Actualities

Considerations Regarding the Therapeutic Conduct in Pregnancy Associated Diabetes Mellitus

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ABSTRACT The consequences of diabetes mellitus on maternal body are evolutive and complex ones. At pregnant women with diabetes mellitus beside hyperglycemia, which is the specific anomaly, there are another risk factors both specific pregnancy factors as general pathologycal factors. This report considers the main classes of medicines used in the treatment of diabetes mellitus associated to pregnancy (preexisting diabetes or gestational diabetes) . We discuss both about the main oral hypoglycemic agents with their advantages or their risks in the treatment of diabetes mellitus in pregnancy as about insulin therapy which is the main choice in the treatment of diabetes mellitus in pregnancy. This paper tries to order the treatment of diabetes mellitus according to the particularities of this disease in pregnancy. This report tries an accord between therapeutic points of view of specialists in Diabetes Mellitus and specialists in Obstetrics

KEY WORDS *diabetes mellitus, oral hypoglycemic agents, gestational diabetes,insulin therapy*

Introduction

The affection of maternal human body by diabetes mellitus is both a complex and evolutive one. In pregnant women with diabetes mellitus, alongside the hyperglycemia that represents the specific metabolic anomaly, there are also present various risk factors connected to pregnancy as well as risk factors related to general pathology.

Among these, there should not be neglected previous or pregnancy determined high blood pressure, excess of body weight, predisposition to thromboembolic disease or the metabolic syndrome. (7)

The treatment of diabetes mellitus in pregnancy is based on pharmacotherapy, on adapting the lifestyle regarding the control of glycemia, of risk factors associated to pregnancy state.

Pharmacotherapy is the most important factor in the treatment and monitoring of pregnancy associated diabetes mellitus. For this to be efficient enough, one should be acquainted to the patient, to the medicines, as well as to the medical guides or recommendations.

Administering anti-hyperglycemic medication involves an initiation stage, a titration adjusting stage and a stage of maintaining dosages. (7)

ORAL ANTI-DIABETIC MEDICATION

Under this title there hide various classes of medicines with a hiypoglycemic effect used in the treatment of general or gestational diabetes mellitus.

SULPHONYLUREAS

They are specific to the treatment of diabetes mellitus type 2, having complex physiological mechanisms mainly represented by the peripheric insulin resistance and the insulin secretory deficit of beta pancreatic cells.

The hypoglycemic effect of sulphonylureas was first noticed by Marcel Jambon in 1942. Consequently, A. Loubatieres' research work has developed this class and starting from 1952 they have been used worldwidely. (Gabriela Roman-2008).

Classification of Sulphonylureas:

I-st Generation: - Tolbutamide, Clorpropamide

II-nd Generation: - Glibenclamide, micronized Glibenclamide, Gliclazide, Gliclazide with prolonged modified release

Sulphonylureas in the Ist generation are characterized by a reduced activity and a larger dosage in comparison to those in the IInd generation that have a higher pharmacokinetic hypoglycemic efficiency and superior safety, thus requiring smaller dosages.

Action Mechanism

The action mechanism of sulphonylureas is a complex one, taking place both at a pancreatic level and at an extrapancreatic one, through ATP dependent potasium channels with an important part played in the role of membrane potentials (17)

At a pancreatic level, the hypoglycemic action of sulphonylureas involves the existence of a

cellular beta insulin secreting potential. Thus, it is produced an increase of insulin secretion and after a certain period of treatment, the insulin plasmatic level goes back to the value prior to treatment. The action of sulphonylureas over the pancreatic cell is performed through the potasium channels.

ATP dependent potasium channels are also localized extrapancreatically: at the level of the cardiac muscle, of the smooth muscles as well as at a neuronal level. The extrapancreatic action performs the amelioration of glycemia level, although the insulin level is normalized only after several months of treatment.

Sulphonylureas have haemovascular effects as they reduce the platelets aggregation and the activity of free radicals, too.

Pharmacology

Sulphonylureas are rapidly and completely absorbed, being possible to detect their levels in blood even after one hour after administration. Their absorbtion is influenced by the food intake or by the type of sulphonylureas. After absorbtion, they are 90-99% bound to the plasmatic proteins, especially to albumins. Their release is mainly performed renally, in sulphonylureas of the Ist Generation and both renally and hepatically in those of the IInd Generation.

Sulphonylureas have an important hypoglycemic effect and from this point of view they are the most efficient besides insulin and metamorphine.

The hypoglycemic effect of sulphonylureas is more reduced in severe hyperglycemia (over 300mg%).

Adverse reactions: weight gain by an insufficiently explained mechanism, probably due to the preservation of previosuly lost energy by glycosuria; hypoglycemia – the most frequent adverse effect.

They are counterindicated in pregnancy and lactation.

MEGLITINIDES

Meglitinides are a class of insulin secretagogue medicines. They stimulate the insulin secretion by similar mechanisms as sulphonylureas, but they are structurally and pharmacologically different from these.(7)

Classification of Meglitinides

In this class there are two compounds used in practice:

-Repaglinide (NovoNorm)

-Nateglinide(Starlix)

Action Mechanism

Meglitinides stimulate the pancreatic insulin secretion by a mechanism that is dependent on the level of glucose, they close the ATP dependent potasium channels, they open the Ca channels, followed by an insulin release(7).

Pharmacology

They are rapidly and completely absorbed after oral administration, the maximum plasmatic concentration being reached in less than one hour. They have a high rate of plasmatic proteins binding, especially albumin, they are metabolized at a hepatic level and eliminated through the billiary system.(12)

In type 2 diabetes mellitus patients, the indications of meglitinides treatment are not controlled by diet or by Medformin monotherapy.

They may be administered as a monotherapy or as an associated therapy. The association with basic insulin in various studies is a benefic one.(4)

Meglitinides are not recommended in pregnancy and lactation.

BIGUANIDES

They contain a guanidic nucleus whose effect is to decrease glycemia without specifying its action mechanism. They have been used since the beggining of the 20th Century and they had a period of maximum use between 1960-1970.

Classification

- Feniletil biguanide(Fenformin)
- Dimethyl biguanide(Metformin)
- Butyl biguadine(Buformin)

The most efficient and used medicine in this class is Metformin.

Pharmacology

Metformin is absorbed at the level of the small intestine, the maximum plasmatic concentration being reached in 90 to 120 minutes. The absorbtion is complete after 6 hours. The elimination is performed 90% renally through glomerular filtration and tubular secretion. The absorbtion and biodisponibility of Metformin are identical in persons with or without diabetes.

The medicine binds to the plasmatic proteins, being found in higher concentrations in salivary glands, intestinal wall, liver and kidneys.

The effect of glycemia decrease occurs after 1-2 weeks, an interval during which Metformin activates the expression of the enzyme genes involved in the hepatic, muscular and adipocytary metabolism.(3)

The hypoglycemic effect is performed through the control of insulin resistance and improvement of sensitivity to the insulin peripheral action. Metformin reduces both basic glycemia and postprandial one. The Metformin monotherapy reduces basic glycemia by 60-70 mg%.

Metformin has a cardiovascular protection effect. It represents the first choice in the therapy of type 2 diabetes mellitus. It may also be

administered in the therapy associated with all the other classes of anti-hyperglycemic medicines, including insulin.

It represents a viable option in the treatment of gestational diabetes. It seems to be a useful alternative to the insulin treatment in pregnant women with an almost normal BMI, with light gestational diabetes, when there are no significant foetal modifications. (22)

The administration of Metformin in pregnant women with gestational diabetes is insufficiently studied, thus requiring furher information and clinical studies in order to prove its safety .(7)

THIAZOLIDINDIONES

Thiazolidindiones represent a relatively new class of anti-hyperglycemic agents whose action is mainly based on the increase of insulin sensitivity at the level of target organs, also having some effects of improvement of the beta-pancreatic cells function.

Classification

In Romania, Rosiglitazone and Pioglitazone are approved as anti-hyperglycemic agents in the therapy of type 2 diabetes mellitus.

Pharmacology

The absorbtion is performed in the intestine. It depends whether the administration is made before or after meals, the ingested food delaying the absorbtion of medicines. The maximum concentration is according to the dosage, while the half-life period is of approximately 3 hours. Thiazolidindiones bind in an approximate percentage of 90% to the plasmatic proteins, especially to albumins.

They are eliminated in a percentage of 55% by faecal matter and 45% by urine, while the metabolism products are eliminated in a percentage of 30% faecal matter, 40% urine. (7).

The main effect of thiazolidindiones is the reduction of insulin resistance by increasing the peripheral insulin sensitivity: hepatic, muscular and adypocytary.

The treatment is performed orally in the monotherapy of diabetes mellitus type 2 patients or in the associated therapy, a double or triple association with Metformin or sulphonylureas, as well as in association with insulin. In the presence of insulin resistance patients with polycystic ovary thiazolidindiones have a comparatively high resistance than the action of Metformin over the ovulatory function, hairsutism, hyperandrogenism and, of course, over insulin resistance (6)

The effects of thiazolidindiones over the cardiovascular risk factors are considered to be healthy ones.

In conclusion, thiazolidindiones represent a relatively new class of hypoglycemic agents with a proven clinical efficiency both regarding glycemia and non-glycemic effects as well.

ALPHA-GLUCOSIDASE INHIBITORS

Their action is represented by the delay of the simple carbohydrates at the level of the small intestine.

Classification

This class of oral antidiabetics is represented by Acarbose, Voglibose and Miglitol.

Pharmacology

Intestinal absorbtion is made in a very low percentage, namely 0,5-5%.(10)

Biodisponibility is reduced by 1-2%, while the maximum plasmatic concentration is reached in approximately one hour. Miglitol is absorbed in the intestine by active mechanisms. It is excreted unmodified by the kidneys and the non-absorbed quantity is excreted by faecal matter.

Alpha-glucosidase inhibitors reversibly bind to the alpha-glucosidase enzymes localized at the level of intestinal cells (enterocytes).

The digestion and absorbtion of carbon hydrates are produced in a slow manner, in the small intestine, instead of being absorbed at the level of the duodenum and the initial part of the jejunum. The carbon hydrates that miss the intestinal digestion continue their passage, reaching the colon where the bacteria transform them in fatty acids, which are subsequently absorbed and metabolized.

The administration of glucosidase inhibitors is performed as a monotherapy in the patients with diabetes mellitus type 2 that are not properly controlled by the hypoglycemic diet. Acarbose may also be adminstered in a combined therapy, together with sulphonylureas, meglitides and even with insulin. Regarding pregnancy and lactation, there has not been yet established a safety of the medicines for the pregnant women.

Acarbose and Miglitol are excreted in small quantities in the maternal milk and therefore they are counterindicated during the confinement period. (7)

INCRETINS (GLP 1 analogues and dipeptidyl-peptidase 4 inhibitors)

Incretins are intestinal hormones that play an important part in the glycemic homeostasis, due to the stimulating action of the insulin postprandial secretion. Its action is due to the GLP 1 effect with the specific receptors at the level of the beta-pancreatic cellular membrane (20)

Classification

GLP1 analogues: Exenatide; Liraglutide

DPP-4 inhibitors: Sitagliptin, Vildagliptin

Pharmacology

Exenatide is administered subcutaneously, the maximum concentration being achieved in two hours. It is metabolised proteolitically and is eliminated by urine, thorugh the glomerular filtration mechanism.

Sitagliptin is administered orally, its absorbtion is rapid, the mean plasmatic concentration being performed in 1-4 hours. It reversebly binds to the plasmatic proteins and it is eliminated in an unmetabolised form by urine in a percentage of 80%

Vildagliptin is administered orally, its absorbtion is rapid, the mean plasmatic concentration being performed in 1-2 hours. It is hepatically metabolised and renally excreted.

Incretins are indicated in the treatment of diabetes mellitus type 2 not controlled by a monotherapy with Metformin or in an oral combined therapy.

The effects of incretins are of signficantly decreasing basic glycemia, of stimulating the proliferation and differentiation of beta-pancreatic cells, both in vitro and in vivo. They determine a progressive weight loss. They are not associated to alterations of the lipidic profile and they have a healthy cardiivascular effect.

In pregnancy, their administration will be performed only if their benefit is higher than a potential risk for the foetus.

BLOCANTS OF THE ENDOCANABINOID SYSTEM

The endocanabinoid system is a physiological endogene system for signaling and control, composed of two canabidoid receptors, their ligands, the endocanabidoids and enzymes responsible for their synthesis and degradation.

This system has a central and peripheral action and it is involved in multiple physiological processes regarding the energetic homeostasis, the control of motor activity, the modulation of stress response, the control of endocrine system, of the cardiovascular and respiratory systems, an anti-proliferative action in tumor cells, fertility, etc.(16)

In the use of current practice, Ribonabant is the blocant of the endocanabinoid system.

Pharmacology

The pharmacokinetics depends on the dosage. In the patients suffering from obesity the half-life period is of 15 days, while the necessary time for reaching a constant level is of approximately 25 days.(7)

The metabolisation is mainly performed by the hepatic cytochrome, the inactive metabolites being eliminated by billiary excretion. 86% of the dosage is excreted by faecal matter as an unaltered medicine and metabolites.

The efficiency of Ribonabant is evidentiated by the reduction of weight and abdominal circumference, by the reduction of glycemia in persons with diabetes mellitus type 2, having a healthy effect over the other cardiovascular risk factors.

There is no information connected to their effect in pregnancy and lactation. Generally, it is considered according to the risk/ benefit ratio.

INSULIN THERAPY

The introduction of insulin treatment represented a huge progress not only regarding the treatment of diabetes mellitus, but also regarding medicine in general.

It is quite important to mention the fact that the introduction and perfectioning of the insulin treatment were materialised through the awarding of three Nobel Prizes: Banting and Macleod in 1923, Sanger in 1958 and Hodgkin in 1964.

We do not think there is any Romanian publication that does not remind us the moment of scientific injustice, namely that of not considering Nicolae Paulescu as the “father” of this discovery.

Until the 1970s the animal insulins had represented the exclusiveness of this treatment. In the following period there appeared the insulins obtained by semisynthesis and afterwards by recombined DNA. In the last decade, there have emerged “analogues” of human insulins obtained by the alteration of the insulin structure in order to achieve various superior pharmacological performances (7)

Insulin Structure and Biosynthesis

It is a hypoglycemic hormone produced by the pancreatic beta cells, while as structure it is a protein formed of two polipeptidic chains containing 51 aminoacids: the A-acid chain formed of 21 aminoacids and the B-basic chain formed of 30 aminoacids. The two chains are joined by two disulphidic bridges.

First, insulin was used in a non-crystalline state and subsequently there was obtained its crystallization. With a neutral pH and in physiological concentrations, insulin is found as monomers, while in high concentrations it forms dimers.

The insulin biosynthesis is performed after the model of polipeptidic hormones synthesis. Its induction is made due to the specific stimulus (glucose) that acts at the level of a gene on cromosome 11 that initiates RNA messemger in the sense of pre-proinsulin and proinsulin forming.

In the Golgi system, this forms immature secretion particles and then, by an enzymatically mediated complex process, insulin and C peptide are finally obtained. The C particles containing insulin are considered to be mature ones.

The process of insulin biosynthesis lasts for approximately two hours. Any kind of anomaly present at the level of the cromosome involved in the insulin biosynthesis generates the production of modified insulin molecules with a significantly reduced receptor-binding capacity. This anomaly is present in a certain category of patients developing diabetes mellitus.

As stated before, the physiological stimulus of the insulin secretion is glucose, which modulates the response to the insulin production according to its concentration. (18)

Insulin penetration at the level of the basic membrane of pancreatic beta cells is performed by various types of ionic channels, among which the most important are the ATP potasium dependent and the electrostatic calcium modulating ones.

As a consequence, the metabolic alteration of insulin secretion from glucose is dependent on the potassium ions concentration and the variations of ADP and ATP concentrations.

The Mechanism of Insulin Action

In essence, insulin has as main effect the facilitating of glucose through the cellular membrane. The insulin receptors are complex polipeptidic structures found in all the vertebrate tissues in a variable number. (21)

The gene of these receptor is localized on the short arm of chromosome 19 . (19)

The essential consequence of insulin binding to specific receptors is the facilitation of glucose transmembranary transport, an effect found in the striated muscle cells, in adipocytes and at myocardium level. Thus, insulin stimulates proteic synthesis in all cells.

In the endothelial cells, the glucose transport is not insulin dependent.

Therefore, the major fuction of insulin is to facilitate the glucose transmembranary and intracellular transport, a process that is performed by some complex proteins called glucose transporters found in the cellular membrane as well as in the membrane of cellular organites. (7)

Pharmacology of Commercial Insulins

The pharmacology of insulins follows their absorbtion at adiministration level, while pharmacodynamics follows the metabolic effects of insulins.

The most rapid absorbtion of insulins is performed at the level of the abdominal cutaneous tissue. It progressively decreases at the level of arms, nates and thighs. The consequence of this observation is the indication that prandial insulins should be administered in the abdominal subcutaneous tissue, while the basic ones in the thigh.

The depth of insulin injection is directly proportional to the absorbtion speed. Intramuscular injection accelerates this absorbtion.(11)

After the absorbtion within the systemic circulation, insulin travels freely or antibody bound (IgG), the second type of circulation being in a progressive decline when the insulin purifying levels increase.(21)

The insulin anitbody binding is a reversible process, but it may decrease the quantitiy of free insulin capable to act upon the receptors. Insulin distribution is made within three compartments:

- plasmatic
- extravascular, with rapid balancing
- extravascular, with slow balancing (it corresponds to the insulin binding to the specific receptors)

Insulin degradation and excretion are produced especially at liver level, 60-80%, as well as at kidney level, 10-20% (2) .

Hepatic degradation is mediated by insulin receptors. At kidney level, insulin is filtrated at a glomerular level and then partially reabsorbed in the proximal contort tubes, where it is degraded. In the final urine, there may be found at most 1% of insulin. (8)

Prandial Insulins

They are insulins with a short period of action, but with a rapid action.

They are administered by injection before meals and they are the only ones used in the treatment of hyperglycemic crises, as well as for insulin pumps.

They are electively administered subcutaneously in the abdominal region, but they may also be administered intramuscularly or intravenously, in case of emergency.

A significant moment in the evlolution of insulin treatment was represented by the synthesis of human insulin analogues with rapid action. For example, Lis-Pro (Humalog), insulin aspart (NovoRapid) or insulin glulisine (Apidra).

Basic Insulins

They have a slower absorbtion and therefore they have a higher duration of action, in comparison to prandial insulins. This delay of absorbtion and prologation of action are performed by the reduction of solubility and by the addition of protamine, zinc or other molecules.

The administration place is the thigh (the medial quadrant).

The basic insulin analogues are glargin (Lantus) and insulin detemir (Levemir).

Mixes of Insulins

The mixes of basic and prandial insulins in the same administration were possible due to their physical compatibility (the same pH).

The major advantage of this association is that of an administration at higher intervals, as this insulin mix sums up all the pharmacological benefits of both insulin types.

Insulin Therapy Conduct

Insulin Administration:

-*subcutaneous administration* is the most used way. The novelty of this way of administration consists in evidentiating the absorbtion speed according to the region where it is injected.

-*intravenous administration* is the election way in the emergency treatment (ketoacidoses, hypersomolar hyperglycemias, etc.). It is performed by continuous intravenous perfusion or by repeated injections at every one hour. There are administered only insulins with a short period of action. (7)

-*intramuscular administration* is an alternative to the emergency treatment when the intravenous way is not an option. The intramuscular administration is performed at the level of arms and thighs.

-*intraperitoneal adminstration* is made with insulin pumps and it has the advantage that it ensures the absorbtion of exogene insulins within the portal circulation. Pharmacologically speaking, it represents the way that is the closest to the physiological one.

-*nose administration* represents a less successful attempt to administer insulins as there is a reduced insulin biodisponibility administered in this way and an important variability of absorbtion.(11)

-*aerosols lung adminstrattion* is a recent way of insulin administration. Insulin administration proved to be good and relatively constant, therefore it may be seen as a viable alternative.

Stages of Insulin Treatment

There are three major stages:

- treatment initiation stage;
- treatment adjustment stage;
- treatment maintaining stage.

Complications of Insulin Treatment

- lipodystrophy: the most frequent form is lipohypertrophy that consists of variable consistency tumefactions with elastic consistency that appear where the insulin was injected.

- insulin allergy: a more and more rarely found complication due to the use of highly purified human insulins.

- refractive disorders: due to rehydration of lens and it does not require an optical correction. It is a transitory disorder.

- insulinic edemas: they are moderate, generalized edemas, produced by the hydroelectrolitic rehydration, especially in previously dehydrated patients and due to the anti-natriuretic effect of insulin; they may be confused to the late pregnancy edemas. Unlike the latter ones, insulinic edemas are transient and they do not require any treatment.

- weight gain: it is due to glycosure elimination and to alterations of the energetic balance, to the reduction of physical effort, to an inadequate diet or to a possible effect that insulin may have on the appetite.

- hypoglycemia: is considered the most frequent complication of the insulin treatment. Its decrease below 50-60mg% may lead to polymorphous symptoms and signs like the vegetative ones (sweats, palpitations, tremblings, hunger) or neuroglycopenic ones (cephalalgia, confusion, speech and beahviour disorders, coma). Hypoglycemias may be light, moderate or severe, while their causes are:

- inhibiting of glucose hepatic production
- inadequate or late food intake
- increase of glucose peripheral use due to physical effort
- errors in insulin administration (reversal of prandial insulin dosages by basic ones, insulin dosages that are too high, high intervals between insulin administration and meals).

The treatment of hypoglycemias is made with:

- 10-15 g of carbon hydrates ingestion in light hypoglycemias
- 20-30 g of carbon hydrates snacks in moderate hypoglycemias
- 1 mg of glucagon intramuscular or subcutaneous administration or 50-100 ml glucose 20% intravenous administration in severe hypoglycemias. (7)

PHARMACOTHERAPY OF DIABETES DURING PREGNANCY

During pregnancy, there may be two particular situations of association: pregnancy associated with pre-existent diabetes mellitus or pregnancy associated with gestational diabetes.

The two associations of pregnancy and diabetes transform the pregnancy in a physiological state with high obstetrical risks, as

there may be developed both maternal and foetal major complications. (6)

The treatment of diabetes-pregnancy association has as purpose the strict control of glycemia, loss of weight excess and blood pressure control. In diabetes mellitus type 1 associated to pregnancy, the recommendations are that the glycemia values should be identical or close to the normal ones.

When pregnancy is associated with gestational diabetes, the continuous monitoring of glycemia values has as objective the normalization of its values, although there is not a consensus of this opinion so far.

Relatively recent information states the fact that within the pregnancy-diabetes mellitus association the most trustworthy parameter defining the glycemic control is the postprandial glycemia after 90 minutes with a values of 110 mg%.(13, 14,15).

Pre-existent Diabetes Mellitus in Pregnancy

In diabetes mellitus type 1 and type 2, there is necessary a pre-existent medical examination to pregnancy, in order to establish the control of glycemia, both during the preconception period as well as during the prenatal post conceptional one.

It is very important to monitor the glycemia during the first 12 weeks of pregnancy, the embryogenesis period for early diagnosis in order to avoid congenital malformations.

Diabetes Mellitus Type 1 and Pregnancy

Glycemia monitoring before pregnancy will be continued during pregnancy in order to prolong insulin therapy in adequate conditions.

Glycemia monitoring also involves adjuvant hygene-dietetic methods like the optimization of lifestyle together with the maintaining of insulin therapy and self-monitorization.

When necessary, insulin therapy will be intensified by the introduction of multiple insulin intakes or by the initiation of insulin therapy with insulin pumps. The latter one has the advantage of the glycemic control with the reduction of glycemia variations and avoidance of hypoglycemias or/ and of postprandial ones.

Ideally speaking, this form of insulin therapy should start before pregnancy, while during pregnancy it should be performed a frequent optimization of basic ratio and boluses (Gabriela Roman)

For the optimization of glycemic contol, it is recommended the use of insulin analogues with rapid action proven to be safe during pregnancy as well. (1)

There is not yet any information that the insulin analogues with rapid action are useful during pregnancy, although there have not been evidentiated any adverse reactions so far.(5)

Diabetes Mellitus Type 2 and Pregnancy

In diabetes mellitus type 2 it is essential that before pregnancy oral medication should be stopped and insulin therapy started as almost all oral antidiabetics are counterindicated during pregnancy or, anyway, the benefit/ risk ratio is more prone to the risk side.

During pregnancy, insulin therapy is efficient, the insulin intake will be thus adjusted in order to ensure the control of glycemias. Insulin therapy with insulin pump is both an efficient and useful method at the same time.

Gestational Diabetes

When a gestational diabetes is diagnosed, at first it should be tried the normalization of glycemia values by lifestyle optimization, by adjusting the caloric intake and by physical activity within the limits imposed by a normal pregnancy.

When diet is insufficient for the adjustment of glycemia values or when basic glycemia values are higher that 95 mg% at the moment of diagnosing gestational diabetes, it is necessary an association of a medicamentary therapeutical method.

Insulin has been the election treatment used until now. There is no indication of electing an insulin therapy type, each one of these being adequate under the condition of maintaining normal values of glycemia. Insulin analogues with rapid action are more efficient in the postprandial glycemic control with a low risk of hypoglycemia (1) .

Among the basic insulins, there are recommended human insulins, as well. Monitoring of glycemias is performed by 7 testings a day, it is very important and it allows the adjusting of insulin dosages. (Gabriela Roman)

The oral antidiabetic treatment in gestational diabetes is a controversed one. From sulphonylureas, only Glibenclamide is considered to have a minimum transfer at the level of placenta, being associated with a low risk of foetal hypoglycemia.

Alpha glucosidase inhibitors, meglinides and glitazones are not involved in the treatment of gestational diabetes.

Theoretically, Metformin may be indicated in the treatment of gestational diabetes, but it penetrates the haematoplacentar barrier and there is not enough proof to support the safety of its use. (9)

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