

P R A C E K A Z U I S T Y N E
położnictwo

Pregnancy in diabetic woman with coexisting hypothyroidism, coronary artery disease and with early onset nephrotic syndrome – a case report

Ciąża u pacjentki z cukrzycą powikłaną niedoczynnością tarczycy, chorobą wieńcową oraz zespołem nerczycowym – opis przypadku

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Abstract

We present a case of pregnancy in 28-years old nulliparous woman with an over 20-years long history of diabetes, hypothyroidism, diabetic nephropathy with nephrotic syndrome, retinopathy and coronary artery disease treated with PCA prior the pregnancy (class H diabetes, according to White classification).

Key words: **pregnancy in diabetic / class. H acc. to White / nephropathy /**

Streszczenie

W pracy przedstawiono przypadek 28 letniej ciężarnej, chorującej na cukrzycę od ponad 20 lat, leczonej także z powodu niedoczynności tarczycy, nefropatii cukrzycowej z zespołem nerczycowym, która przed ciążą przeżyła ostry zespół wieńcowy, leczony za pomocą PCA (cukrzyca kl. H wg White).

Słowa kluczowe: **cukrzyca i ciąża / klasa H cukrzycy wg White /
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A case report

A 28-years old female was referred to our Department by her primary care gynaecologist for further treatment in the 10th week of an unplanned pregnancy. She suffered from type 1 diabetes since the age of 7 and remained within a care of a local diabetes outpatient unit. Being 21 years old, the patient was referred to a tertiary level academic centre for diabetic patients for further evaluation and treatment because of poor metabolic control, but she did not accept offered intensive insulin therapy. At the age of 22 she was diagnosed with simple retinopathy. Diabetic kidney disease was diagnosed a year later because of proteinuria. She has had recurrent urinary tract infections but kidney function before pregnancy was not evaluated. Being 26-years old, the patient developed arterial hypertension and was diagnosed with hypothyreosis – treatment with ACE-inhibitors and thyroxine was introduced. In the same year, she had acute myocardial infarction and required PCA and stenting of the right coronary artery.

She used to be a poorly cooperative individual, reporting irregularly for follow-up visits. She also discontinued medication on her own and did not follow recommendations concerning diet, insulin therapy and smoking cessation. Several years prior to the cardiac ischemic event she used oral contraceptives against diabetologists' recommendations. During the last two years preceding her pregnancy, she did not appear for a follow-up at all and no data on her status was available.

During the first antenatal hospitalisation in our Department, we confirmed pregnancy and recalculated her gestational age: according to our ultrasonic scan that was the first one in her pregnancy. The patient was diagnosed to be at 7th weeks' gestation (GA 7). We obtained full range of metabolic parameters and checked her renal function (patient's gestational data is summarised in Table I).

As she wished to continue the pregnancy, we arranged additional consultations of a nephrologist and cardiologist. Echocardiography did not reveal any changes in myocardium function and minimal mitral valve insufficiency. Her thyroid function was properly controlled.

During the first hospitalisation, we focused on improvement in treatment and current metabolic control. The patient was offered intensified training with special attention to control of fluid and sodium intake, blood glucose monitoring and insulin self-administration. She switched from multiple daily insulin injections to insulin pump therapy. Apart from this, she was treated with methyl dopa (3x250/dmg – 4x500mg/d at the end of pregnancy), bisoprolol (2x5 mg/d from the second trimester of pregnancy), furosemide (30-60mg/d), Aspirin 75mg/d and enoxaparine (0,4IU/day). Urinary tract infections were treated with antibiotics according to results of serial urine cultures.

During consecutive hospitalisations (GA 10, GA 14, GA 18, GA 22 and the last stay in the Department from the 23rd week of gestation to the delivery in the 33rd week of gestation) we focused on monitoring of patient's general status with a particular attention paid to maintaining improved metabolic control, antihypertensive therapy and monitoring renal function that proved to be difficult mainly due to recurrent urinary tract infections with massive bacteriuria and proteinuria. Her metabolic control improved from the 11th week of gestation (HbA_{1c} range between 6.7% and 5.5%).

Due to retinopathy deterioration, patient underwent two series of photocoagulation, in the 16th and 18th week of gestation. As she developed anaemia resistant to iron supplementation, erythropoietin (1000 IU/ once a week) was commenced in the 22nd gestational week. Urinary protein excretion decreased at GA 11 but then increased continuously, with a decrease in total serum protein level, alterations in lipid profile characteristic for nephrotic syndrome (with a total cholesterol up to 515mg/dl and triglycerides up to 360 mg/dl) and massive oedema. From gestational age of 26 weeks on, serum creatinine concentration increased and reached 1.6mg/dl at 30th week of gestation. Creatinine clearance decreased to 59mL/min at 32nd week. To maintain renal function and reduce oedema, the patient was given fresh frozen plasma preparations from 11th week and at 24th week methylprednisolone 4mg once a day was added to reduce increasing proteinuria.

During the last trimester, we also instituted measurement of body mass once a week and daily fluid intake and output, due to massive oedema. Because of serious maternal condition, we arranged regular consultations of nephrologist and ophthalmologist.

We also strictly monitored foetal wellbeing using serial USG with Doppler examination and CTG from the 26th week of gestation on. Detailed foetal scanning both in the first and in the second trimester revealed no foetal malformations and foetal growth adequate to a gestational age. From the 26th week onward, we assessed foetal wellbeing and development once a week using greyscale and Doppler examination and non-stress tests.

At GA 32, due to further deterioration in renal function, we decided to perform cesarean section. After administration of a total dose of 24mg betamethasone to improve fetal lung maturity, she delivered an immature son weighting 1550g; the Apgar score was 6 and 7 at 1 and 5 minute, respectively. The newborn required a hospitalization in the NICU until the 32nd day of life for treatment of a mild-grade RDS and neonatal sepsis. He was discharged home in a good condition.

In the 13th day of puerperium, due to further deterioration in renal function, the patient was transferred to Department of Nephrology of our University for further diagnostics and treatment. Finally, two months after the delivery, a renal biopsy was performed to find out a reason for nephrotic syndrome in our patient. The biopsy yielded 9 glomeruli and 1 completely sclerotized. They were enlarged, with slightly or moderately increased cell number and markedly increased mesangial matrix. Mesangiolytic was found in one glomerulus. Two glomeruli demonstrated thickened afferent or efferent arterioles with hyalinosis. Numerous fibrotic foci and lympholytic infiltration were seen in the interstitial space. Immunofluorescent staining showed diffused immunoglobulin A (IgA), IgG and focal IgM deposits. The histopathological diagnosis was glomerulosclerosis due to IgA nephropathy and diabetic kidney disease.

The patient received six intravenous methylprednisolone pulses (500mg each every 4-6 weeks), followed by prednisolone 30mg/d p.o. and cyclophosphamide (1g i.v. every month, 6 times). Two months later, her blood pressure was 130/80mmHg, Hb 11.5 g/dL, RBC 3.7 T/L, daily protein loss 1.9g/24 hrs, serum creatinine of 1.7mg/dL and estimated GFR (MDRD) 54mL/min/1.73m².

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Table 1. Maternal data throughout gestation.

Maternal parameter	GA 7	GA 11	GA 14	GA 18	GA 19	GA 22	GA 24	GA 26	GA 28	GA 30	GA 32	Days postpartum		
												3	6	11
Average daily glycemia [mmol/dL]	7.3	6.7	6.4	8.8	6.1	6.1	6.1	6.4	6.7	5.5	6.1			
HbA _{1c} [%]	9.7	7.8	6.3	6.1	5.7	6.2	5.8	5.7	5.7	6.1	6.7			
Basal insulin requirement [IU/day]	35	35	21	35	37	37	39	39	40	40	40			
Total serum protein [g/L]	5.4	4.2	4.4	4.2	4.3	3.9	4.2	4.2	3.7	3.6	3.1			4.1
Serum ureic acid [mg/dL]	5.5	4.6	4.8	5.9	4.9	5.7	5.4	6.3	6.3	4.8	5.8			
Serum urea [mg/dL]	42	47	48	51	55	47	51	62	53	55	67			
Creatinine [mg/dL]	0.7	0.7	0.9	0.9	1.1	0.9	0.9	1.1	1.3	1.6	1.5	2.0	2.1	2.5
Serum K ⁺ [mmol/L]	4.9	4.2	4.5	5.6	4.5	4.4	4.6	3.7	4.4	4.5	5.3			
GFR [ml/min/24 hrs]	117	122	65	67	100	96	73	94	82	69	59	37	33	29
Daily proteinuria [g/24 hrs]	6.1	neg	4.9	4.9	13.7	5.5	9.9	15.4	12.7	20.5	14.3	14.0	20.3	22.1
Triglycerides [mg/dL]	116.9	175.1	250.6	439.7	270.6	437.6		341.7	392.5	360.4				337.9
LDL-cholesterol [mg/dL]	122.0	210.6	219.7	352.7	258.3	278.6		265.9	357.8	345.6	277.2			251.2
HDL-cholesterol [mg/dL]	89.1	111.0	107.6	91.8	107.4	83.5		69.7	106.0	97.4	70.8			38.2
Total cholesterol [mg/dL]	234.5	356.6	377.4	532.5	457.7	449.6		404.0	542.3	515.0	471.7			357.0
Hb [mmol/L]	7.8	6.6	6.5	6.5	5.2	5.8	5.5	5.8	5.6	5.5	5.5			
RBC [T/L]	4.1	3.6	3.4	3.2	2.7	3.0	2.9	3.1	2.9	2.6	2.6			
Hct [L/L]	0.37	0.32	0.30	0.28	0.27	0.28	0.26	0.28	0.26	0.26	0.24			
Serum Fe concentration [mcg/dL]		135.6	103.5	99.9		95.0	59.0							

Discussion

Diabetic vascular disease is commonly recognised as a major factor associated with impaired perinatal outcome. Different authors report vasculopathy, particularly renal disease (nephropathy), as a strong risk factor for preeclampsia, iatrogenic prematurity and increased maternal and neonatal mortality and morbidity [1, 2, 3]. Moreover, ischemic heart disease is considered as a serious contraindication to pregnancy itself and all data concerning this population of diabetic women is scarce and many years old [4, 5, 6, 7, 8].

In our patient, we report a diabetic pregnancy complicated with a proliferative retinopathy, ischemic heart disease and renal disease that was initially diagnosed as a diabetic nephropathy due to a long-lasting and poorly controlled diabetes. Early onset of a nephrotic proteinuria in our patient suggested coexistence of pre-gestational diabetic kidney disease (DKD) and other glomerular disease.

Although a marked reduction of proteinuria followed improved glycemic control, the relapse of the nephrotic syndrome a few weeks later confirmed our primary hypothesis. Throughout gestation, we excluded such possible causes of the nephrotic syndrome as lupus nephropathy, systemic vasculitis and antiphospholipid syndrome as all tests for these disorders were negative. Small dosage of methylprednisolone was given throughout pregnancy, to inhibit worsen of nephritic function. This steroid doesn't cross the placenta, so at the moment of risk of premature delivery we decided to give bethamethason to stimulate lung maturation, that is known to be impaired in diabetic pregnancy.

A primary glomerular disease imposed on the DKD remained as the most probable cause. A renal biopsy was considered to establish a targeted therapy as it was demonstrated that pregnancy itself does not increase risk of complications for this procedure [9].

However, due to recurrent UTI and absence of rapidly progressing glomerulonephritis requiring an aggressive treatment, the biopsy was postponed until after the delivery [10]. A recently published retrospective analysis of perinatal outcome in pregnancies complicated with severe preeclampsia manifesting as the nephrotic syndrome revealed that most of women recovered after delivery but authors noted a 30% perinatal mortality in newborns and 68% were born with a small for gestational age birth weight [11]. The clinical course of the kidney disease in our patient confirms the suggestion that proteinuria may be an independent risk factor for pregnancy related decline in renal function, better than blood pressure or renal function at baseline [12]. The marked decline of renal function in our patient appeared at GA 32 and was a reason for early delivery.

The kidney biopsy in our patient revealed focal and segmental glomerulosclerosis due to IgA nephropathy and changes characteristic for DKD. This finding supports the opinion, that early onset nephrotic syndrome in pregnancy, even in patients with diabetes and already diagnosed DKD indicates a nondiabetic chronic renal disease coexisting (or not) with DKD. Some data suggest that women with IgA nephropathy, focal sclerosis like those with membrano-proliferative glomerulonephritis or reflux nephropathy develop a permanent renal failure more frequently than those with other renal disorders [10]. Our case also adds to previous observations that early-onset nephrotic syndrome in pregnant woman with diabetes should always be considered as a symptom of a nondiabetic kidney diseases and represents a significant challenge for medical care providers. No simple recommendations can be given in any particular case, which should be managed by an obstetrician with a special interest in a high risk pregnancy and a nephrologist.

In our patient, we also report a rare case of pregnancy in a woman with a type II autoimmune polyglandular syndrome. In nonpregnant population, TPO antibodies are found in 14-30% of individuals with type 1 diabetes [13]. Scarce data is available on coexistence between thyroid dysfunction and type 1 diabetes in pregnant women, reporting a prevalence of autoimmune thyroid diseases between 22,5 and 30% in this population [14, 15]. To our knowledge, no data on perinatal outcome in women with APS-II is available. Association between maternal autoimmune thyroid dysfunction and fetal maldevelopment is well documented and in our patient we did not note any perinatal complications that could be attributed to this condition [16]. However, in our patient thyroid disease was diagnosed and treated prior to pregnancy and thyroid hormones remained within reference values throughout gestation.

Surprisingly, we did not note foetal complications typical for diabetic nephropathy, particularly placental insufficiency manifesting as an intrauterine growth restriction and reduced amount of amniotic fluid (oligohydramios). Also serial Doppler examinations of materno-fetal circulation showed no abnormalities suggestive of chronic foetal hypoxia and non-stress tests performed in the IIIrd trimester showed no changes in foetal behaviour characteristic for a chronic distress.

We also did not observe deterioration in maternal cardiac function, as echocardiography performed in the Ist and early third trimester found only slight impairment of cardiac function of no haemodynamic significance. We presume it could be the most important factor associated with an overall positive perinatal

outcome we achieved in this complex case.

In our patient, we present a model case when, apart from a very serious maternal condition, a good perinatal outcome was achieved thanks to increased maternal motivation and strenuous efforts of a multidisciplinary team. Due to lack of pregnancy planning we had to use symptomatic treatment. Therefore, preconception care in such patients remains of vital importance for increasing maternal and offspring's odds.

General improvement in a quality and effectiveness of medical care in diabetic patients that we have witnessed in the recent decades results in longer life-expectancy and better quality of life, therefore increased number of women with type 1 diabetes and microvascular complications decides to give birth. Moreover, population of women with diabetes also mirrors a general trend of making a decision on pregnancy later than in previous generations. Therefore, diabetic care providers have to be prepared for pregnancy with chronic microvascular complications shifting from rarity to a more common option. Fortunately, constant improvement in fetomaternal and neonatal medicine allows us to get good perinatal outcome both for mothers and their children.

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