Perinatal outcome in pregnancies with gestational diabetes

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SCHOOL OF MEDICINE

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List of abbreviations

BMI: Body Mass Index

C-section: Cesarean section

DKA: Diabetic Keto Acidosis

DM: Diabetes Mellitus

DVT: Deep Vein Thrombosis

FFA: Free Fatty Acids

GDM: Gestational Diabetes Mellitus

GLUT-4: Glucose transporter Type 4

HAPO study: Hyperglycemia and Pregnancy Outcome study

HbA1c: Hemoglobin A1c, glycated hemoglobin

hPL: human Placental Lactogen

IRS-1: Insulin Receptor Substrate 1

L/S ratio: Lecithin/Sphingomyelin ratio

mRNA: messenger Ribo Nucleic Acid

NT: Normal Tolerance to glucose

OGTT: Oral Glucose Tolerance Test

p85α: regulatory subunit of Phosphoinositide-3-kinase

PI-3K: PhosphoInositide 3 Kinase

TNFα: Tumor Necrosis Factor α

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1. Summary

Title: Perinatal Outcome in Pregnancies with Gestational Diabetes

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The aim of this graduate thesis was to explore the perinatal outcome of gestational diabetes mellitus in our referral center in Zagreb.

All over the world, physicians are faced with many challenges when it comes to diabetes, metabolic syndromes or other endocrinological disturbances.

Modern lifestyles, especially western diets create a favorable background for the emergence of this type of conditions. This environmental factor coupled with genetic predispositions results in an increased interest for GDM as it is a partially a preventable disease.

In our study, we used a database of 2362 pregnant women suffering from this condition.

We found that these women had a statistically higher prevalence of hypertension before and throughout the pregnancy. This risk factor led to a higher number of operative delivery (C-sections).

Newborns also presented with a higher proportion of macrosomia than in the general population. This feature; in addition to the serious neonatal complications such as hyperbilirubinemia, hypoglycemia and respiratory disturbances, justifies the use of c-sections as a mode of delivery.

Our results emphasize the importance of proper follow up of women in pregnancy; starting from early screening to appropriate management using modern imaging techniques and adequate nutritional approach.

Key words: gestational diabetes mellitus, hypertension, macrosomia, neonatal complications, operative deliver

2. Preface

Definition and epidemiology

Gestational Diabetes Mellitus (GDM) is defined as the state of carbohydrate intolerance that has its onset or first recognition during pregnancy. It affects up to 15% of pregnancies worldwide.[1] Because GDM is such a heterogeneous entity, estimates of occurrence vary with ethnic diversity of the populations under study, geographic area, screening frequency, and diagnostic criteria.

In Croatia, it is present in 5% to 15% of pregnancies according to the new criteria established by the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study.

Endocrinological changes

Pregnancy, due to many endocrinological changes, is a physiological pro-diabetogenic state.

The associated insulin resistance emerges in the 2nd trimester and is more prominent in the late 3rd trimester, while in the 1st trimester a slight increase in the insulin sensitivity has been observed. [2]

This increase in insulin resistance results in increase in maternal and fetal glucose, free fatty acids (FFA) and amino acids. These changes are essential for the regulation of energy metabolism and fetal growth.

Interestingly enough, in normal pregnancies, the insulin sensitivity is decreased by 30% to 60% compared to healthy non pregnant women.[2]

In both GDM and in pregnancies with NT (normal tolerance to glucose) an increase of the hepatic glucose production of 30% has been observed.[3] This happens despite an increased fasting plasma insulin in GDM compared to pregnancies with NT, and confirms the existence of a hepatic insulin resistance.

Biopsy samples taken during cesarean sections demonstrated a decreased GLUT-4 transporter concentrations in adipocytes but not in the muscles of women with GDM[4].

Knowing that muscles are responsible for 80% of total insulin-dependent glucose uptake, one can conclude that this defect does not cause the insulin resistance.

Focus has then shifted towards the study of the post-receptor level.

In human skeletal muscle, impaired insulin receptor autophosphorylation was found. More precisely; obese women with GDM showed a decrease in tyrosine phosphorylation of the insulin receptor β-subunit.

Also; the impaired suppression of FFA by insulin in GDM has been related to a decrease in the tissue IRS-1 protein level and an increase in p85α subunit of PI-3K in adipocytes.

The pathogenesis of the metabolic changes in GDM is still unclear, but the study of hormonal changes seems to explain the impaired glucose and lipid homeostasis.

The hormones relevant to our study are the following: hPL, progesterone, estrogen and Prolactin.

Human Placental Lactogen (hPL) is a protein hormone produced by the placenta. It antagonizes the effects of insulin which would normally inhibit the lipolysis (breakdown of triglycerides into FFA in the adipocytes) and also uses the excess glucose in the liver to synthetize FFA. The latter would then be transported as lipoproteins back to the adipocytes in order to form triglycerides. This means that insulin has an anabolic effect in adipose tissue.

On the contrary, under the influence of hPL, one can observe an increase in the lipolysis and therefore an increase as well in the FFA concentration in the plasma.

In combination with the maternal hyperinsulinemia, hPL increases the protein synthesis, which provides a source of energy for the fetus.

And finally, it is worth mentioning that the increase in hPL level parallels the development of the insulin resistance.

The second hormone we will consider is Progesterone.

Progesterone, is a steroid hormone also secreted by the placenta. In fasting women with NT, progesterone increases the insulin concentration without leading to a hypoglycemia, thereby indicating a resistance to insulin.

This resistance is then observed even in the context of an absence of glucose intolerance.

The third hormone we will consider is Estrogen.

Estrogens activity is based on hepatocyte stimulation to increase the concentration on cortisol-binding globulin. The adrenal cortisol production is then raised to maintain free cortisol levels. Although glucocorticoids antagonize insulin action, no direct connection has been established between free cortisol levels and insulin resistance.

The last hormone that was documented is Prolactin. Also known as luteotropic hormone or luteotropin; it is a peptide produced by the pituitary gland.

So far, its increase doesn't seem to have an influence either.

The role of adipocytokines and cytokines has also been investigated.

TNF α seems to be a better indicator of insulin resistance than placental hormones and cortisol[5].

The increase in TNF α levels parallels the increase in insulin resistance. In addition; it induces leptin expression, which has been associated with chronic hyperinsulinemia in the late second trimester of pregnancy.

The plasmatic leptin concentrations correlate with the glycemic control, the insulin resistance, the body weight and the overall maternal weight gain during pregnancy. Therefore; leptin at the entry of the prenatal care could be an important predictor of the expected postpartum weight reduction.

Adiponectin on the other hand, suppresses the TNFα activity, and increases the hepatic glucogenosis and insulin sensitivity.

In several cases of insulin resistance, hypoadiponectinemia was documented.[2]

In women with GDM, adiponectin mRNA levels were decreased (in biopsy samples taken from abdominal subcutaneous tissue). Although it was present in cord blood, levels were slightly lower than in offspring of healthy women[6].

Finally the last adipocyte secreted hormone that is investigated is resistin. This peptidic hormone, in mice model, seems to cause a decrease in insulin sensitivity. Its precise role during normal and diabetic pregnancies is still not clear[7].

Risk Factors

Several anamnestic risk factors have been identified. They include a previous history of GDM, recurrent spontaneous abortions, unexplained intrauterine fetal death, previous infant with major congenital anomalies, previous macrosomic infant, recurrent preeclampsia, recurrent candidiasis, family history of DM in first-degree relatives and history of polyuria, polydipsia or glycosuria.

Other risk factors are well known such as maternal age over 30 years, excessive weight gain during pregnancy (weight>18kg), maternal obesity (BMI>27kg/m2 or pregnancy weight) and development of polyhydramnios and/or fetal macrosomia in present pregnancy.

Diagnosis

The most common diagnostic test recommended for GDM is the 2 hour oral glucose tolerance test (OGTT).

It is conducted with a 75mg glucose load that the patient drinks within 5minutes after a fasting sample is drawn.

Glucose level is then measured at 1, and 2 hours.

The thresholds recommended by the HAPO study represent odds ratios of 1.75, and are fasting plasma glucose 92 mg/dl (5.1 mmol/L), 1-hour 180 mg/dl (10 mmol/L), and 2 hours 153 mg/dl (8.5 mmol/L).[8]

The test is considered positive if one values is abnormal.

Current treatment

Treatment revolves around good glycemic control as it will be discussed later on.

During the second trimester of pregnancy, the need for insulin is higher and complications due to hypertension can be controlled pharmacologically by using methyldopa or nifedipine as a chronic therapy.

Problems encountered during pregnancy

For most women, GDM does not cause noticeable signs or symptoms.

Our main concern is to prevent maternal and neonatal complications which will be further discussed. These include perinatal mortality and congenital malformations but also increased maternal morbidity and mortality.

3. Hypothesis

Women with GDM have adverse perinatal outcome in relation to healthy pregnant women.

4. Objectives

The focus of this graduate thesis was to explore the perinatal outcome in pregnancies with GDM from the maternal and neonatal perspectives.

5. Material and Methods

The study included database of 4195 singleton pregnancies. Of all, there were 2362 women with gestational diabetes mellitus according to WHO criteria (based on HAPO study recommendations). All women with gestational diabetes mellitus were treated with diet, and the inclusion of insulin in therapy was exclusion criteria for study. The patients gave birth at University Hospital Centre Zagreb (UHC Zagreb), Department of Obstetrics and Gynecology. The ethical committee of UHC Zagreb gave approval for the use of data.

Numerical data were described by the mean value (arithmetic mean) and standard deviation in the case of normal distributions. In other cases, data were described by the median and the boundaries of interquartile range. Distribution normality of numerical variables was tested by the Shapiro-Wilk test. Student t test was used for analysis of normally distributed numerical variables and Mann-Whitney U test was used for analysis in the cases of deviation from normal distribution. Connection of normally distributed numerical variables was evaluated by the Pearson correlation coefficient r, and in the cases of deviation of normal distribution by the Spearman correlation coefficient ρ. Level of significance was set as $\alpha=0,05$. All of the data were statistically analysed by the program MedCalc Statistical Software version 13.1.2 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

6. Results

We found slight age difference between the two groups of patients. The pregnancy weight gain was greater in control group, whereas pregestational BMI was greater in GDM group. This is an encouraging result, meaning that patients with GDM were strictly controlled for weight gain since they are a high risk population.

Table 1. Age and weight of patients

	Group			
	Control	GDM	Z	P
	Mean (SD)	Mean (SD)		
Age (years)	30,1 (5,4)	31,8 (5,4)	-9,855	< 0,001
Pregnancy weight gain (kg)	14,8 (5,6)	12,9 (6,3)	10,229	< 0,001
Pregestational BMI (kg / m ^{2})	23,9 (4,4)	26,1 (7,1)	-11,274	< 0,001

BMI – Body Mass Index; Z-Mann-Whitney U test value; P-probability

The prepregnancy hypertension was more frequent in the group of GDM patients, being 5 times greater than in the control group.

Table 2. The frequency of preexisting hypertension

			Preexisting hypertension		Total
			No	Yes	
Group	Control	N (%)	1820 (99,3)	12 (0,7)	1832 (43,7)
	GDM	N (%)	2279 (96,6)	79 (3,4)	2358 (56,3)
Total		N (%)	4099 (97,8)	91 (2,2)	4190 (100)

χ^2 = 35,251; P < 0,001.

Women with gestational diabetes more frequently had hypertension during pregnancy as well. Of all women with hypertensive disorder, 73 in GDM group had preeclampsia.

Table 3. Hypertension during pregnancy

			Hypertension during pregnancy		Total
			No	Yes	
Group	Control	N (%)	1743 (95,1)	89 (4,9)	1832 (43,8)
	GDM	N (%)	1997 (85)	355 (15)	2352 (56,2)
Total		N (%)	3740	34	4184 (100)

$\chi^2 = 120,074$; $P < 0,001$.

The rate of preterm delivery was greater in the group of women with gestational diabetes.

Table 4. Preterm delivery frequency

			Pregnancy outcome			Total
			Miscarriage	Preterm delivery*	Term delivery	
Group	Control	N (%)	55 (3,0)	156 (8,5)	1622 (88,5)	1833 (43,7)
	GDM	N (%)	12 (0,5)	309 (13,1)	2041 (86,4)	2362 (56,3)
Total		N (%)	67 (1,6)	465 (11,1)	3663 (87,3)	4195 (100)

$\chi^2 = 60,115$; $P < 0,001$.
*Post hoc: $\chi^2 = 21,684$; $P < 0,001$.

The rate of cesarean section was greater in group of women with gestational diabetes. The rate in control group was 18,1% and was similar to the state average rate of cesarean section. The rate was 35,2% in GDM group, as shown in table 5.

Table 5. Operative delivery

			Pregnancy termination		Total
			Vaginal	SC	
Group	Control	N (%)	1490 (81,9)	330 (18,1)	1820 (43,5)
	GDM	N (%)	1530 (64,8)	831 (35,2)	2361 (56,5)
Total		N (%)	3020 (72,2)	1161 (27,8)	4181 (100)

$\chi^2 = 149,219$; $P < 0,001$.

The rate of newborns large for gestational age (i.e. > 90 percentile) was greater in group of women with gestational diabetes. There was no difference for small for gestational age newborns

Table 6. Newborn growth in relation to GDM

			Growth percentile			Total
			<10	10-90	>90*	
Group	Control	N (%)	96 (5,4)	1399 (79,0)	277 (15,6)	1772 (44,5)
	GDM	N (%)	148 (6,7)	1540 (69,7)	521 (23,6)	2209 (55,5)
Total		N (%)	244 (6,1)	2939 (73,8)	798 (20,0)	3981 (100)

$\chi^2 = 45{,}025$; $P < 0{,}001$.
*Post hoc: $\chi^2 = 38{,}775$; $P < 0{,}001$.

The incidence of fetal macrosomia differed between newborns. The GDM group of women had macrosomic infant more often.

Table 7. Frequency of macrosomia

			Macrosomia			Total
			Yes*	No	Hypotrophic	
Group	Control	N (%)	311 (17,6)	1366 (77,1)	95 (5,4)	1772 (43,2)
	GDM	N (%)	479 (20,5)	1703 (73,0)	151 (6,5)	2333 (56,8)
Total		N (%)	790 (19,2)	3069 (74,8)	246 (6,0)	4105 ()

$\chi^2 = 8{,}980$; $P = 0{,}011$.
*Post hoc: $\chi^2 = 5{,}264$; $P = 0{,}022$.

Most frequent neonatal complications included hyperbilirubinemia, hypoglycemia, infection, Cushingoid appearance and transitory respiratory disturbance. The group of mothers with gestational diabetes during pregnancy had more often infants with some of abovementioned complications. There was no significant difference for rare complications such as hip dysplasia, clavicle fracture or cephalhematoma.

Table 8. Frequency of neonatal complications

			Neonatal complications		Total
			No	Yes	
Group	Control	N (%)	1723 (94,7)	97 (5,3)	1820 (43,5)
	GDM	N (%)	2060 (87,3)	301 (12,7)	2361 (56,5)
Total		N (%)	3783 (90,5)	398 (9,5)	4181 (100)

$\chi^2 = 64{,}822$; $P < 0{,}001$.

Of all children 98,3% had no congenital malformation. The group of mothers with GDM had more than two folds greater frequency of congenital malformations, mostly cardiac.

Table 9. Frequency of congenital malformations

			Congenital anomalies		Total
			No	Yes	
Group	Control	N (%)	1804 (99,1)	16 (0,9)	1820 (43,5)
	GDM	N (%)	2307 (97,7)	54 (2,3)	2361 (56,5)
Total		N (%)	4111 (98,3)	70 (1,7)	4181 (100)

χ^2 = 11,537; P = 0,053.

There was statistically but not clinically significance in gestation at birth between two groups. Mothers with GDM had newborns with greater newborns weight. Apgar scores in first and fifth minute were clinically non-significant.

We found significant correlation between maternal weight gain during pregnancy and newborns weight (r = 0,459; P < 0,001). As mothers had greater weight gain during pregnancy newborns weight was greater.

Table 10. Birth weight and Apgar score in relation to GDM

	Group			
	Control	GDM	Z	P
	Mean (SD)	Mean (SD)		
Gestation (weeks)	39 (4)	39 (2)	-2,457	< 0,001
Newborn's weight (grams)	3338,8 (797,3)	3450,0 (707,0)	-4,773	< 0,001
Apgar score 1st min.	10 (1)	9 (1)	5,081	< 0,001
Apgar score 5th min.	10 (1)	10 (3)	0,258	0,797

BMI – Body Mass Index; Z-Mann-Whitney U test value; P-probability

7. Discussion

Table 3 showed us the prevalence of hypertension in women suffering from GDM. This pregnancy induced hypertension when associated with proteinuria is defined as a clinical entity called preeclampsia.

In the literature it is mentioned that this pathology occurs in 20% of diabetic pregnant women, which is 3 times more frequently than in healthy pregnant women and significantly increases perinatal mortality and morbidity.[9, 10].

According to the data of the Obstetrics and Gynecology Clinic in Zagreb, the perinatal mortality of diabetic pregnant women with pre-eclampsia in a period of 40 years is high and amounts to 20,6% in relation to 3,5 of normotensive diabetic pregnant women

It seems appropriate at this point to mention the other relevant conditions that women with GDM might encounter during their pregnancy such as infections or DKA.

Infections are significantly more frequent in diabetic pregnant women than in healthy ones.

Pyelonephritis can be expected in 4% of diabetic women, and in only 1% of pregnant women in the non-diabetic population.

Significant bacteriuria is also frequent and amount to about 40% in pregnancies with diabetes [11, 12].

It is interesting to note that hypertension is also more frequently observed in pregnant women with bacteriuria than in those with sterile urine. [13]

Diabetic ketoacidosis (DKA) is a rare (less than 1% of cases) but a serious complication.

Bearing in mind the development of insulin resistance during pregnancy, lipolysis and ketogenesis also increase and therefore DKA can occur even with minimal hyperglycemia.

DKA is accompanied by a high fetal loss, which amounts to 20%. It should be treated quickly, in a similar manner than in non-pregnant patients. [13]

Now that we have analysed the maternal complication that women encounter, the next logical step is to observe the type of delivery that is chosen.

As shown in table 5, women with GDM tend to have a higher rate of cesarean sections.

A recent study showed that GDM significantly increased the risk of emergency cesarean delivery (adjusted odds ratio 1.9, 95% confidence interval 1.03-3.5, p = 0.039) only among nulliparous women, adjusted for age, body mass index, and gestational weight gain[14];

When considering elective C-section, in patient with type 1 diabetes, they should be performed on a morning list to enable the patient to return to oral intake and normal insulin regimen by the following morning.

Prophylactic antibiotics should be administered in both cases[15] and DVT prophylaxis should as well be given to obese women.

As shown in table 7, the most characteristic feature of the newborns is macrosomia.

This condition is a frequent complication in pregnancies of women with diabetes. The exact incidence depends on the definition used. It is often defined by a birth weight >4000g or greater than 90% for the gestational age.

Macrosomia potentially affects up to 10% of pregnancies and has been reported in 20-25% of the infants in women with diabetes and in 7-10% of them when using a cut-off value of 4500g. [16, 17]

The most dangerous condition related to macrosomia is shoulder dystocia.

The incidence of shoulder dystocia increases with the birth weight and is affected by maternal diabetes as well.

Langer et al, reported a 21,8% incidence of shoulder dystocia in diabetic women delivering infants weighting more than 4500g compared to 7,5% in non-diabetics.[20]

Estimation of the birth weight are based on the parietal diameter, the head circumference, the abdomen circumference and the femur length.

Many neonatal complications have been documented in the literature.
Among all these complications, respiratory distress is the most serious complication for the neonate. Fetuses affected by GDM are at elevated risk (perhaps 5- to 6-fold greater) of lung immaturity compared with age-matched controls. [Oxygen supplementation, ventilatory support, and surfactant replacement are among the treatments available, and care may require consultation with a neonatologist.[18]

Amniocentesis is also performed to assess the fetal maturity. The lecithin-sphingomyelin L/S ratio being not significantly different from the one in healthy women, phosphate-diglycerol seems to be a more reliable parameter in estimating neonatal respiratory distress.

Hypoglycemia, which is one of the most obvious complications, results from fetal hyperinsulinemia, and should be treated and monitored every hour until stabilization.

Finally, polycythemia is a result of chronic intrauterine hypoxemia and placental insufficiency secondary to poor glycemic control. Hypoxemia causes increased fetal erythropoietin release and subsequent polycythemia. When these erythrocytes break down, there is increased incidence of hyperbilirubinemia at days to weeks after birth.[19]

Long-term effects include an increased incidence of childhood obesity, early adulthood type 2 diabetes mellitus, and intellectual-motor impairment.

Neonates born to women with GDM also present with a higher prevalence of congenital malformations as we showed in table 9.

Progresses in modern medicine have enabled us to monitor the growth of the fetus thanks to ultrasound technique and consequently to detect these malformations.

A detailed ultrasound examination should be performed between 18 and 20 weeks to detect possible abnormal development of spine, head, kidney and heart.

During the last trimester, from the 34^{th} or the 36^{th} weeks of pregnancy, the need for insulin decreases physiologically, as more glucose is transferred to the fetus.

Therefore more frequent ultrasound examinations are required to monitor the fetal growth and measure the quantity of the amniotic fluid.

8. Conclusion

The most valuable tool that physicians can use besides prevention and adequate screening is appropriate glycemic control.

Our main goal is to maintain optimal glycemic concentration. This is why pregnancy is not recommended before obtaining an HbA1c value <7%.

Ideal fasting blood glucose values in pregnancy are between 3,6mmol/L and 3,8mmol/L, and postprandial blood glucose less than 7,0mmol/L.

Women with GDM should be encouraged to self-care through a healthy diet and physical activity and self-monitoring.

A simple diet individually adjusted is also recommended. Supplementation with folic acid (5mg/day) should continue until the 12^{th} week of pregnancy.

The necessary energy intake is about 25-30kcal/kg of the ideal body weight, divided into six daily meals and it consists of 55% of carbohydrates, 20% of proteins and 25% of fat.

Blood glucose monitoring is crucial as well.

Measures should be taken before breakfast, 2h after breakfast, before lunch, 2h after lunch, before dinner, 2h after dinner, before bedtime and at about 3am.

Treatment with insulin can also introduced.

When this therapeutic option is chosen; intensive conventional insulin treatment is done as follows:

The patient can take long acting insulin in the evening before going to bed, or 2 injections of medium acting insulin every 12h to maintain a basal level. Before meals, injections of short acting insulin can be taken.

Insulin pumps are more frequently used since they deliver continuous insulin injection.

Regulation of the glycemia should be done every 2 weeks, and self-monitoring daily.

GDM is therefore a condition that requires a multidisciplinary approach, involving the obstetrician of course; but also nutritionists, endocrinologists and neonatologists.

Only through this surveillance and patient education and awareness, we can hope to decrease the chances of these women and their newborns to develop diabetes mellitus and its systemic complications later in life.

9. Acknowledgements

I would like to thank my mentor Josip Juras for the quality of his time, his availability and kindness.

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11. Biography

Yasmine Yakouta Atoui was born in Algeria in 1989.

After graduating from high school in Toulouse (France), she completed a Bachelor in Life Sciences in 2010 in the Faculty Pierre et Marie Curie in Paris.

She then moved to Zagreb to enroll in the University of Medicine in the English program.

After obtaining her diploma, she plans to apply for the internship in Zagreb and take the national licensing examination.

Besides medicine, she is interested in literature, traveling, dance and languages.