Study of the evolution of the placenta and fetal pancreas in the pathophysiology of growth retardation intrauterine due to restricted maternal diet

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ABSTRACT

Context: Intrauterine growth retard (IUGR) continues to be a significant perinatology problem at the end of this century. The nature of the etiologic agent, the time when the attack occurred during pregnancy and its duration affect the type of IUGR.

Objective: To study the evolution of fetal pancreas and placenta between the 18th and 21st day of pregnancy in rats submitted to maternal protein-calorie restriction.

Design: Randomized controlled trial on laboratory animal.

Sample: Forty-one normoglycemic pregnant Wistar rats.

Intervention: Rats were divided into six experimental groups according to their access to food and date of cesarean section (18th or 21st day): control with free access to food; diet restricted to 25% introduced on 1st day of pregnancy; and diet restricted to 25% after the 3rd day of pregnancy.

Main measurements: Newborn weight, placenta weight, histopathological study (morphological histochemistry)

Results: Maternal protein-calorie malnutrition caused intrauterine growth retard (IUGR) after the 18th day of pregnancy. Dietary restriction did not interfere with the morphology of the fetal pancreas and the immunohistochemical study of the placenta showed that glycogen stores were decreased between the 18th and 21st day in the control group and in a diet restricted to 25% from the first day of pregnancy. Dietary restriction after the 3rd day of pregnancy led to low placental glycogen concentrations on the 18th day and disappearance on the 21st day.

Conclusion: The pathophysiology of IUGR due to maternal protein-calorie restriction in rats is related to lower placental weight and low placental glycogen stores.


INTRODUCTION

Intrauterine growth retard (IUGR) continues to be a significant perinatology problem at the end of this century. The nature of the etiologic agent, the time when the attack occurred during pregnancy and its duration affect the type of IUGR.

Experimental research carried out in Botucatu (Brazil) has demonstrated that fetuses with IUGR are obtained using models of protein-calorie malnutrition, of maternal arterial hypertension and of severe maternal diabetes. Placental weight is lower in protein-calorie malnutrition and in the presence of renovascular arterial hypertension, but in spontaneously hypertensive rats (SHR) the placental weight of newborn rats with IUGR is identical to that of the normal young of appropriate weight.

An interesting aspect has been observed in the model of diabetes and pregnancy in rats: the same placental weight and histopathological aspects are associated with opposite deviations in fetal growth, i.e. macrosomia in moderate diabetes and IUGR in severe diabetes.

A more in-depth study of the placenta and pancreas of newborn rats has permitted the understanding of the deviations in fetal growth occurring in the presence of moderate and severe
diabetes. Calderon et al.\textsuperscript{14} demonstrated that the placentas of newborn rats with moderate diabetes presented an evolution of glycogen composition similar to that of the young of normal rats, i.e. glycogen was present on the 18th day of pregnancy and disappeared by the 21st day. Newborn rats with severe diabetes showed increased glycogen deposition in the placenta from the 18th to the 21st day of pregnancy. Calderon\textsuperscript{12} demonstrated that the endocrine pancreas of newborn rats with moderate diabetes has large islets with increased insulin production, as observed by immunohistochemistry using specific antibodies.

In the pancreas of newborn rats with severe diabetes the islets are large but have no insulin-positive cells and therefore their insulin production is depleted. Since moderate diabetes is a model of fetal macrosomia, we may infer that maternal hyperglycemia causes fetal hyperglycemia and hyperinsulinism. This leads to the removal of glycogen deposited in the placenta which, converted into energy, increases the weight of newborn rats. In severe diabetes, a IUGR model, severe maternal hyperglycemia causes intense fetal hyperglycemia leading to depletion of fetal pancreatic function. The lack of insulin production by the fetal pancreas at the end of pregnancy does not permit the removal of glycogen stores from the placenta and the fetus does not grow in an adequate manner.

The use of a restricted diet for the treatment of diabetic rats\textsuperscript{13} showed that non-diabetic pregnant control rats had IUGR, a fact previously observed by others.\textsuperscript{6,7} Doubt remained as to whether the physiopathological mechanism of intrauterine growth retardation due to the restricted diet is similar to that observed in diabetic rats. Study of the evolution of the fetal pancreas and of the placentas of normal pregnant rats submitted to a restricted diet, which has proved to be a model for IUGR,\textsuperscript{17} would permit the evaluation of this physiopathology.

The general objective of the present investigation was to study the physiopathology of intrauterine growth retardation in fetuses in pregnant rats submitted to protein-calorie malnutrition, on the

Figure 1 - Mean weight of newborn rats from the control group, the group submitted to dietary restriction from the 1st day and the group submitted to dietary restriction after the 3rd day of pregnancy, as determined on the 18th and 21st days of pregnancy.

Figure 2 - Mean weight of the placentas from the control groups, the group submitted to dietary restriction from the 1st day and the group submitted to dietary restriction after the 3rd day of pregnancy, as determined on the 18th and 21st days of pregnancy.

Figure 3 - Percentage of small for gestational age newborn rats from the control group, the group submitted to dietary restriction from the 1st day and the group submitted to dietary restriction after the 3rd day of pregnancy, as determined on the 18th and 21st days of pregnancy.
basis of evolution of the placenta and of the fetal pancreas. Specific objectives were: a) analysis of the placentas on the 18th and 21st days of pregnancy in terms of weight, morphology and composition of glycogen deposits, and b) morphologic analysis of the pancreas of newborn rats obtained on the 18th and 21st days of pregnancy.

**METHODS**

The study was conducted on 41 normoglycemic pregnant Wistar rats supplied by the central animal house of the Botucatu Campus, UNESP.

After pregnancy was confirmed, the rats were assigned at random to the following experimental groups according to the diet used and the gestational age at the time of resolution, i.e. the 18th or 21st day:
1) control group receiving a standard diet *ad libitum* and submitted to cesarean section on the 18th day (n = 7);
2) control group receiving a standard diet *ad libitum* and submitted to cesarean section on the 21st day (n = 10);
3) group submitted to a restricted diet introduced on the 1st day of pregnancy and to cesarean section on the 18th day (n = 6);
4) group submitted to a restricted diet introduced on the 1st day of pregnancy and to cesarean section on the 21st day (n = 6);
5) group submitted to a restricted diet introduced on the 3rd day of pregnancy and to cesarean section on the 18th day (n = 6);
6) group submitted to a restricted diet introduced on the 3rd day of pregnancy and to cesarean section on the 21st day (n = 6).

**Calculation of food ingestion.** The calculation of dietary restriction to 25% of normal was based on the mean weekly ingestion calculated as g/100 g rat weight compared to the group receiving a diet *ad libitum*.

**Newborn weight.** After removal of the uterus and separation of the placenta, newborn rats were weighed and classified as small (SGA), appropriate (AGA) and large (LGA) for gestational age of 18 and 21 days as compared to the mean and standard for the control group.

**Histopathology.** The placentas were separated from their membranes, weighed and processed for histopathological study (morphology and

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**Figure 5** - Pancreas of newborn rats obtained on the 18th day of pregnancy from the group receiving the diet *ad libitum* (A), the group submitted to protein-calorie restriction from the 1st day (B) and the group submitted to protein-calorie restriction after the 3rd day of pregnancy (C) in Hematoxylin-Eosin.
histochemistry). The material was embedded in paraffin, sectioned and stained with hematoxylin-eosin (HE). The thickness of the maternal-fetal exchange surface and the presence of cytotrophoblastic cells were scored from + to +++ according to intensity.

Histochemical analysis was performed by the periodic acid Schiff (PAS) reaction for the identification of glycogen deposits on the placental membrane on 18th and 21st days of pregnancy. The intensity of the PAS reaction was scored from + to +++ and compared between the 18th and 21st day in the experimental groups.

The fetal pancreases were resected, pooled for each litter and processed for morphohistology. The material was stained with HE and morphology was compared between the experimental groups. Ten Langerhans islets per slide were analyzed in terms of size, borders and quantity of vacuoles in the cell cytoplasm. Size was scored as small, medium or large, the borders were scored as regular or irregular, and the quantity of vacuoles as reduced (+), moderate (+++) or intense (+++).

Photomicrographs of the major histopathologic and histochemical features of the placentas and of the fetal pancreases were obtained.

**Statistical methods.** Data concerning newborn

| Table 1 - Qualitative results of the morphologic study of pancreatic islets from newborn rats belonging to the control group and to the groups submitted to dietary restriction from the 1st day and after the 3rd day of pregnancy, obtained on the 18th and 21st days of pregnancy |
|-----------------|-----------------|-----------------|-----------------|
| Groups          | Islet borders   | Islet size*     | Quantity of vacuoles* |
| Control at 18th day | irregular       | small/ medium   | ++/ +++         |
| Control at 21st day   | regular         | small/ medium   | +/ ++          |
| Restriction from 1st day to 18th day | irregular        | medium/ small   | ++/ ++         |
| Restriction from 1st day to 21st day | regular         | medium/ small   | ++/ ++         |
| Restriction from 3rd day to 18th day | irregular        | small/ medium   | ++/ ++         |
| Restriction from 3rd day to 21st day | regular         | small/ medium   | ++/ ++         |

* The scores were attributed according to predominance on the slides evaluated.

**Figure 5** - Pancreas of newborn rats obtained on the 21st day of pregnancy from the group receiving the diet ad libitum (A), the group submitted to protein-calorie restriction from the 1st day (B) and the group submitted to protein-calorie restriction from the 3rd day of pregnancy (C) - in Hematoxylin-Eosin.
weight and placental weight were analyzed by fully randomized factorial analysis of variance. Non-parametric tests were used for SGA, AGA and LGA data, with calculation of the $\chi^2$ statistic and with level of significance set at $p < 0.05$ for all tests.

RESULTS

The 41 rats produced 471 young; the mean number of newborns per rat was 12.9 in the control group, 9.8 in the group submitted to dietary restriction from the 1st day of pregnancy, and 10.0 in the group submitted to dietary restriction after the 3rd day of pregnancy. On the 18th day of pregnancy, mean newborn weight was higher in the group submitted to dietary restriction after the 3rd day. When pregnancy was resolved on the 21st day, fetal weight was decreased in the group of pregnant rats submitted to dietary restriction, and more intensely in the group in which restriction was started after the 3rd day (Figure 1). The placentas of rats submitted to dietary restriction were larger than those of the control on the 18th day of pregnancy. At the end of pregnancy, the weight of the placentas of rats submitted to dietary restriction from the 1st day of pregnancy was the same as the weight of control rats and higher than that of the group submitted to dietary restriction after the 3rd day (Figure 2).

On the 18th day of pregnancy, no increase incidence of SGA newborn rats was observed in the restricted groups, compared to the controls. When the restricted groups were compared with each other, the percentage of SGA young was higher in the group submitted to dietary restriction from the 1st day of pregnancy. On the 21st day there was a clear occurrence of retarded intrauterine growth in the young from malnourished mothers (Figure 3).

The pancreases of the newborn rats showed characteristics of pancreatic islet maturation that were similar for all six groups studied (Table 1 and Figures 4 and 5).

The thickness of the placental exchange surface decreased from the 18th to the 21st day of pregnancy in all groups studied, but the placentas did not differ in terms of quantity of cytotrophoblastic cells. Placental glycogen stores were normal on the 18th day and decreased by the 21st day of pregnancy in the control groups and in the groups with dietary restriction introduced on the 1st day of pregnancy. In contrast, placental glycogen stores had already decreased by the 18th day of pregnancy in rats submitted to dietary restriction on the 3rd day of pregnancy (Table 2 and Figures 6 and 7).

DISCUSSION

Maternal protein-calorie restriction reduces offspring size. This effect has also been reported in studies using protein-calorie malnutrition, in which greater occurrence of abortion and/or fetal resorption is attributed to maternal malnutrition. The restricted diet, reducing offspring size, is however seen to be sufficient to maintain fetal weight up to the 18th day of pregnancy. This is probably due to

<table>
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<th>Groups</th>
<th>Cytotrophoblastic cells*</th>
<th>Exchange surface thickness*</th>
<th>Glycogen intensity*</th>
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<tr>
<td>Control at 18th day</td>
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<td>Restriction from 3rd day to 18th day</td>
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*The scores were attributed according to predominance on the slides evaluated.
the vicarious action of the placenta occurring with its increased weight (Figures 1 and 2). The evolution of pregnancy up to the 21st day shows that protein-calorie restriction is a model for IUGR (Figure 3) associated with decreased placental weight (Figure 2), confirming previous reports.

The correlation of fetal weight with placental weight has been clinically documented in studies evaluating appropriate, small and large for gestational age newborns. These investigators concluded that in the presence of intrauterine malnutrition low-weight newborns have small placentas, showing a clear relationship between fetal nutrition and placental weight. Experimental studies on malnourished rats throughout pregnancy have demonstrated lower birth weight, a higher neonatal mortality rate, and placental damage consisting of reduced weight, number of cells and protein amounts.

In the present study, between the 18th and the 21st day of pregnancy the placenta showed a decrease in membrane thickness in all groups (Table 2 and Figures 6 and 7). Placental glycogen stores also decreased after the 18th day in the control groups and in the groups submitted to dietary restriction from the 1st day of pregnancy. In the groups submitted to dietary restriction after the 3rd day of pregnancy, glycogen stores were already smaller on the 18th day and disappeared by the 21st day of pregnancy (Table 2 and Figures 6 and 7). Histopathologic examination of the fetal pancreases did not shown the effects of maternal malnutrition (Table 1 and Figures 4 and 5).

The present results show that the physiopathological mechanism of IUGR in the presence of maternal dietary restriction seems to differ from that occurring in diabetes. In diabetes, placental glycogen stores are not utilized and converted to energy for fetal growth, due to the lack of fetal insulin. The action of severe maternal hyperglycemia depletes the fetal pancreas, which loses the ability to produce insulin at the end of pregnancy. In the presence of intrauterine protein-calorie malnutrition the fetal pancreas develops normally, demonstrating that insulin, the fetal growth hormone, is not sufficient, per se, to guarantee appropriate fetal development. Small placentas with low glycogen deposits seem to play the most important role in the etiology of IUGR due to

**Figure 6** - Placentas of rats receiving the diet ad libitum (A) and of rats submitted to protein-calorie restriction from the 1st day (B) and after the 3rd day of pregnancy (C), obtained on the 18th day of pregnancy - in Hematoxylin-Eosin and Periodic Acid Schiff.
protein-calorie malnutrition introduced after the 3rd day of pregnancy.

In the groups submitted to dietary restriction from the 1st day of pregnancy, fetal development was normal up to the 18th day because of the vicarious action of the placenta and of the glycogen stores. The continuation of maternal malnutrition up to the 21st day was associated with decreased fetal weight and increased incidence of intrauterine growth retardation even though placental weight was maintained and glycogen stores evolved normally. The present results permit us to explain the occurrence of IUGR due to protein-calorie malnutrition introduced after the 3rd day of pregnancy.

CONCLUSIONS

Maternal protein-calorie malnutrition was the cause of IUGR in rats, with the following physiopathologic peculiarities:
1) When dietary restriction was started on the 1st day of pregnancy fetal development was normal up to the 18th day because of the vicarious action of the placenta and the quantity of glycogen stored in the placenta. From the 18th to the 21st day, fetal weight reduced, with an increased incidence of SGA newborns without decreased stores of placental glycogen.

2) When dietary restriction was started after the 3rd day of pregnancy, regardless of the vicarious action of the placenta up to the 18th day, fetal development was impaired during the final period (18th to 21st day), with placental weight decreasing and the percentage of SGA newborns increasing. Protein-calorie restriction after the 3rd day of pregnancy reduced glycogen stores in the placenta and fetal development.

3) Protein-calorie malnutrition did not interfere with the development of the fetal endocrine pancreas.

REFERENCES


Figure 7 - Placentas of rats receiving the diet ad libitum (A) and of rats submitted to protein-calorie restriction from the 1st day (B) and after the 3rd day of pregnancy (C), obtained on the 21st day of pregnancy - in Hematoxylin-Eosin and Periodic Acid Schiff.
RESUMO

**Contexto:** O retardo do crescimento intra-uterino (RCIU) continua sendo importante problema em perinatologia neste final de século. A natureza do agente etiológico, o período da gestação em que ocorreu o insulto e a sua duração influenciam o tipo de RCIU.

**Objetivo:** Estudar a fisiopatologia do retardo de crescimento intrauterino (RCIU) em ratas, decorrente da restrição protéico-calórica materna, em relação à evolução do pâncreas fetal e placenta entre o 18º e 21º dias de prenhez. **Tipo de estudo:** Ensaio clínico randomizado em animais de laboratório. **Participantes:** 41 ratas prenhes, normoglicêmicas, da raça Wistar. **Intervenção:** Constituíram-se seis grupos experimentais: controle, com dieta “ad libitum” e cesárea, respectivamente, no 18º e 21º dias de prenhez. Antes desse período não ocorreu RCIU, porque a desnutrição materna diminuiu o número da prole e a placenta tornou-se vicariante. A restrição alimentar não interferiu com a morfologia e o desenvolvimento fetal. In: Congresso Médico-Acadêmico de Botucatu 3, 1994, Botucatu. Anais. Botucatu: CAMED, Faculdade de Medicina, UNESP.

**Resultados:**
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