

## Research Article

# MORPHOLOGICAL CHANGES IN WISTAR RAT FETUSES FROM PROGENITORS WITH SUCROSE-INDUCED METABOLIC SYNDROME

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**ABSTRACT:** Women exhibiting the components of metabolic syndrome before the pregnancy have a high risk of fetal placental dysfunction, even fetal death. Moreover, glucotoxicity has been linked to birth defects. These issues have motivated checking the possible association between a metabolic syndrome and morphological damages in the conception product. In this paper, morphological alterations produced on the fetus by the metabolic syndrome of progenitors were determined in an experimental model. The bio-model was developed in Wistar rats by supplying them with 35 % sucrose from the intrauterine stage up to eighteen weeks of age. Subsequently, crossing was performed, the pregnancy was confirmed, and blood pressure was checked. Two groups of pregnancy were formed; metabolic syndrome and healthy control. Cesarean section was performed on day twenty of gestation, in order to make the corresponding first segment studies of reproductive toxicity. Maternal parameters such as body and organ weight were assessed. Weight, crown-rump length and total number of fetuses by group, as well as skeletal and soft tissue of the fetuses were recorded. Hematoma was the main external change found, as well as there was significant decrease in fetuses' weight of metabolic syndrome parents' group. In these fetuses, the absence of Xiphoid and Sterne brae was reported as the principal developmental delays in bone tissue and no noticeable damage was observed in soft one. These results suggest that the metabolic syndrome morphologically affects the conception product.

**Key words:** Metabolic syndrome, Developmental delays, Xiphoid, Sterne brae, Hematoma.

## INTRODUCTION

The metabolic syndrome (MS) is a controversial clinical entity that appears with large phenotypic variations in people with an endogenous predisposition. It was genetically determined and influenced by environmental factors (SO'Neill and O'Driscoll 2015). Women presenting aspects of MS before the pregnancy, such as obesity, chronic hypertension, diabetes mellitus and dyslipidemia, have a high risk of placental dysfunction and even fetal death (Grieger *et al.* 2018). Caudal regression syndrome has been observed in offspring of diabetic women, shown to influence on weight and size at birth. Hyperglycemia or gestational diabetes and metabolic syndrome *per se*, have shown to influence on weight and size at birth (Seghieri *et al.* 2002, Hernández and Mericq 2011). Moreover, hormonal and metabolic alterations that occur during pregnancy may cause birth defects (Grieger *et al.* 2019, Metzger *et al.* 2019). Maternal diseases that alter their normal

metabolism may have direct effects on the fetus, as potential disruptors of fetal intrauterine environment. In this sense, the metabolic syndrome is an issue of significant importance and urgency due to global epidemic of obesity, diabetes mellitus, arterial hypertension and its subsequent influence on population reproductive health (Smith and Ryckman 2015, Dojki and Bakris 2016, Albai *et al.* 2018).

Researches on both human and animal subjects has revealed that obesity during pregnancy can elevate the risk that offspring will exhibit dysregulation of body weight and develop obesity (Long *et al.* 2010, Kim *et al.* 2014). Different animal models of gestational obesity have showed fetal macrosomia and growth restriction. (Hayes *et al.* 2012, Sferruzzi-Perri *et al.* 2013).

In several countries, animal models with induced MS have been developed and research is being conducted. Some clinical and morphological complications have been verified in newborn of parents with a metabolic

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syndrome or hyperglycemia (dos Prazeres *et al.* 2015). *In vitro* and *in vivo* studies have associated glucotoxicity with congenital malformations (França-Silva *et al.* 2016, Khosrowbeygi *et al.* 2016, Persson *et al.* 2019). However, the possible causal association between a MS and malformations or developmental delays in soft and skeletal tissue has not been tested *in vivo*.

A sucrose induced MS bio-model was carried out at the Experimental Toxicology Unit in Villa Clara (Cuba). The purpose of this study was to determine the morphological alterations produced in fetuses due to MS in their parents.

## MATERIALS AND METHODS

### Animals

The Animal Ethics Committee of the Experimental Toxicology Unit from Medical College of Villa Clara, Cuba, approved the experimental protocol, according to ARRIVE guidelines (McGrath *et al.* 2010). Male and female Wistar rats were used. Once the experiment concluded, female rats with MS were sacrificed by an anesthetic overdose, followed by cervical dislocation. (Close *et al.* 1997)

All rodents and their food were purchased at the National Center of Laboratory Animal Production (Havana, Cuba). Animals were kept in specific pathogen-free conditions. Rats were housed in polycarbonate cages (Tecniplast, Buguggiate, Italy) with mesh bottoms, spacing of 11 mm × 11 mm and a floor area of 1,800 cm<sup>2</sup>. Room temperature was 22±2°C on a 12h photo-schedule. Access to a standard diet of laboratory chow and water was *ad libitum*.

### Sucrose metabolic syndrome induced

The MS was induced from birth to twenty weeks of life, by providing 35 % sucrose solution *ad libitum* in drinking water, which ensured that main characteristics of the disease were developed (González-Madariaga *et al.* 2015). Two females and one male with sucrose-induced metabolic syndrome were mated. Likewise, we proceeded with the healthy group parents, which were given water without sucrose. The introitus of female rats was checked early every day to prove sexual contact during the night. Sperm presence in the female indicated the zero day of gestation. Afterwards, two experimental groups (n=10) were formed with pregnant rats: MS and Healthy Control (HC) Groups.

Blood pressure was recorded by non-invasive method (Widdop and Li 1997) based on indirect measurement of pressure by the tail of the rat. It was used as a measuring of blood pressure mark (CODA-UEA) containing sensor

to indirectly capture blood pressure values, recording systolic blood pressure (SBP) and diastolic blood pressure (DBP) expressed in mmHg.

### External changes and recording of the number, size and fetuses' weight

Pregnant rats underwent cesarean section at 20 days of gestation. This action prevented the mother rats to engulf malformed newborns and stillborn. Cesarean section was performed under ether anesthesia. Mother rats underwent a U-shaped incision in lower abdominal region. Then the number of corpora lutea, embryo sacs, early and late resorptions, sexing of the fetus by mother, gravid uterine weight, visceral fat weight, liver, heart and mother kidneys weight, were registered.

The macroscopic identification of external malformations was carried out after the extraction of the fetuses (Rosario and Arencibia 2003). Once the external analysis of fetuses was completed, evaluations of total number, crown-rump length and weight of fetuses were made, in order to detect possible differences between experimental groups.

### Assessment of congenital malformations in soft and skeletal tissue

Afterward a portion of the fetuses was used for external examination (26 MS' fetuses and 32 of HC) of bone and the other half for analyzing soft tissue.

### Preparation and examination of skeletal tissue

For fetuses processing, transparent technique was used (Rosario and Arencibia 2003). Fetuses were at first fixed in 95% alcohol, for three days. Then they were transferred to acetone in order to dissolve fats that would otherwise hinder the view of the bony structures. On the fifth day study samples were washed with 95% alcohol and maintained there for 24 hours. Upon completion of this procedure, fetuses were immersed in 1% potassium hydroxide until the bones were clearly visible through the muscle. Then they were transferred to Alizarin Red S and after the third day were immersed in Mall's solution toward red coloration of the bones and transparency of non-calcified tissues (Dawson 1926).

The analysis was performed in order to determine skeletal abnormality and lack of ossification (Manzon and Kang 1989). The head bones were examined for size, shape, addition or absence of bone. Vertebrae were examined in the trunk region, verifying their absence or addition. The ribs were examined as to the number, size, location, fusion, thoracic ribs number on each side. The Sterne brae were analyzed taking into account the number,

failure and incomplete calcification. The presence or absence of xiphoid, omission or incomplete calcification were evaluated. The main centers of ossification belonging to the long bones *i.e.*, fore limbs were examined later.

#### Preparation and examination of soft tissue

Fetuses selected for analysis of soft tissue were immersed in Bouin's fixative, which was prepared the day before caesarean section. In order to perform a detailed examination of fetuses' viscera, the Wilson's cutting technique was applied in search of internal organ malformations (Manzon and Kang 1989).

#### Statistical analysis

Data were analyzed using SPSS software for Windows version 22 (2013). A descriptive analysis of the data was conducted to know its nature and main trends. Contingency tables were used for recording and analyzing the relationships between variables xiphoid and Sternebrae absence. Parametric and non-parametric test were used for maternal and litter parameters. Values of  $p < 0.05$  were considered significant.

## RESULTS AND DISCUSSION

### Outcomes of pregnant rats

The maternal parameters are shown in Table 1. Progenitor rats, which were induced MS blood pressure, reached  $143/110 \pm 9.98/8.76$  mmHg at the time of pregnancy. These high and significantly superior values to those of the control group showed that the pregnant rats developed hypertension as one of the components of MS.

The values of the progenitor's biometric parameters before the interruption of pregnancy were increased in the MS group. The meaningful increase of body weight in the group of mothers with a metabolic syndrome was one of the results in the study. Moreover, the visceral fat weight (VFW) of the progenitor rats with a metabolic syndrome was much higher than HC ( $p < 0.01$ ). This result justifies that the weight of the pregnant rats in MS group was the result of increasing VFW and not of pregnancy *per se*.

### Comparison of the number, weight and CRL of fetuses

The total number of fetuses in the MS group was lower than HC one (45.58%). Unlike HC rats, this result correlates with the finding of resorption in pregnant rats with MS. The weights of the MS group fetuses were statistically lower than in the HC group ( $p < 0.05$ ). No

differences between CRL of MS and HC were observed (Table 1).

### Analysis of external findings in fetuses from rats with a metabolic syndrome

Twelve fetuses of the group from parents with MS developed bruises (28%) in different regions of the anatomy, as well as early and late fetal resorptions in 16 % of the sample. Both outcomes were not observed in the control group (Table 2). The corpora lutea number was the same to fetus number, including early and late resorption. Nevertheless, a limitation of this research was no reporting the implant sites. Further research could be necessary to avoid the possible underestimation in number of fetuses.

### Skeletal tissue malformations

The variables for detecting skeletal tissue damage were only identified in MS group corresponding to sternbrae and xiphoid absence (Table 2). Eighteen and twelve out of fifty-eight fetuses were observed without stern bras and xiphoid, representing 31 and 20.7 % of the sample

**Table 1. Maternal and fetal parameters. The values are expressed as Mean  $\pm$  SD.**

Maternal data	HC	MS
Systolic Pressure (mmHg)	121 $\pm$ 3.56	143 $\pm$ 9.98**
Diastolic Pressure (mmHg)	96 $\pm$ 2.83	110 $\pm$ 8.76*
MBWb (g)	196.00 $\pm$ 5.77	200.80 $\pm$ 13.29
MBWe (g)	277.00 $\pm$ 8.37	300.13 $\pm$ 10.70*
BWG (g)	76.20 $\pm$ 17.77	103.47 $\pm$ 6.44*
VFW (g)	6.98 $\pm$ 3.02	13.94 $\pm$ 1.61**
G UW (g)	53.55 $\pm$ 15.61	59.14 $\pm$ 8.07
AMWG (g)	28.32 $\pm$ 1.22	44.32 $\pm$ 14.51*
Litter data		
Number of fetuses	63	43
Birth weight (g)	4.24 $\pm$ 1.39	4.10 $\pm$ 0.50*
CRL (cm)	3.69 $\pm$ 0.45	3.35 $\pm$ 0.24
Early Resorptions	0	4
Late Resorptions	0	3

\*\* $p < 0.01$  \* $p < 0.05$  MS: Metabolic Syndrome group. HC: Healthy Control group. MBWb: Maternal Body Weight at the Beginning of the gestation. MBWe: Maternal Body Weight at the End of the study. BWG: Body Weight Gain. LW: Liver Weight. VFW: Visceral Fat Weight, G UW: Gravid Uterus Weight, AMWG: Adjusted Maternal Weight Gain, CRL: Crown-Rump Length.

**Table 2. Fetuses' external findings.**

	MS	HC
Number of litters	10	10
Number of fetuses	43	63
Bruises	12 (27.9)	0 (0)
Absence of Xiphoid	10 (38.5)	2 (6.3)
Absence of Sternebrae	15 (57.7)	3 (9.4)
A1S	5 (19.2)	3 (9.4)
A2S	6 (23.1)	0 (0)
A5S	4 (15.4)	0 (0)

MS: Metabolic Syndrome group. HC: Healthy Control group. Absence of a sternbrae (A1S). Absence of two sternbrae (A2S). Absence of five sternbrae (A5S). Values given in parentheses represent percentage.

respectively. The MS group recorded a 57.7 % of sternbrae absence and 38.5 % of absence of xiphoid, in respect of HC fetuses. These values were significantly higher than the healthy group ( $\chi=0$ ), where only three cases of absence of the first stern bra and two cases of absence of the xiphoid were detected. These findings seem to be developmental delays more than malformation.

#### Malformations in soft tissues

In the assessment of soft tissue, no significant changes were reported, beyond the finding of two possible expansions of the lateral cerebral ventricle in fetuses from progenitors with MS. Some research has associated maternal obesity to development of numerous pathologies in mothers and offspring, highlighting aspects related to hypertension and diabetes mellitus gestational, intrauterine growth retardation, fetal defects and stillbirth (Marchi *et al.* 2015, Godfrey *et al.* 2017, Kapoor and Kean 2017).

More important than the weight gain in pregnancy *per se* is the body fat distribution. The role of visceral fat in the development of insulin resistance has been extensively considered, specifically its association in early stages of pregnancy with risk factors for gestational diabetes (De Souza *et al.* 2016). The significant increase in visceral fat of pregnant rats with a metabolic syndrome ( $p=0.009$ ), obtained in our study, could be related to the alterations observed in the offspring. Malformations or congenital anomalies were usually developed in the embryonic stage. One of the simplest strategies for screening for these abnormalities is seeking external defects by inspection and comparison to healthy individuals.

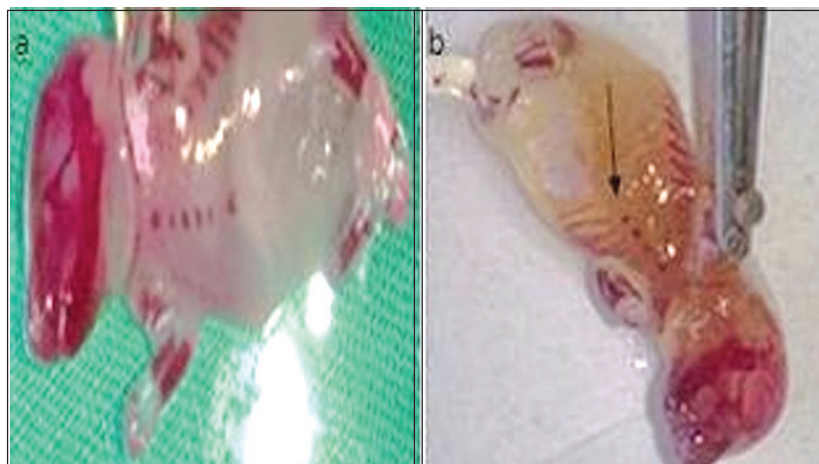
Recognized external bruises agreed with those described by other researchers about Type II Diabetes Mellitus (Albai *et al.* 2018, Eriksson and Wentzel 2016). As it was pointed, the mothers with MS presented high values of blood pressure and this factor duplicates the bruising risk (Marchi *et al.* 2015, Roman *et al.* 2011). The presence of bruises in progenitors' descending fetuses with MS could suggest a bigger bias to development vascular accidents.

In literature, some recent researches show that hyperglycemia and diabetes are closely related to embryonic death (Martino *et al.* 2016). Eclampsia in women is also associated with spontaneous abortions and fetal death (Baumfeld *et al.* 2015, Weissgerber and Mudd 2015).

The most common manifestations of teratogenicity could be often deficiencies in prenatal growth or death of the developing organism (Ujházy *et al.* 2005). The CRL of the fetuses of both groups was similar ( $p>0.05$ ). This behavior coincides with a study conducted in rats with a



**Fig. 1.** Shows fetuses from parents with MS, which were found to have bruises in the dorsal region.



**Fig. 2.** Congenital malformations in skeletal tissue. **Panel-a:** Ossification full of sternbrae and xiphoid in healthy fetus. **Panel-b:** incomplete ossification of the sternbrae in MS fetus. The arrow indicates the absence of the fifth sternbrae and absence of xiphoid.

metabolic syndrome induced by different concentrations of lead, where no differences in the size were found (Omar *et al.* 2016).

The fetuses' weight of the MS group was statistically lower than the HC group ( $p < 0.05$ ). These results are supported by the presence of hypertension in pregnant women with proven MS. It has been reported, that low birth weight fetuses of mothers with MS may be related to this component of the syndrome (Smith and Ryckman 2015). Moreover, MS around period of organogenesis has been linked to a spectrum of developmental disorders where retarded growth is included (Mitanchez and Chavatte-Palmer 2018). In nutritional studies in pregnant, it was observed that infants showed reduced growth as asymmetric type, where the weight, body mass index (BMI) and weight index (WI) diminished, but not the body length. This phenomenon is possibly due to acute nutritional deprivation, particularly fatty acid, during the period of the highest growth since the length was not affected (Sánchez-Muñiz *et al.* 2013)

These results demonstrate the sensitivity of this ossification marker to suffer alteration during the pregnancy of progenitors with a metabolic syndrome. Kaufman suggests to examining these bones because they are the main centers of ossification (Kaufman 1992). Arsenic as a teratogen was used in Wistar rats and it was noted the sensitivity of bone tissue to suffer malformations (Quiterio-Pérez *et al.* 2013). Another study also links oxidative stress, as one of the causatives in osteogenic differentiation (Wang *et al.* 2017). The result can suggest that the MS induces bone tissue damage in offspring, specifically at the stage of embryonic development, because it precludes the complete ossification degree of the stern bras and xiphoid.

## CONCLUSION

The metabolic syndrome was related to a decrease in the number of live fetuses, at the expense of an increase of early and late reabsorptions. The number and body weight of fetuses from parents with MS were lower than HC group. Significant developmental delays represented by the absence of xiphoid and sternbrae were noted. Bruises observed in MS fetuses could relate the metabolic syndrome to more risk of vascular accidents in prenatal life.

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