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Pathophysiology of diabetes in pregnancy

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Summary . - Pregnancy is attended by extensive hormonal readjustements on the part of the mother. Almost every endocrine tissue participates in adaptive changes that maintain the metabolic state of the woman during normal pregnancy. Endocrinologic and metabolic adaptations characterizing pregnancy in women with normal carbohydrate metabolism also inpinge upon the metabolism of the diabetic during pregnancy. In the diabetic woman the impairment of metabolism which follows the modifications of endocrinologic adaptations induces a compromised metabolic "milieu" in both the foetal blood and amniotic fluid in which swallows the fetus, promoting several damages according to the gestational age in the conceptus. Disturbances of intermediary metabolism undoubtly play a major role in the etiology of complications of diabetic pregnancy. However an increasing amount of evidence is accumulating that suggests that abnormalities of immune function may also be operative in both the mother and fetus as well as in placenta. Finally there is limited information on the long-term prognosis of infants born to mothers with pre-gestational and gestational diabetes mellitus. Follow-up studies have mainly focused on two aspects: the risk of appearence of diabetes later in life, and psychosomatic development. Genetic aspects and the role of metabolic disorders during pregnancy must be once again emphasized.

Key words: carbohydrate, metabolism, pregnancy, diabetes mellitus, amniotic fluid, cord blood immunology, placenta, diabetic complications, drugs.

Riassunto *(Fisiopatologia del diabete in gravidanza).* - In gravidanza si verificano notevoli modificazioni ormonali nella madre. Nella gravidanza normale quasi ogni organo endocrino partecipa per mantenere un nuovo assetto metabolico. Gli adattamenti endocrini e metabolici che caratterizzano la gravidanza normale si hanno ovviamente anche in quella complicata da diabete. Nella diabetica la compromissione del metabolismo conseguente agli adattamenti endocrini della gravidanza induce un'alterazione del "milieu" del sangue fetale e del liquido amniotico provocando numerosi danni al feto in rapporto all'epoca gestazionale in cui tali eventi si verificano. Le alterazioni del ricambio certamente esercitano il ruolo principale nella genesi delle complicanze nel diabete e gravidanza. Tuttavia, numerose evidenze indicano che un ruolo importante nella genesi delle complicanze materno-fetali viene esercitato anche da alterazioni immunologiche. Infine le informazioni sulla prognosi a lungo termine nei nati di madri con diabete gestazionale o pregestazionale sono scarsi e si sono limitati soprattutto alla comparsa di un diabete o allo sviluppo di alterazioni psicosomatiche. Gli aspetti genetici ed il ruolo dei disordini metabolici durante la gravidanza vengono a loro volta sottolineati.

Parole chiave: ricambio glicidico, gravidanza, diabete mellito, liquido amniotico, cordone ombelicale, immunologia, placenta, complicanze del diabete, farmaci.

Introduction

The people of the Mediterranean areas have common geographical condition, historical and cultural affinity, many resemblances in the diet. On the other hand, differences exist in health organisations among the countries of the Mediterranean areas, and regional differences in the occurrence of diabetes mellitus and its complications, especially for diabetes in pregnancy, are marked.

In this article we report the main features of endocrine and metabolic derangement in the diabetic mother and foetus.

Carbohydrate metabolism in normal and diabetic pregnancy

In the first half of pregnancy, as a consequence of the progressive increase of estrogen and progesterone hormones both a β-cell hyperplasia and insulin hypersecretion is induced in the mother. The effect of these hormonal adaptations is an increase of peripheral glucose utilisation and glycogen storage associated with a reduction of glucose production and lower fasting blood glucose values. The metabolic modifications are anabolic and are due to the increase of sex steroids plus hyperinsulinemia.

In the second half of pregnancy, in addition to the increase of sex steroids and insulin secretion, a progressive increase of cortisol and placental hormones (hCS: human somatomammotropin; prolactin) appears. The result of these adjustments is a "diabetogenic" effect due to insulin resistance, reduction of glycogen stores, increased hepatic glucose production and, as a consequence, a reduction of glucose tolerance. At this time a "facilitated anabolism" during feeding, coexists with an "accelerated starvation" during fasting [1]. These metabolic changes ensure glucose and aminoacids to the foetus.

From the physiopathological point of view, the transfer of the nutrients through the placenta from the mother to the foetus is very important. In fact glucose crosses the placenta by a simple diffusion, aminoacids need an active transport and free fatty acids with a gradient dependent. In addition, ketone bodies cross easily by diffusion whereas insulin does not cross through.

In diabetic pregnancy, because of an absolute or relative insulin deficiency, there is a reduced uptake and/or a hyper-production of nutrients by the diabetic mother, and therefore a condition of hyper-alimentation for the embryo or the foetus [2], with relative consequences according to time of pregnancy. This condition in early pregnancy may induce congenital anomalies, whereas a precocious over-stimulation of fetal β-cells leads to hyper-insulinemia that is the main cause of foetal morbidity in diabetic pregnancy. The same condition may be involved in later complications in the offspring of diabetic mother.

A correlation between the diabetes degree and perinatal mortality (PNM) was firstly reported by White [3] from which is derived the classification of diabetes in pregnancy. A clear correlation between metabolic control and the occurrence of congenital malformation has been also reported by Miller *et al.* [4] using HbA1c determination in early pregnancy. In addition a close correlation between a poor metabolic control during pregnancy and foetal morbidity is well documented by several reports [5-8].

Our investigations in the amniotic fluid, the foetus and the placenta

Amniotic fluid

It should be noted that the foetus is surrounded by the amniotic fluid, that he produces and swallows continuously. The amniotic fluid is rich of nutrients such as glucose which decreases progressively in normal pregnancy, but not in diabetic pregnancy, especially when there is a poor metabolic control. Therefore the foetus receives from the diabetic mother more nutrients through placental blood and by ingestion of amniotic fluid. In addition, insulin and other protein hormones do not cross the placenta, therefore their concentration in the amniotic fluid derives from the foetus: so the assay of these hormones in the amniotic fluid may have a diagnostic and prognostic use.

In diabetic pregnancy we observed [9, 10] significantly greater insulin (IRI) and C-peptide (CPR) concentrations in the amniotic fluid collected in late pregnancy, as well as lower glucagon (IRG) values, when a poor metabolic control was present (Fig. 1). Correspondingly, foetal morbidity was associated with higher amniotic fluid glucose, insulin and C-peptide concentrations (Fig. 2).

More recently [11] we observed that metabolic derangements - greater glucose, insulin and C-peptide concentrations - are evident already in early pregnancy in the amniotic fluid of diabetic women (Fig. 3).

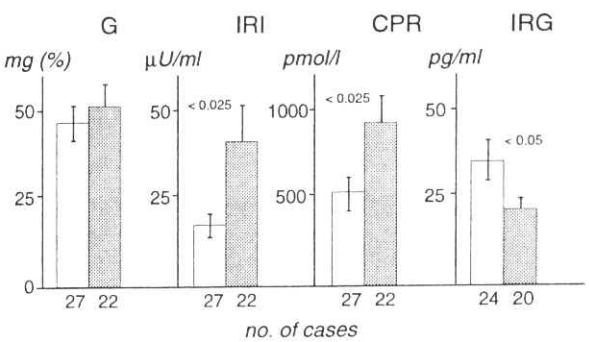


Fig. 1. - Amniotic fluid glucose (G), insulin (IRI), C-peptide (CPR) and glucagon (IRG) in relation to maternal metabolic control: good (□), poor (▨).

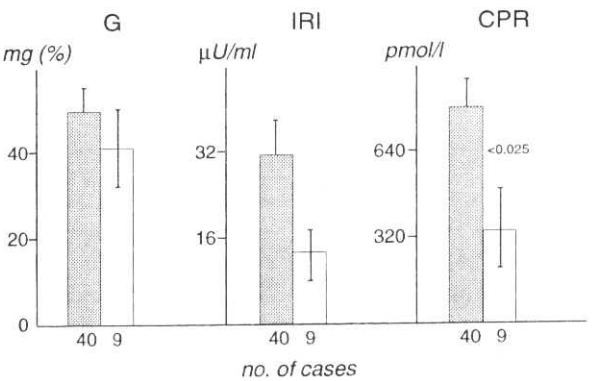


Fig. 2. - Glucose (G), insulin (IRI) and C-peptide (CPR) in the amniotic fluid after arginine tolerance test in diabetic pregnancy with (▨) and without (□) fetal morbidity.

These studies demonstrated that islet hormones in the amniotic fluid of diabetic pregnancies may be related to several neonatal complications and that they are correlated with maternal metabolic control and diabetes degree.

Cord blood

We evaluated α- and β-cell function in cord blood of diabetic and non diabetic pregnancies.

At birth, in the cord blood and the first week of life, we observed [12-14] higher C-peptide and lower plasma glucagon values in infants of diabetic mothers than in control infants, especially when a poor metabolic control was present in the diabetic woman (Fig. 4). Cord

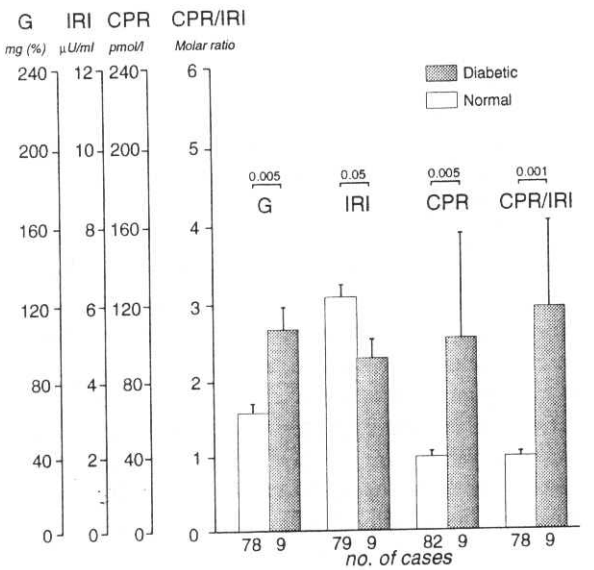


Fig. 3. - Amniotic fluid glucose (G), insulin (IRI), C-peptide (CPR) and CPR/IRI molar ratio in early pregnancy of normal and diabetic women.

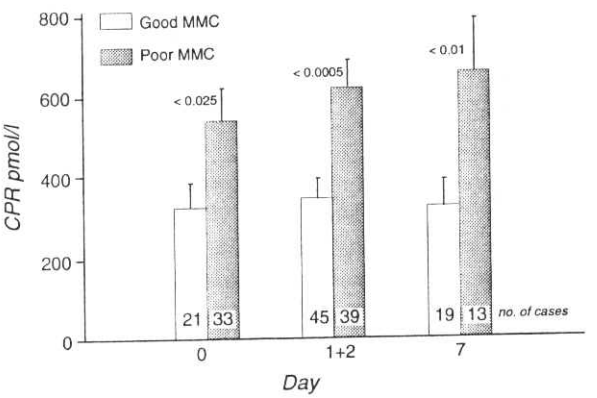


Fig. 4. - C-peptide levels at birth and during the first week of life in infants of diabetic mothers (IDM) in relation to maternal metabolic control (MMC).

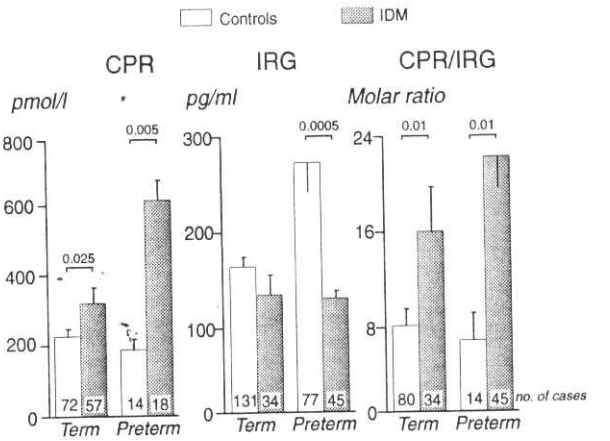


Fig. 5. - C-peptide (CPR), glucagon (IRG) and CPR/IRG molar ratio in cord blood of term and preterm newborn infants of control and diabetic pregnancy (IDM).

blood C-peptide and CPR/IRG values molar ratio, in addition, were significantly higher in term as well as preterm infants of diabetic mothers in comparison to control infants (Fig. 5).

Finally a β-cell hyperfunction, evaluated both in the amniotic fluid and cord blood (cordocentesis), was found in diabetic pregnancy throughout pregnancy as early (weeks 16-24) and late (weeks 34-36) gestation, at birth (cord blood) and in the first week of life (newborn's peripheral blood) (Fig. 6).

The studies on islet hormones in cord blood further suggest that the infant of diabetic mother, in the foetal life, at birth and in the first week of life, shows a β-cell hyperfunction, together with an α-cell inhibition correlated with the maternal metabolic control and diabetes degree. This condition is evident in early as well as in late gestation.

Immune aspects

Immunogenicity of exogenous insulin decreased from animal to monocomponent and finally to human insulin [15, 16]. Furthemore, all exogenous insulins may induce insulin antibody (IBC: insulin binding capacity) and insulin-anti-insulin complexes (ins-IAb) in the diabetic patient. We observed that insulin antibodies (IgG) easily cross the placenta and we found a correlation [17] between maternal insulin antibody level, foetal hyperinsulinemia, prevalence of foetal morbidity as well as a greater occurrence of gestosis in the mother (Fig. 7).

Immunocomplexes (Ins-IAb), unlike insulin antibodies that are IgG, do not cross the placenta, however their production is lower with the use of human insulins in comparison to animal or monocomponent insulins [16, 18]. We found a positive correlation between foetal Ins-IAb and cord blood C-peptide.

Therefore we suggested that the transplacental passage of insulin antibodies and a hyperproduction of insulin-anti-insulin complexes may have an additional

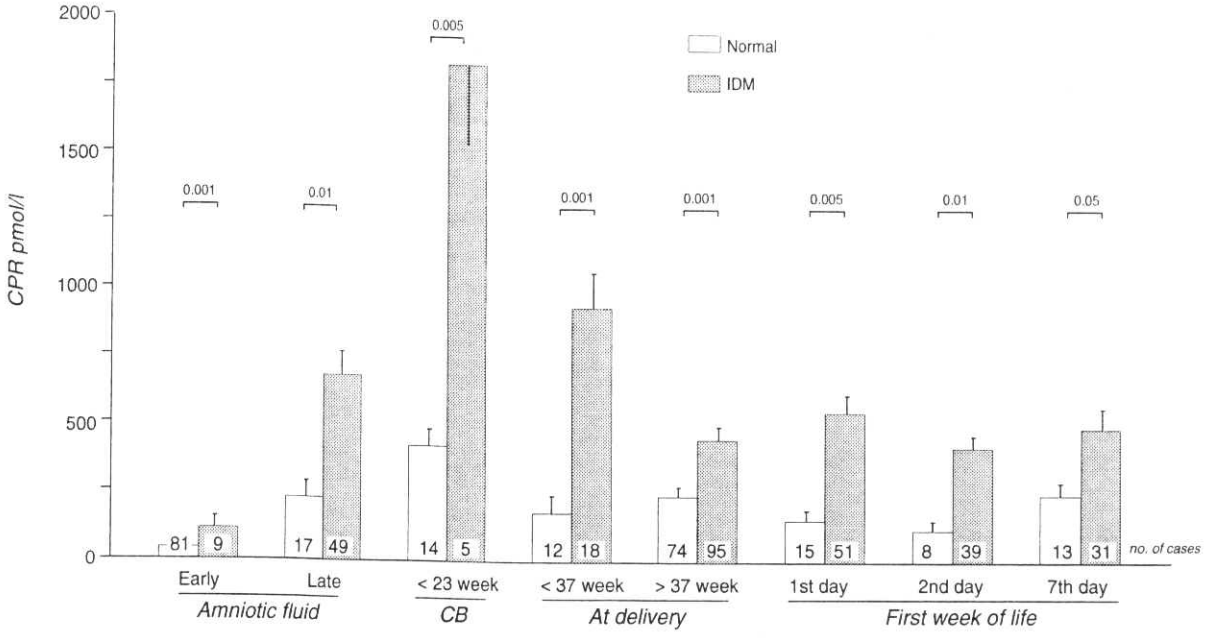


Fig. 6. - C-peptide (CPR) concentrations in the amniotic fluid, cord blood (cordocentesis and at delivery) and peripheral blood in normal infants and infants of diabetic mothers (IDM).

role in the development of β-cell hyperfunction, modifying the Pedersen's hypothesis of hyperglycaemia-hyperinsulinemia (Fig. 8).

More recently we reported elsewhere [9] the prevalence of type 1 immune markers in gestational and type 2 diabetic pregnant women. The prevalence of auto-antibodies against glutamic acid decarboxylase (GAD) was similar in GDM (3.4%) and NIDDM (3.6%) and greater than in control pregnant women (0%), suggesting that the two diabetic populations share the same disease. These results, although very preliminary, are stimulating in a better knowledge of the intriguing feature of gestational diabetes and merit further investigation.

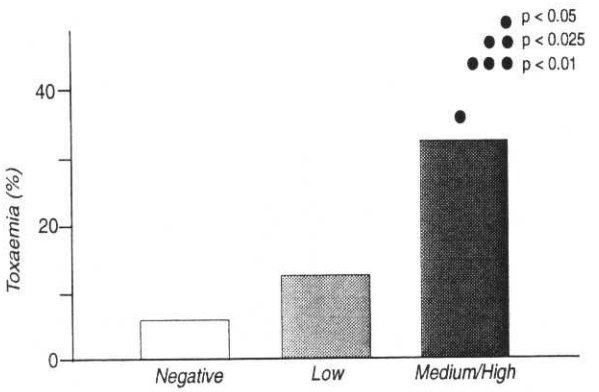
Placenta

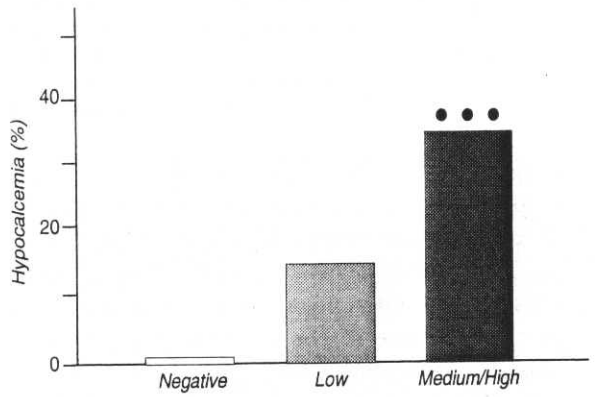
The placenta plays a central role in maintaining an adequate transport of maternal fuels to the foetus [20]. Glucose is the main substrate in the foetal metabolism, therefore the glucose transport has a key role in the regulation of the substrate available for the foetus. On the other hand glucose transport is mediated by a class of proteins, the glucose transporters (GLUT), and they are influenced by insulin [21, 22]. In fact large amount of maternal insulin is employed in the placenta which is rich of receptors of this hormone [23]. Very few knowledge there is concerning placental glucose transporters. Two glucose transporters, the GLUT 1 and GLUT 3, have been isolated in the placenta [24] but their physiological role is even understood. Preliminary results on these transporters in the human placenta of control and diabetic pregnancy are reported elsewhere by us in this book. In summary our preliminary studies show a decrease of GLUT 3 in the placenta of diabetic pregnancies as compared to normal women. In addition, among the diabetic women, a decrease of GLUT 3 in late pregnancy was observed. Finally a correlation between glucose transporters and the placental weight was observed in normal as well as in diabetic pregnancy. These very preliminary studies suggest further investigations in order to better elucidate foetus-maternal correlations at the placental level, where a modified milieu may exert its effects. In fact, hyperglycaemia alters maternal-foetal glucose transfer kinetics [20] and a parallel relationship between maternal glucose concentrations and utero-placental consumption or maternal-foetal transfer has been shown [25, 26]. These observations suggest that maternal diabetes may affect GLUT 1 and 3 gene expression in the placenta.

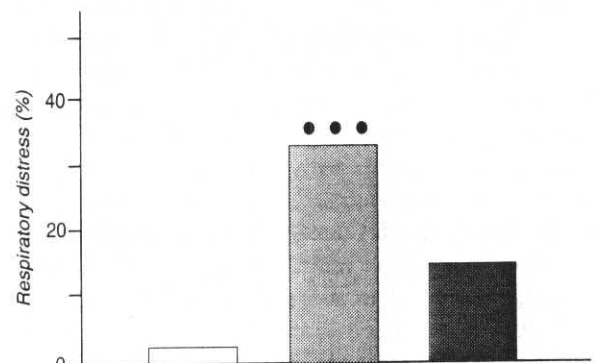
Diabetic complications

The presence of diabetic complications deep modifies foetal-maternal metabolism [27, 28]. We report here our experience [29-32] about the occurrence of micro-vascular impairment in diabetic pregnancy and its correlations with metabolic derangements of both the mother and foetus.

An early kidney impairment, as evaluated by measurements of microalbuminuria, has been found to be correlated with the diabetes degree and it was significantly greater in type 1 White Class D, and in women with longer diabetes duration (Fig. 9). In addition diabetic women with microalbuminuria values above 50







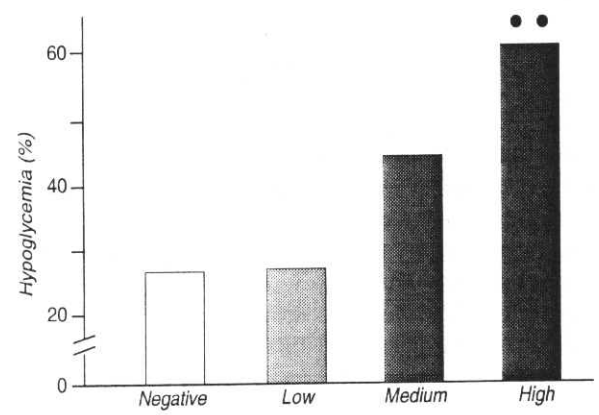


Fig. 7. - Insulin antibody levels (InsAb) and maternal/newborn complications.

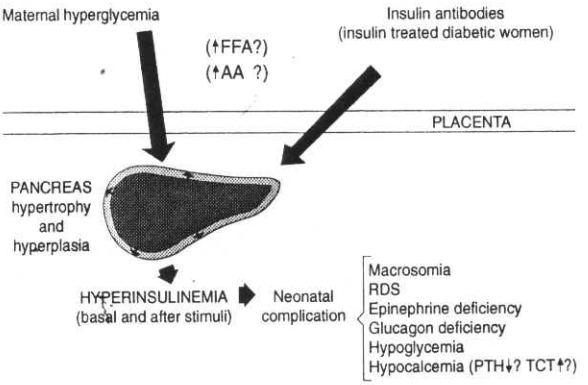


Fig. 8. - Hyperinsulinemia and neonatal complications.

micrograms per minute showed a higher prevalence of perinatal mortality and congenital malformations (Fig. 10).

Blood pressure monitoring during pregnancy was studied in the last three years [33]. Greater nocturnal diastolic blood pressure values were correlated with a poor metabolic control, longer diabetes duration, a higher prevalence of retinopathy and a greater percentage of perinatal mortality.

Diabetic retinopathy was also investigated by us in diabetic pregnancy [34]. A correlation has been found between adapto-electroretinography (AERG) responses

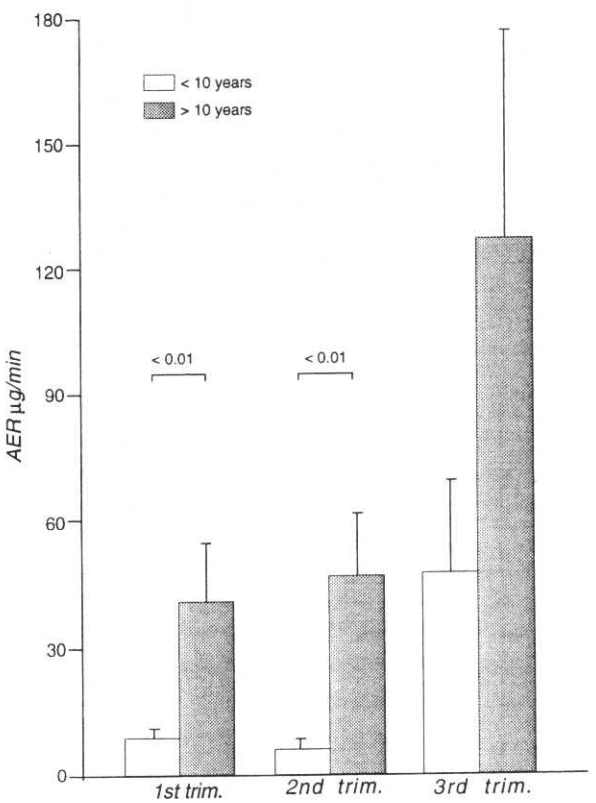


Fig. 9. - Microalbuminuria (AER) during diabetic pregnancy and diabetes duration.

and metabolic (HbA1c) control. In addition a higher materno-foetal complication rate in patients with more severe and frequent AERG alterations during pregnancy was observed.

Drugs

Finally we have the opportunity to investigate in the last two decades which role might be played by the use of oral agents (OHA) in the treatment of type 2 diabetes during pregnancy [35].

It should be noted that do not use these drugs in pregnancy and we avoid them from the first visit, or in type 2 women who are planning a pregnancy. However many diabetic women arrive to our observation after conception under OHA treatment. The treatment at conception with OHA and during at least the first 8 weeks (before they contacted our clinic) was studied. In diabetic women with a same degree of diabetes (White Class B) we observed that OHA treatment was associated with a higher occurrence of congenital malformations in comparison to treatment with insulin or diet alone (Fig. 11). In addition, cord blood C-peptide and C-peptide/glucagon molar ratio were significantly higher in pregnancies treated with oral drugs (Fig. 12). This observation suggests that an early and temporary administration of oral hypoglycaemic agents in diabetic pregnancy may induce an overstimulation of foetal β-cells function together with an α-cell inhibition in the foetus and newborn infant.

These data suggest that oral drugs given during the embryogenic period may have a direct or indirect teratogenic effect in diabetic pregnancies and, in addition, may induce in early pregnancy an over-stimulation of foetal β-cells, which may be manifest at birth in the cord blood.

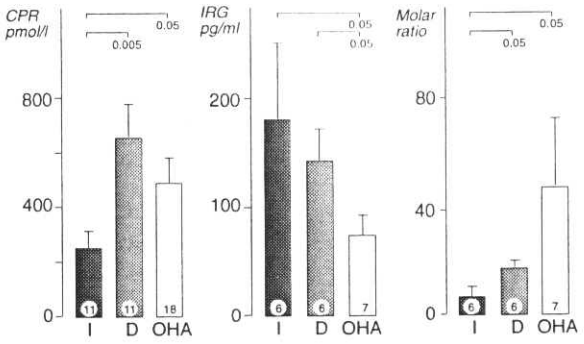


Fig. 12. - C-peptide (CPR), glucagon (IRG) and CPR/IRG molar ratio in cord blood of infants of diabetic mothers (IDM) of White Class B according to maternal treatment at conception (insulin: I; diet: D; oral hypoglycemic agents: OHA).

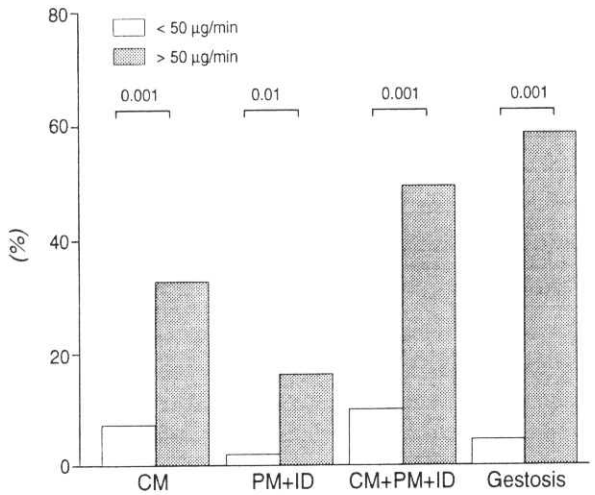


Fig. 10. - Foetal (congenital malformations: CM; perinatal mortality: PM; intrauterine death: ID) and maternal complications in diabetic pregnancy according to the first trimester microalbuminuria (AER) values: < 50 (96 cases) and > 50 µg/min (12 cases).

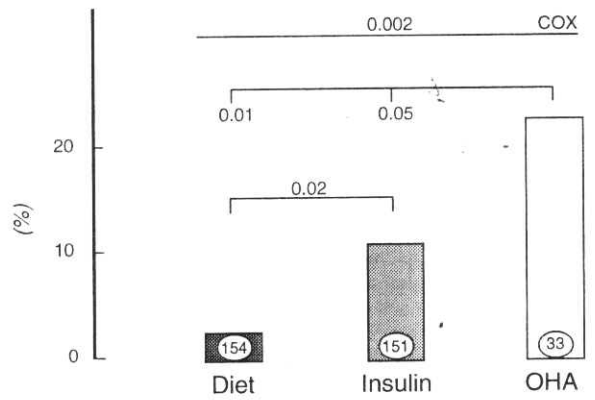


Fig. 11. - Percent congenital malformations (CM) in 338 patients according to treatment at conception.

Conclusions

In this article is reported our experience on the investigation of diabetes in pregnancy over the last two decades focusing the main physiopathological aspects of metabolic impairments of glucose metabolism. Our studies have been addressed to both the diabetic mother and foetus during pregnancy, to the amniotic fluid and placenta. In addition we observed the influence on the metabolic derangements of diabetic complications (early kidney impairment and eye function, hypertension). Finally the role of oral drugs, employed at conception or early pregnancy, on foetal islet function and outcome has been investigated.

Altogether these results emphasize the need to reach a good metabolic control as soon as possible, better if before conception (in the case of pregestational diabetes), especially when diabetic complications are already present.

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