertension of 140/90 mm Hg, developed superimposed hypertension of 150/100−160/110 mm Hg causing premature deliveries at 34−35 weeks. Thus, hypertension is a separate risk factor which affects the pregnancy despite normoglycemia.

5 Course of pregnancy

Antepartum monitoring for fetal distress is important in the management of diabetic pregnancies especially those complicated by nephropathy. Our experience supports the view that diabetic women with proteinuria, reduced creatinine clearance and hypertension should be admitted to the hospital for intensive obstetric care at 26−28 weeks' gestation [5]. It seems that intensive fetal monitoring by daily fetal movements count, repeated NST followed by CST when indicated, ultrasound imaging for fetal growth and assessment of the fetal biophysical profile are the best predictors for fetal condition. Fetal distress established on the basis of diminution of fetal movements, suspicious NST and positive CST was found in one of our cases; we presume that prompt delivery of this infant at 34 weeks' gestation prevented stillbirth. The primary cesarean section rate in diabetic pregnancies complicated by nephropathy is high mainly due to the more frequent need for premature delivery of a pregnant woman at risk with an uripe cervix and a fragile fetus [12]. In our group of White's class F patients the cesarean section rate was 75 percent, whereas our current primary rate for patients in White's class B, C and D is 45 percent.

In recent years, the frequency of respiratory distress syndrome (RDS) in infants of diabetic mothers has shown a marked decline, from 23 percent to 8 percent [13]. This is related mainly to the ability to carry pregnancies to term according to tests of fetal well being and the use of amniocentesis for assays of fetal lung maturity. Nevertheless, the prevalence of RDS remains higher (24%) in infants of class F diabetic mothers, which probably reflects the more frequent need for premature delivery in this group. Two infants in our series, delivered at 34 and 35 weeks' gestation developed RDS, one despite maternal dexamethasone administration. At the time of follow-up examination no infant had any signs of residual pulmonary disease.

In conclusion, the major predictors in the outcome of pregnancies complicated by diabetic nephropathy are the glycemic levels sustained before and during pregnancy, and the degree of superimposed hypertension. Nevertheless, it is difficult to relate the improved perinatal outcome in White's class F pregnancies to any one factor. The features of our program which may contribute to improved results, besides closer attention to control of hyperglycemia and hypertension, include motivation of patients to maintain bed rest for prolonged periods, intensive use of fetal monitoring tests, amniocentesis for the evaluation of lung maturity and improvements in neonatal care.

Summary

Diabetes mellitus is a high risk complication of pregnancy and this is particularly true whenever long standing diabetes is complicated by diabetic nephropathy.

Five cases are reported of diabetic pregnancy complicated by nephropathy. Four women delivered healthy babies, and one patient aborted spontaneously in the 9th week of gestation.

It is suggested that first and foremost in complicated diabetic pregnancy strict normoglycemia should be adhered to prior and all through pregnancy. Our findings based on these cases also suggest that:

a) Pregnancy does not adversely affect the renal status of a diabetic woman or vice versa. Creatinine clearance is not worsened by the course of pregnancy in the majority of these patients and proteinuria per se does not add additional risks to pregnancy or outcome.

b) Hypertension is a separate risk factor affecting the pregnancy despite normoglycemia.

c) Motivation of these patients to maintain normoglycemia as well as bed rest for prolonged periods, intensive use of fetal monitoring, evaluation of fetal lung maturity and improved neonatal care may contribute to improved perinatal outcome.

Keywords: Diabets mellitus, diabetic nephropathy, diabetic pregnancy.

Zusammenfassung

Schwangerschaft und diabetische Nephropathie
Ein Diabetes mellitus in der Schwangerschaft ist eine mit einem hohen Risiko behaftete Komplikation. Dies gilt insbesondere, wenn ein schon lange bestehender Diabetes mit einer Nephropathie vorliegt.

Wir berichten über 5 Schwangerschaften mit Diabetes und Nephropathie. Vier Frauen wurden von gesunden Kindern entbunden. Bei einer Frau trat in der 9. Schwangerschaftswoche ein Spontanabort auf.

Im Vordergrund steht, daß bei einer diabetischen Schwangeren von Anfang an und über die gesamte Schwangerschaft eine strikte Normoglykämie angestrebt werden sollte. Darüberhinaus zeigen die untersuchten Fälle folgendes auf:

a) Die Schwangerschaft hat keinen ungünstigen Einfluß auf den renalen Status und umgekehrt. Bei der · Mehrzahl der Patientinnen verschlechterte sich die Kreatinin-Clearance im Verlauf der Schwangerschaft nicht; eine Proteinurie per se stellt kein zusätzliches Risiko für die Schwangerschaft oder den Zustand des Neugeborenen dar.

b) Unabhängig von der Normoglykämie ist der Hypertonus ein separater Risikofaktor mit Einfluß auf die Schwangerschaft.

c) Zu einem verbesserten perinatalen Outcome können beitragen: Motivierung der Patientinnen, eine Normoglykämie aufrechtzuerhalten sowie Bettruhe über längere Phasen einzuhalten, eine strenge Überwachung der Schwangerschaft, Bestimmung der fetalen Lungenreife und eine verbesserte Versorgung des Neugeborenen.

Schlüsselwörter: Diabetes mellitus, diabetische Nephropathie, Diabetes and Schwangerschaft.

Résumé

Grossesse compliquée de néphropathie diabétique
Le diabète est une complication à haut risque de la grossesse et celà est particulièrement vrai lorsqu'une longue histoire diabétique est compliquée par une néphropathie diabétique.

On rapporte cinq cas de grossesse chez des diabétiques compliquées de néphropathie. Quatre femmes ont accouché d'enfant bien portants et une patiente a avorté spontanément au cours de la 9è semaine de gestation.
On suggère qu'en tout premier lieu, au cours des grosses-

se avec diabète compliqué, il faut obtenir une glycémie normale stricte avant et tout au long de la grossesse.
Nos données fondées sur ces cas suggèrent également que:

a) la grossesse n'affecte pas de façon néfaste la fonction rénale de la femme diabétique et vice versa. La clearance de la créatinine n'empire pas au cours de la grossesse chez la majorité de ces patientes et la protéinurie per se n'est pas un risque additionel pour la grossesse ou son issue.

b) l'hypertension est un facteur de risque séparé au cours de la grossesse malgré une normoglycémie.

c) la motivation de ces patientes pour maintenir une normoglycémie aussi bien qu'un repos prolongé au lit, l'utilisation intensive du monitoring fœtal l'évaluation de la maturité pulmonaire fœtal et des soins néonataux approprié peuvent contribuer à assurer un devenir néonatal amélioré.

Mots-clés: Diabète sucré, grossesse chez la diabétique, néphropathie diabétique.

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