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Hyperbilirubinemia in neonates and the time of maternal screening for gestational diabetes mellitus

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AUTHORS' CONTRIBUTION: **(A)** Study Design · **(B)** Data Collection · **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** Funds Collection

SUMMARY

Introduction. It is well-known that treatment of gestational diabetes mellitus (GDM) decreases the risk of complications, such as: miscarriage, fetal macrosomia, hypoxia, perinatal injury, hypoglycemia, hyperinsulinemia, hyperbilirubinemia and polycythemia. Due to discrepancies in epidemiological studies, there are constant debates regarding the optimal time of maternal screening for GDM and initiation of therapy.
Aim. The aim of the study was to determine if expediting the diagnostic and therapeutic window for gestational diabetes below 24 weeks of gestation could decrease the incidence of pathological hyperbilirubinemia in neonates.
Material and methods. We conducted a survey-based study to estimate the incidence of complications in neonates in 2 groups of mothers: with (studied group) and without gestational diabetes (controls).
Results. The mean incidence of hyperbilirubinemia was higher in the studied group than in controls, with dominating pathological jaundice. Our analysis did not show any statistically significant differences concerning the incidence of complications and the time of therapeutic interventions (<24 weeks, 24–28 weeks, ≥29 weeks).
Conclusions. The period between 24 and 28 weeks of gestation is an optimal time for therapeutic intervention in gestational diabetes in order to decrease the incidence of hyperbilirubinemia in the postnatal period.
Key words: gestational diabetes mellitus; complications; hyperbilirubinemia; macrosomia

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INTRODUCTION

Current evidence suggests that maternal hyperglycemia is not beneficial for fetal development and postnatal condition of the child. These complications, however, can be minimized if gestational diabetes mellitus (GDM) is adequately treated [1–3]. The pathogenesis of GDM is complex and associated with impaired carbohydrate tolerance which is usually observed in the second half of pregnancy. This problem concerns 3–6% of pregnant women [4]. Neonates born of mothers with GDM more frequently present with hyperbilirubinemia, polycythemia, hypoglycemia, hypocalcemia, hypomagnesemia, infections and macrosomia [5–7]. The incidence of hyperbilirubinemia in neonates of mothers with GDM ranges from 8 to 30% of cases and is caused by functional immaturity of the liver, decreased levels of glucuronic acid and increased polycythemia-associated hemolysis [8]. The international joint statement concerning detection of gestational diabetes is still being prepared since the determination of the most optimal time for screening and diagnostic recommendations evokes doubts due to considerable discrepancies in population-based studies [9–14]. The current recommendations of the Polish Gynecologic Society and Polish Diabetes Association indicate that screening of pregnant women should involve an oral glucose tolerance test (OGTT) with 75 g of glucose. Taking these guidelines into account, as well as following the American recommendations, diagnostic tests in women without GDM risk should be conducted between weeks 24–28 of gestation [15,16]. It turns out, however, that when screening is conducted at the end of this period, potential therapeutic intervention is shorter compared with the situation in which

diagnostic tests are conducted at the beginning of this period. Despite the fact that the probability of normal pregnancy, without maternal and fetal complications, declines with the duration of diabetes, it is assumed that early GDM diagnosis corresponds with a longer treatment period and normalization of blood glucose levels, which might minimize complications.

AIM

The aim of the study was to answer the question whether early diagnostic and therapeutic interventions (<24 week of pregnancy) could reduce the rate of neonatal complications and decrease the incidence of pathological hyperbilirubinemia. To do this, we conducted a retrospective analysis of medical histories of mothers and their children born between 2008–2010 in the Fifth Department of Gynecology and Obstetrics of the Second Specialist Hospital in Bytom of the Medical University of Silesia in Katowice, Poland. We characterized the group of women with GDM, conducted an obstetric assessment of this group and specified the influence of GDM on neonatal development and condition in the postnatal period. The study was conducted from March to April 2012.

MATERIAL AND METHODS

The study included 100 women with gestational diabetes mellitus (mean age: 30, range: 19–42). The investigation was based on the author-prepared questionnaire. It was initially validated on the basis of 10 medical histories of women and their children hospitalized in the Obstetrics Unit of the Department of Gynecology and Obstetrics. The control group included 100 women (mean age: 28, range: 17–38) with normal singleton pregnancies. None of the neonates from the investigated and control groups was hospitalized in the Neonatal Intensive Care Unit. All neonates had bilirubin levels monitored, starting from the determination of its level in the umbilical blood. The tests were conducted in the Laboratory of the Second Specialist Hospital in Bytom. The demographic characteristics and details from the obstetric interview as well as condition of neonates after birth for both studied and control groups are presented in Table 1. Based on typical criteria (bilirubin concentration, time and value of bilirubin increase), 2 groups were distinguished: physiological and pathological hyperbilirubinemia. On the basis of the manner of GDM therapy, the following subgroups were distinguished: G1– managed with diet and physical exercise, as well as G2 – managed with diet, exercise and insulin.

The data were analyzed in the STATISTKA software (StatSoft, Poznan 2010). The level of statistical significance was assumed at $p<0.05$.

RESULTS

Hyperbilirubinemia was observed in both the studied group and controls in 42 neonates, with higher incidence in the former (1.5:1; 25% vs 17%, respectively) (Fig.1.). The mean bilirubin levels in the neonatal serum were similar in both groups (mean: 14.8 mg/dl vs 14.2 mg/dl; $p>0.05$). Two types of jaundice (physiological and pathological) were observed in both groups. Pathological jaundice was twice as common in the studied group as in controls ($p=0.04$) (Fig. 2). Cesarean section was more commonly indicated in GDM mothers (57% vs 32%) (Fig. 3), and all neonates were diagnosed with pathological jaundice.

The mother's age had no influence on the incidence of hyperbilirubinemia in either of the groups. Most mothers from both groups had secondary or higher education (79% vs 64%),

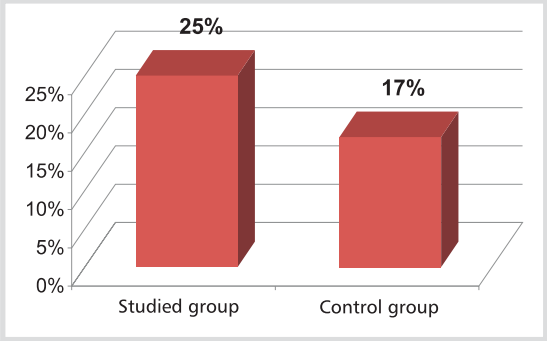

Fig. 1. Incidence of hyperbilirubinemia

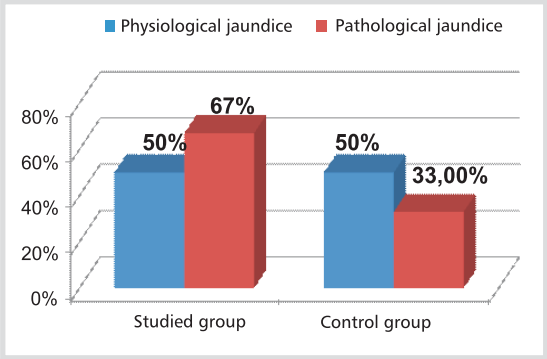

Fig. 2. Incidence of physiological and pathological jaundice

but this variable did not affect hyperbilirubinemia. Neonates of pluriparas presented with jaundice nearly twice as often (26 vs 16). Neonates born of women with GDM G1 had hyperbilirubinemia nearly 3 times more frequently (18 vs 7) with a statistically significant prevalence of pathological jaundice (p=0.04) (Fig. 4). The GDM screening test conducted between weeks 24 and 28 was more often carried out in the control group (56 vs 44). The evaluation of the incidence of physiological and pathological jaundice depending on the time of diagnosis and initiation of therapy (<24 weeks, 24–28 weeks, ?29 weeks) revealed that in groups <24 weeks and ?29 weeks, physiological jaundice was more common than pathological jaundice. When, however, GDM was diagnosed between weeks 24–28, pathological jaundice was more common (55.60% vs 68.75%) (Fig. 4). In both studied and control groups, children were born between the 37th and 40th week of gestation. There was no relationship between the gestational age and pathological jaundice (p>0.05). The average birth weight was similar in both groups. There were 4 and 5 neonates with birth weight >4,000 g in the studied group and in controls, respectively (p>0.05) (Fig. 5).

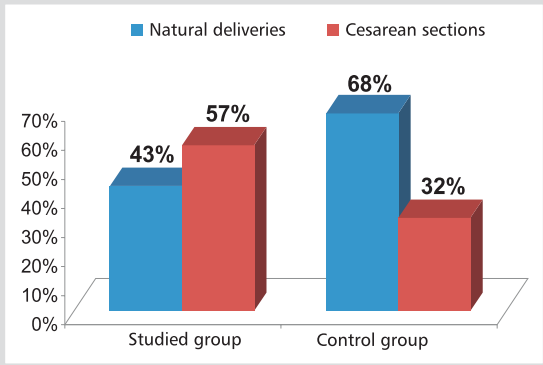

Fig. 3. Frequency of natural deliveries and cesarean sections

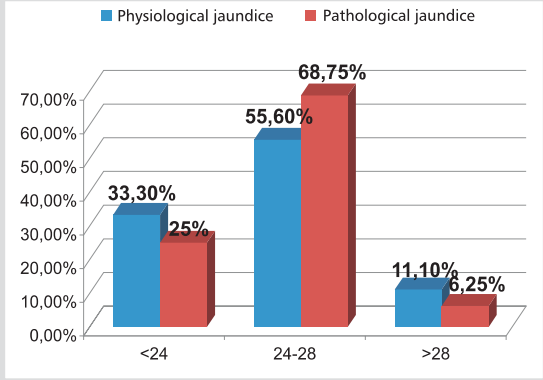

Fig. 4. Incidence of pathological and physiological jaundice depending on the time of GDM treatment initiation

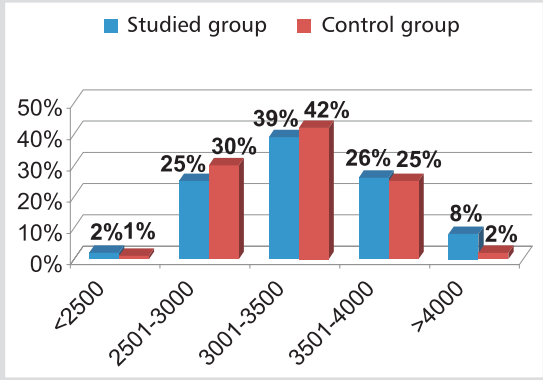

Fig. 5. Distribution of birth weight

The condition of the neonates after delivery and signs of hypoxia were assessed on the Apgar scale. Apgar score of ≤3 and ≤7 did not increase the incidence of pathological jaundice. The analysis of the manner of nutrition (natural feeding, mixed feeding, formula) showed that natural feeding increases hyperbilirubinemia.

The analysis of overall complications as well as hyperbilirubinemia, macrosomia, hypoxia and indications for a cesarean section revealed no statistically significant differences depending on the time of GDM diagnosis and the manner of therapy (Table 2).

Positive urine culture was obtained in a total of 8 neonates, more frequently in the studied group (p<0.05).

DISCUSSION

Hyperbilirubinemia can disturb fetal development at each stage. According to literature data, it occurs in 8–30% of neonates born of mothers with GDM [8]. The study presented above revealed that hyperbilirubinemia occurred in every 5th neonate, both in studied patients and in controls. In the studied group, the incidence reached 21% and was higher than in controls. The clinical efficacy of GDM therapy, assessed by the incidence of its complication, i.e. hyperbilirubinemia, occurred to be satisfactory. Pregnant women with GDM require specialist and close monitoring by an obstetrician and diabetologist in reference centers in order to decrease the incidence of hyperbilirubinemia below 15%. Pregnancy complicated with diabetes is a high-risk pregnancy. Effective treatment involves an adequate diet, engaging in physical exercise and, if necessary, using insulin [7,17].

It has been demonstrated that combined therapy (diet and insulin) decreases fetal complications [7,17,18]. The study presented above, however, has not shown any influence of combined therapy on decreasing the incidence of pathological hyperbilirubinemia.

Moreover, the investigation has not demonstrated that earlier initiation of GDM treatment would have a considerable influence on improving treatment efficacy as far as the incidence of hyperbilirubinemia is concerned. Children of women who started GDM therapy earlier presented pathological jaundice more rarely (not statistically significant). The optimal time for diagnosis and initiation of GDM treatment remains undefined. The study of Hillier et al. has shown that implementation of treatment before week 24 of gestation significantly reduces the risk of complications in women [16]. It has also been found that insulin sensitivity in women declines as pregnancy progresses and, therefore, the period between week 24 and 28 is the most optimal for GDM diagnosis [1,2,19]. However, this time period is considered as a period of variable sensitivity concerning GDM detectability and decreased efficacy of treatment

Tab. 1. Characteristics and demographics of the studied group and controls

	Studied group	Control group
Mother's age (17-42lat)	30 (+/- 3,8)	28 (+/- 5,7)
Secondary and higher education	79 (79%)	64 (64%)
Miscarriage	17 (17%)	16 (64%)
Oral glucose tolerance test 24–28 weeks	44 (44%)	56 (56%)
Onset:		
<24	36 (36%)	
24-28	55 (55%)	
>28	9 (9%)	
Type of therapy:		
Diet	71 (71%)	
Insulin therapy	29 (29%)	
Caesarean section	57 (57%)	32 (32%)
Gestational age:		
37 weeks	20 (20%)	13 (13%)
38 weeks	37 (37%)	36 (36%)
39 weeks	23 (23%)	25 (25%)
40 weeks	20 (20%)	26 (25%)
Birth weight	3336g+/- 0,382	3260g+/-0,432
Respiratory disorders	7 (7%)	1 (1%)
Hyperbilirubinemia		
physiological	9 (9%)	9 (9%)
pathological	16 (16%)	8 (8%)
Apgar:		
0-3 pkt	1 (1%)	0 (0%)
4-7 pkt	6 (6%)	1 (1%)
8-10 pkt	93 (93%)	99 (99%)

Tab. 2. Relationship of the gestational age and initiation of therapy with GDM treatment considering overall complications, hyperbilirubinemia, macrosomia, hypoxia and cesarean section

Gestational age and initiation of GDM treatment	Overall complications*		Hyperbilirubinemia		Macrosomia		Hypoxia		Cesarean section	
	G1 ** n=71	G2*** n=29	G1 ** n=71	G2*** n=29	G1 ** n=71	G2*** n=29	G1 ** n=71	G2*** n=29	G1 ** n=71	G2*** n=29
<24 weeks	15 (21,12)	8 (27,58)	2 (2,81)	1 (3,44)	1 (1,40)	0 (0)	2 (2,81)	1 (3,44)	11 (15,49)	5 (17,24)
24-28 weeks	21 (29,57)	10 (34,48)	8 (11,3)	3 (10,34)	2 (2,81)	1 (3,44)	1 (1,40)	0 (0)	17 (23,94)	8 (27,57)
≥29 weeks	11 (15,49)	6 (20,68)	1 (1,40)	0 (0)	2 (2,81)	1 (3,44)	0 (0)	1 (3,44)	11 (15,49)	5 (17,24)
p	>0,05		>0,05		>0,05		>0,05		>0,05	

* Overall complications: (hyperbilirubinemia, macrosomia, hypoxia and cesarean section); ** G1 – treatment with diet and exercise; *** G2 – treatment with diet, exercise and insulin

if the screening results present very high values. It has been shown that GDM therapy enables reduction of various gestational complications. The authors of the ACHOIS study, for instance, mention a reduced risk of mortality, perinatal injury, miscarriage and macrosomia [2]. Moreover, the MFMU Network's GDM study has confirmed these conclusions and also demonstrated a reduction in the incidence of gestational complications [3]. It must be emphasized that, in both these studies, the mean time of treatment initiation after screening was week 29 of gestation. It was slightly later than the recommended diagnostic and therapeutic window (24–28 week), but did not have negative effects on GDM treatment. That is why it can be concluded that the period between 24 and 28 weeks of gestation is an optimal time for therapeutic intervention in gestational diabetes in order to decrease the incidence of hyperbilirubinemia in the postnatal period.

CONCLUSIONS

1. The period between 24 and 28 weeks of gestation is an optimal time for therapeutic intervention in gestational diabetes in order to decrease the incidence of hyperbilirubinemia in the postnatal period.
2. It has not been shown that therapeutic intervention implemented earlier than in the 24th week of gestation is more effective in the prevention of diabetic complications in neonates.

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