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ORIGINAL PAPER

Gestational Diabetes Mellitus (GDM) in the Republic of Kosovo: a Retrospective Pilot Study.

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Background: GDM is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy. Pregnancy causes some insulin resistance in all women, but only a few develop GDM. **Objective:** To test the hypothesis that women with GDM have impaired regulation of blood iron storage and transport, decreased renal function due to decreased glomerular filtration rate and occurrence of urinary tract infection (UTI). **Study design and Methods:** Incidence of blood iron storage was investigated in n=30 pregnant kosovar women with GDM after mild of pregnancy and in n=30 pregnant women without GDM (years 2010-2012). **Results and Discussion:** Baby weights, both systolic and diastolic BP, creatinine, albumin, lymphocytes, monocytes, WBC and granulocytes in both groups were within their normal ranges in both groups. Compared to control group, glucose was higher in women with GDM (mean ± SD: 7.43±2.23 mg/dL vs. 4.33±0.63 mg/dL; P<0.001). Women with GDM had also higher RBC (mean ± SD: 4.4±0.8 % vs. 3.8 ± 0.3 %; P<0.005) and HGB (mean ± SD: 13.0±3.2 g/dL vs. 11.2±1.4 mg/dL; P<0.05), and decreased renal functionality (MDRD-GFR: 92.8 ± 25.8 g/dL vs. 108.2 ± 38.2 g/dL; P<.05).**Conclusion:** There is a potential association between iron status and GDM. The role of iron from diet and/or from supplementation in GDM pathogenesis needs still to be examined. In addition we have observed a decrease of glomerular filtration rate in women with GDM. Due to the lack of studies on the relationships between GDM and UTI, and to the retrospective design of the present investigation, it is difficult to establish whether UTI may be a GDM causal factor or a consequence of GDM symptoms, signs and/or of its correlated pathologies. Key words: Gestational diabetes, preeclampsia, blood iron regulation, urinary tract infections, oxidative stress.

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1. INTRODUCTION

GDM is a condition in which pregnant women without previously diagnosed diabetes begin exhibiting high blood glucose levels during pregnancy, accounting for the ~ 90% of all pregnancies complicated by diabetes (1). GDM affects around the 7% of all pregnancies and, depending on the population sample and diagnostic criteria, its prevalence may range from 1 to 14% (2).

Accepted classical risk factors for GDM are: previous diagnosis of GDM or pre-diabetes, impaired glucose tolerance, or impaired fasting glycemia, a family history revealing a first degree relative with type 2 diabetes, maternal age – a woman's risk factor increases as she gets older (especially for woman over 35 years of age), ethnic background (those with higher risk factors include African-Americans, Afro-Caribbeans, Native Americans, Hispanics, Pacific Islanders, and people originating from south Asia, overweight, obesity or severe obesity increases the risk by a factor 2.1, 3.6 and 8.6, respectively, a previous pregnancy which resulted in a child with a high birth which resulted in a child with a high birth weight (>90th centile, or >4000 g (8 lbs 12.8 oz), previous poor obstetric history (3, 4). In addition to this, statistic show a double risk of GDM in smokers (5). Babies born from mothers affected by GDM are typically at increased risk of macrosomia (6, 7, 8). And of additional problems such as the development of childhood obesity and of type 2 diabetes later in life. Women with GDM are at a significantly higher risk of developing preeclampsia or hypertension after pregnancy compared to healthy subjects (9), probably due to presence of preexisting common risk factors for both GDM and hypertension (10). Other studies have shown that GDM may be also associated to increased blood iron storage and transport (11, 12).In addition, different studies on the prevalence of urinary tract infections (UTI), symptomatic and/or asymptomatic bacteriuria in different populations of female diabetic patients reported contrasting results, showing that they can be either increased (13); or unchanged to this diabetic complication compared to non-diabetic subjects (14).

Hence, the aim of this study was (a) to furnish a preliminary description of the pathophysiological conditions of two selected population of Kosovar women with and without GDM, and (b) to evaluate the

effects of diabetes on the impairment of blood iron physiological control, blood pressure and renal functionality status, and susceptibility to develop UTI.

2. EXPERIMENTAL STUDY DESIGN AND METHODS

Patients, pregnant women (n=60) were recruited from the Obstetric-Gynecologic Clinic of Prishtina (QKUK, Republic of Kosovo) during the years 2010/2012 and divided in two groups on the basis of diagnosis: GDM group (n=30) and control group (CTR, total n=30 without GDM, of which n=18 had normal clinical pregnancy status and n=12 treated for preeclampsia). All women gave delivery by Cesarean delivery exception for 6 patients for which delivery was stimulated by oxitocin administration. Patients were followed-up from 2010 to 2012. The measurements of blood parameters glycaemia, creatinine, albumin, lymphocytes, monocytes, granulocytes, white blood cells, red blood cells, haemoglobin, Glomerular filtration rate (GFR) was estimated using the modification of diet in renal disease (MDRD) algorithm [15]. Urine analysis with microscopy epithelial cells, leukocytes, bacteria, oxalate crystals and erythrocytes, as well as histological examination were carried out using standard assay procedures of laboratory of Biochemistry of the University Clinical Center of Kosovo (UCCK). The presence/absence of vaginal infections was established using standard microbiological protocols in institute of microbiology in the University Clinical Center of Kosovo (UCCK). Vaginal wet mount was observed with microscopy by placing the specimen on a glass slide and mixing with a salt solution.

Continuous clinical variables were compared by two-tailed pairwise Student's *t* test for independent measurements with Bonferroni's correction for multiple comparisons and discrete variables by Fisher's exact test. Computations were conducted on original data and on log transformed data to reduce the effect of skewness. Minimal level of significance of the difference was set at P<0.05. The data matrices for computations were built with an OpenOffice Calc Spreadsheet for Linux (v. 3.2.1), and all computations were done with R-commander GUI for R (v. 1.5–6) [16].

3. RESULTS AND DISCUSSION

In Table 1 and Table 2 are reported means, standard deviations and quintiles for the monitored physiological parameters (weights of babies, weeks of gestation at clinical visit, systolic and diastolic BP), blood biochemical parameters (creatinine, glucose, albumin, hemoglobin), blood cells profile (lymphocytes, monocytes, red blood cells (RBC), white blood cells (WBC) and granulocytes), and renal functionality determined in pregnant women with and without GDM respectively.

Gestation duration was lower than the full term of 40 weeks for normal delivery in both groups. The gestation time before delivery was 2.7 weeks shorter in group II (35.8 ± 2.5 weeks) compared to group I (38.5 ± 2.2 weeks, P<0.001). Mean values of babies weight, and mothers' systolic and diastolic BP, creatinine, albumin, WBC and granulocytes in both groups were within their normal ranges, with no significant difference between the two groups (P>0.05). However, for both groups, women falling into the two highest quintiles (IV and V) showed systolic and diastolic BP higher than reference values. In both groups, lymphocytes and monocytes mean values and quintiles were significantly elevated in respect to the matched reference values for the CTR group (17). Probably resulting from the presence of infections in both groups (see paragraph 3.2). As expected, blood glucose was higher in group I (mean ± SD: 7.43 ± 2.23 mg/dL vs. 4.33 ± 0.63 mg/dL; P<0.001), on account of their diabetic status. Women in this group had also higher RBC (mean±SD: 4.4±0.8 % vs. 3.8±0.3 %; P<0.005) and HGB (mean ± SD: 13.0 ± 3.2 g/dL vs. 11.2 ± 1.4 mg/dL; P<0.05). Women with GD showed decreased renal functionality, as evidenced by the significant decrease of their mean GFR value in respect to that of women with preeclampsia (MDRD-GFR: 92.8 ± 25.8 g/dL vs. 108.2 ± 38.2 g/dL; P<0.05).

The high concentration of mitochondria in placenta, one of the major sources of free radicals in living organism, may be a causal/concurrent condition in the development of GDM, due to the oxidative stress that may be induced by the impairment of their activity. In particular, iron, which is abundant in placenta, is one of the most important generators of highly reactive free radicals in both normal and pathological conditions (18). Our findings that blood iron, in terms of blood HGB and RBC, is significantly elevated in pregnant women affected by GDM compared with women with preeclampsia (Hb: 13.0 ± 3.2 g/dL vs.11.2 ± 1.4 g/dL; P<.05) are in good agreement with those recently reported in a similar study by Afkhami-Ardekani et al. (11). In this study the concentrations of serum ferritin, iron, transferrin saturation and HGB, MCV, and MCH were significantly higher in Iranian pregnant women with GDM (Hb: 13.4 ±1.1 g/dL vs. 11.8 ± 1.4 g/dL; P<.001), indicating a potential association between increased iron status and GDM. A few years earlier,

	Mean	SD	Quintiles				
			(I)	(II)	(III)	(IV)	(V)
Baby weight (g)	3697.7	600.0	2655.0	3242.0	3552.0	3700.9	**4204.0**	**5200.0**
Gestation (weeks)	38.8	2.5						
BPdiastolic (mm$_{Hg}$)	85.2	13.0	70.0	70.0	80.0	**90.00**	**94.0**	**120.0**
BPsystolic (mm$_{Hg}$)	133.8	16.1	110.0	120.0	**130.0**	**138.0**	**140.0**	**180.0**
CREA (mM)	67.3 (35-80)	10.5	27.0	55.2	64.4	69.8	75.0	**133.0**
GLU (mg/dL)	7.43 **** (4-4.3)	2.23	2.66	**5.44**	**7.20**	**7.60**	**9.62**	**11.00**
ALB g/L	32.9 (23-42)	5.1	24.1	28.9	31.2	34.0	36.8	**43.0**
Hb (g/dL)	13.0* (9.5-15)	3.2	9.1	10.7	11.8	12.3	14.0	**23.4**
WBC (10^3/L)	11.7 (5.6-16.9)	5..0	6.2	8.2	9.8	10.7	13.3	**29.5**
LYMPHOCYTES (%)	22.9 (1-3.6)	7.8	**11.2**	**16.1**	**19.8**	**24.3**	**27.6**	**39.4**
MONOCYTES (%)	6.0 (0.1-1.4)	2.3	**2.7**	**4.2**	**5.0**	**6.3**	**7.8**	**13.2**
GRANULOCYTES (%)	68.9 (45-74)	15.8	6.2	64.4	69.4	**74.1**	**79.9**	**86.1**
RBC (10^{12}/L)	4.4 *** (2.72-4.43)	0.8	3.3	3.7	4.0	**4.5**	**4.9**	**7.0**
GFR MDRD	92.8* (>60)	25.8	**39.0**	78.0	83.0	90.2	**107.0**	**164.6**

Table 1. Pregnant women with GD (normal ranges in brackets from ref 17. *P<0.05; ***P<0.005; ****P<0.001 compared to CTR group. (tab.2). Values exceeding refernces values are in bold.

	Mean	SD	Quintiles					
			(I)	(II)	(III)	(IV)	(V)	100%
Baby weight (g)	3408.5	737.3	1890.0	2966.0	3258.0	3612.0	3960.0	**4560.0**
Gestation (weeks)	38.5	2.2						
BPdiastolic (mmHg)	79.9	14.2	35.00	70.0	80.0	**84.0**	**90.0**	**100.0**
BPsystolic (mmHg)	129.8	16.7	100.0	120.0	120.0	**130.0**	**140.0**	**170.0**
CREA(mM)	61.8 (35-80)	10.1	36.0	55.2	59.8	64.4	70.8	78.0
GLU(mg/dL)	4.33 (4-4.3)	0.63	3.31	3.80	4.04	4.45	**5.02**	**5.47**
ALB(g/L)	34.4 (23-42)	2.6	28.5	31.9	33.8	35.0	36.5	40.2
Hb(g/dL)	11.2 (9.5-15)	1.4	8.40	10.5	11.1	11.6	12.2	13.6
WBC (10^3/L)	9.8 (5.6-16.9)	2.1	7.1	7.9	8.5	10.2	12.9	14.1
LYMPHOCYTES(%)	19.8 (1-3.6)	4.5	**12.8**	**15.8**	**18.4**	**21.2**	**22.1**	**34.0**
MONOCYTES(%)	5.2 (0.1-1.4)	1.0	**3.5**	**4.1**	**5.3**	**5.6**	**6.1**	**7.9**
GRANULOCYTES(%)	74.8 (45-74)	4.7	65.0	71.2	73.3	76.5	**78.7**	**83.2**
RBC (10^{12}/L)	3.8 (2.72-4.43)	0.3	3.2	3.6	3.6	3.9	4.2	**4.9**
MDRD-GFR	108.2 (>60)	38.2	73.0	86.2	98.8	109.0	118.8	282.0

Table 2. Control pregnant women (normal ranges in brackets from ref. 17. *P<0.05; ***P<0.005; ****P<0.001 compared to CTR group. (tab.2). Values exceeding refernces values are in bold.

Chan and colleagues concluded that increased iron storage and transport, (e.g. elevated serum ferritin), early in gestation are associated with an increased risk of GDM (12). The results of their study suggested that this association, at least in part, may be mediated by the maternal fat mass and obesity. Similar conclusions were reported in 2002 by Lao and colleagues working on a population of Chinese pregnant women (19). These authors found that high maternal hemoglobin (more than 13 g/dL) at the initial prenatal visit in a population of Chinese women is an independent risk factor for GDM. In another study the same authors found that maternal hepatitis B surface antigen (HBsAg) carriage could explain in part the association between increased serum ferritin concentration with GD, and that the HBsAg carrier status is an independent risk factor for GDM (20).

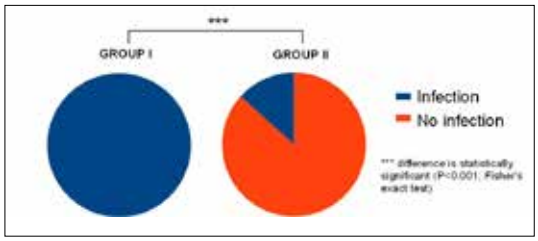

Figure 1. Results of examination between GDM and CTR groups

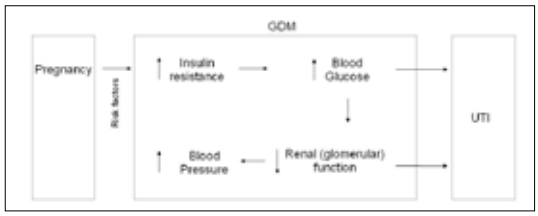

Figure 2. Prevalence of UTI in GDM

The decrease of renal functionality we found in pregnant women affected by GDM (115.3±16.0 vs 101.3±18.5 (Table 1 and Table 2) without significant increase of BP, indicated that this loss of renal functionality was probably associated to a glomerular damage still in an early stage of development. By contrast, as shown in Figure 1, the loss of renal functionality observed in pregnant women with GD was paralleled by a highly significant elevation of UTI compared to those affected by BP dysfunctions (100% vs. 13.3%, P<0.001). These results were in good accordance with those from previous studies reporting that mothers affected by GDM are at higher risk of complications from UTI along with preeclampsia, hypertension, and Cesarean delivery (21). In particular, the predisposition to UTI in DM and GDM may result from several factors. Susceptibility to this kind of infections seems to increase with longer duration and greater severity of diabetes. As different studies have investigated the role of UTI in preeclampsia (22, 23, 24, 25, 26). The role of UTI in GDM is poorly investigated and understood (27). Only few studies have shown that UTI caused by different bacteria are common in women with GD, and that their growth is probably due the favorable growth conditions induced by high blood and urine glucose. The results of the present study support this conclusion, as well evidenced by the dramatic difference in the UTI prevalence found for the pregnant women belonging to the GDM group and to the CTR group, in which only those in GDM group were affected by diabetes (Figure 1).

4. CONCLUSIONS

The results reported in this study have shown that women affected by GDM have, apart higher blood glucose, enhanced blood iron transport and storage, decreased renal performance and higher prevalence of UTI. Hence, it can be hypothesized that the strikingly higher prevalence of UTI in GDM may originate from the cascade of events summarized in the scheme reported in Figure 2. The insulin resistance and the increase oxidative stress mediated by the impaired of iron metabolism associated to pregnancy status and further elicited by GDM, leads to the enhancement of blood glucose, which is known to trigger detrimental processes damaging the renal glomerular filtration system, which in turn lead to the progressive increase of BP. The consequent rise in urine glucose concentration and enhanced tissue permeability may then 'open the way' to the diffusion of microorganisms and pathogens into the urinary tract. These findings, although limited by the low number of subjects involved and by to its retrospective design, warrant to keep supporting the research on appropriate measures and methodologies for the prevention, the treatment and the management of all the different multifaceted aspects of GDM including UTI iron intake monitoring, to ensure better and safer pregnancy outcomes.

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