Ph D
Thesis

PREGNANCY ASSOCIATED WITH DIABETES

ABSTRACT

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**Keywords:** diabetes, pregnancy, trophoblastic, intravillous or extravillous structures.
GENERAL PART

Introduction

Pregnancy is a physiological, repeating until a certain age, in which the only time in human physiology, is tolerated for a limited time, the presence of hetero-grafts.

It is the only situation in which the body "host tissues" genetically different, without rejection phenomena.

It is one of the reasons why a pregnant body is "nuanced" general biological and immunological different from non-pregnant state.

But the pregnancy, although it is a normal physiological state, can take specific pathological aspects. There are many "anomalies" which realise a chapter of pathology caused by pregnancy or pregnancy associated.

Diabetes mellitus. General dates

Is defined as a syndrome characterized by a complex disorder of energy metabolism of the body, involving changes in the metabolism of carbohydrates, protein, lipid and other metabolites.

They are due to be a defect in insulin secretion or a combination of pancreatic beta cell’s hipofunction together with a degree of peripheral insulinresistance. There are four classic types of diabetes:

- Autoimmune type 1 (1A);
- Idiopathic (1B);
- Predominantly insulin resistant type 2 / Low Insulin production ;
- Other specific type of gestational diabetes ;

Diabetes complication

Possible mechanisms involved in the genesis of chronic complications of diabetes: genetic factors, biochemical disturbances, the glycation process, polyol pathway activation, activation of protein kinase C, oxidative stress, lipid metabolism changes, hemostatic changes.


Other chronic complications of diabetes mellitus: impaired skin, diabetic osteoarthropathy, infections, liver damage.
Hormonal aspects with metabolic implications in pregnancy.

Endocrine changes occurring during pregnancy are of an unexpected complexity and variety. The placental hormone production and metabolism plays an essential role in mother-child symbiosis.

The placental hormones interest chiefly feto-maternal metabolisms. Carbohydrate metabolism is also influenced by some placental hormone secretion clearly.

Steroid hormones:
- estrogen,
- progesterone.

Protein hormones:
- chorionic gonadotrophic hormone (HCG),
- placental lactogen hormone (HPL).

Other placental hormonal secretions.

Maternal complications in pregnancy associated with diabetes are
Complications directly related to carbohydrate metabolism disorder: ketoacidosis, hypoglycemia, hyperglycemia.

Complications from diabetes effects on pregnancy: abortion, early eclampsia, infectious complications, preeclampsia, hidramniosul, early delivery, fetal distress, maternal mortality.

Considerations for gestational diabetes.
It is glucose intolerance, occurred during a pregnancy, existing only during pregnancy, which after the pregnancy will be reclassified into another type of diabetes when glucose intolerance persists.

There is an influence of gestational diabetes on pregnancy and influence of pregnancy on diabetes

Therapeutic considerations are presented in diabetes associated with pregnancy.

The main classes of drugs are:
- oral antidiabetics (sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, endocannabinoid system blockers, etc.)
- Insulin
PERSONAL PART

Study of Pisa

During 1.10.2010-31.01.2011 I realised a training in obstetrics: In Santa Chiara Hospital, University of Pisa, led by Professor Andrea Genazzani clinic, during which I could study the cases of diabetes associated with pregnancy admitted to clinic.

Tracking of pregnant women in Italy, Tuscany was formalized by decree of the Ministry of Health in 1998.

Tuscany region's health service has developed a protocol for monitoring physiological pregnancy aims to:
- Standardization of control pregnant women in Tuscany and achieve a minimum standard tracking it;
- Establishment of Joint Assistance Strategies specialty: gynecology, obstetrics, general medicine;
- Creating a "ricettario" physiological load to facilitate access to medical services;
- Promote basic principles of preventive medicine.

Paraclinical follow protocol of physiological pregnancy includes the following determinations:
Quarter I:

Week 7 Investigation: blood group, Rh factor, Coombs test, complete blood count, transaminases, glucose, creatinine, VDRL, IgG and Ig M to rubella virus and toxoplasma, CNTA anti-HCV, anti HIV ate examination, urine summary.

Week 11-13 obstetric ultrasound.

Week 12-13 exfoliative cytology

Quarter II:

Week 14-17 urine test summary.

Week 19-21 obstetric ultrasound.

Week 19-22 urinalysis test.

Quarter III:

Week 26-27 complete blood count, urinalysis test, glucose tolerance test.

Week 30-33 obstetric ultrasound.

Week 31-32 urinalysis test.

Week 34-36 test for strep vaginal beta hemolytic.

Week 35-36 complete blood count, HBsAg, prothrombin time, partial thromboplastin time, fibrinogen levels, urinalysis test.
Week 38-39 urinalysis test.

Week 40-41 cardiotocography (NTS), ultrasound evaluation of amniotic fluid.

From this study we observed that the profile of a pregnant woman in the studied group is that of a woman over 30 years old, at first pregnancy and first delivery, with blood group O or A, Rh D positive, with family history of diabetes, which deliveries by cesarean section a fetus that is not usually macrosomic, with a good Apgar score, although the pH of arterial and venous blood from umbilical cord is not the best.

All these patients with diabetes mellitus type 1 or type 2 or gestational had a good metabolic control.

**Ultrasound investigations study**

Tracking a pregnancy usually involves a screening ultrasound investigations covering most of gestation and timely to capture any of fetal abnormalities and fetal annexes

- This is for pregnant diabetic next suggestion screening ultrasound:
  - Weeks 8-10: ultrasound measurement of cranio-caudal length;
  - Weeks 20-22: high-resolution ultrasound, fetal ultrasound in cases of suboptimal diabetic control (HbA1c abnormal first prenatal visit);
  - Week 24: ultrasonographic assessment of fetal growth;
  - Week 32: repeat ultrasound for fetal growth; Week 36: estimation of fetal weight by ultrasound.

Basically I watched as the group of pregnant women studied to be a minimum of three ultrasound examinations space thus:

- Evaluation in the first quarter - preferably between weeks 10 and 13 to the test in the double.
- Evaluation in Quarter II preferably around 22 weeks gestation.
- Evaluation in the third quarter at week 36.
  - In general I found followed frequent ultrasound abnormalities of diabetes of pregnancy.
  - These were: Identification of congenital malformations
    - neural tube defect
    - heart abnormalities
    - fetal macrosomia
• Abnormalities of amniotic fluid
• non-placental immun anasarca.

**Hystopathological study**

Placental development is characterized by three distinct periods:

In early pregnancy, produce a series of critical processes of proliferation and differentiation predominantly trophoblastic leading to the formation of extravillous structures. Placenta anchor in the uterus and placenta uterine spiral arteries remodeling in vessels with less resistance occur later.

In the second period, newly formed villi are mature, going through various stages of a multistage process.

End of gestation is associated with expansion by increasing villous placental.

Summarizing personal observations along with the data reported and discussed in the literature consulted, the spectrum of the most common placental morphologic changes in structures can be observed in placentas from mothers with diabetes is:

- Villous immaturity:
  1. Diameter villous increased;
  2. Reticular hipercells stroma and Hofbauer cells proliferation; highlighted stromal fibroblasts;
  3. Excess Langhans cells (citotrofoblast);
  4. Increased basement membrane thickness;
  5. Unusual capillary villi increased densification with hipercells stroma;
  6. "Chorangiosis"
- Villous oedema;
- Syncytial knots;
- Fibrinoid necrosis (fibrinoid intravilos);
- Fibrin thrombs.

Pathogenesis of placental changes is still far from fully understood but there is a general opinion that the extent and degree is not only determined by the severity and duration of maternal diabetes but also depends on the degree of metabolic control during pregnancy.

**Conclusions**

Analyzing the studied group in terms of maternal, fetal, ultrasound and histopathological parameters I obtained several results.

Share pregnant women over 30 and 35 is the majority (75.61%), most (56.10%) were the first pregnancy and first delivery (75.61%) predominated the blood group 0 and A (43.90%
each) and Rh positive (92.68%), with a family history of diabetes (41.46%), with significant
weight gain (63.89% over 12 kg), most delivered at term (73.17%), most deliveried by
cesarean section (77.78%).

Infants of diabetic mothers presented macrosomia in relatively low percent (only
13.16% had more than 4000 grams), all had a good Apgar score at birth (over 8), although the
pH was decreased both venous and arterial blood (65.79% / 71.05%), placenta was
proportionally greater than the optimal weight 73.69% of cases and amniocentesis was used
during pregnancy unless 17.5% of cases.

Diabetes mellitus was carefully monitored. Although fasting glucose was increased to
68.29% of the cases and postprandial glucose to 73.17% of cases, elevated glycated
hemoglobin was found only in one case (of the 9 who had made this investigation). The
management of "anti-diabetic" was complex. Diet alone (24.38%) in combination with basal
insulin (21.49%) or basal insulin doses and three meal (26.63%) were the most commonly
used regimens.

Tracking ultrasound pregnancy proved to be difficult in the absence of universal
protocols, widely accepted, so that the clinic using a protocol that we developed in this paper.
The analysis of ultrasound examinations have revealed several anomalies present in fetus of
diabetic pregnant. Thus were identified anencephaly and higroma cystic neural tube defect,
heart abnormalities, macrosomia fetuses, absence of diastolic flow or diastolic return can
highlight impending fetal death or death "in utero". The cases were identified with excess of
amniotic fluid or hidramniosul placental non-immune anasarca.

Spectrum of the most common placental morphologic changes in structures can be
observed in placentas from mothers with diabetes have a high interindivudual and local
variability and include: villous immaturity (villous diameter increased, reticular stroma
hipercells looking Hofbauer cells and highlighted stromal fibroblast proliferation, excessive
Langhans cells - citotrofoblast-, increased basement membrane thickness, densification
increased capillary unusual villi, the stroma hipercells - "chorangiosis"), villous oedema,
syncytial knots, fibrinoid necrosis (fibrinoid intravilos) and fibrin thrombs.

General characteristics of morphological changes of placentaes studied were low or moderate
intensity, length and available for some of them, such as fibrinoid necrosis and stromal
fibrosis, this inconsistent, generally characteristic pattern for diabetes treated and monitored
properly.
CURRICULUM VITAE

My name is Maria Lavinia Gheorman, I was born on 07.oct.1983 the city of Craiova. Elementary and secondary school I've been in Craiova at School No. 22. In 1998, the competition, I became a student of Carol I National College of Craiova I graduated in 2002.

In 2002 we supported the entrance examination and I attended the Medical University of Craiova, Faculty of Medicine, which I graduated in 2008 with average 9.78 license exam.

In the same year we supported residency contest after which I became a resident physician in the specialty of Diabetes, Nutrition and Metabolic Diseases with a training period of five years.

Currently I am in the third year of training in this specialty. Undertake training in Clinical Diabetes Clinical Emergency Hospital of Craiova.

I was admitted to 01.oct.2008 stage specialty training in Obstetrics and Gynecology doactorala led Univ. Dr. Nicolae Cernea, period ended on 20. sept.2011. after this period I worked doctoral thesis titled burden associated with diabetes.