The triad macrosomia, obesity, and hypertriglyceridermia in gestational diabetes

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Aims: Offspring of women with gestational diabetes (GD) have more macrosomia than newborns of normal mothers. We studied macrosomia frequency, possible pathogenesis, and main predictors of its appearance at different gestational ages.

Materials and Methods: A total of 1870 pregnant women with GD were recruited in primary care centres and maternity hospitals in the Argentine provinces of Corrientes, Chaco, Buenos Aires, and in Buenos Aires City: 1088 completed gestation and delivered an infant. We collected clinical and metabolic data, personal and obstetric history, and gestational and delivery characteristics. Presence of macrosomia was analysed in the whole population, the entire pregnancy, and in each trimester of gestation. Data were statistically analysed and values were expressed as mean ± SD and percentages. The study protocol was approved by the Ethics Committee and all participants signed informed consent.

Results: Macrosomia was found in 12.9% of newborns and obesity in all mothers with no significant differences between mothers with/without macrosomic offspring. In early pregnancy, the main significant indicators of macrosomia were: history of dyslipidaemia (5.6% vs 1.2%, respectively) and macrosomia in previous pregnancies (27% vs 13%, respectively). However, the third trimester showed a significant combination of higher BMI, FBG, and triglycerides.

Conclusions: Offspring of women with GD presented macrosomia in 12.9% of cases, maternal history of dyslipidaemia and macrosomia in previous pregnancies being early predictors. The combination of maternal obesity, FBG, and hypertriglyceridermia became significant during the last trimester of pregnancy.

KEYWORDS
GDM, lipids, macrosomia, metabolic impairments, obesity, pregnancy, triglyceride

1 INTRODUCTION

Gestational diabetes (GD) is glucose intolerance manifested during pregnancy, based on the diagnostic criteria of the Latin American Diabetes Association (ALAD), its prevalence in Argentina is 4.7%. Women with GD have a higher risk of developing complications during pregnancy (preeclampsia), and their newborns have a higher risk of developing short-term adverse events (macrosomia, neonatal hypoglycaemia, respiratory distress syndrome, and neonatal cardiac dysfunction), as well as long-term metabolic dysfunctions.

These negative impacts on the mother and the newborn can be significantly reduced by early diagnosis and adequate treatment combining adoption of a healthy lifestyle and medication.
Foetal macrosomia occurs in 15–45% of newborns of mothers with GD compared to 12% of newborns of normal mothers; these macrosomic infants have a higher risk of becoming overweight/obese at an early age and of developing T2D later in life. Several studies suggest that epigenetic alterations in different foetal genes could result in transmission of GD and T2D from mothers to offspring.

Regarding maternal complications, if the baby is atypically large, vaginal birth is more complicated, with a risk of prolonged labour during which the foetus may be stuck in the birth canal, requiring instrumental delivery (by forceps or vacuum), or even an unplanned or emergency caesarean section. During delivery, risk of laceration and tearing of vaginal tissue is greater than with a normal size baby; muscle between the vagina and the anus may also tear (perineal tear).

There is also a high chance of uterine atony. The uterine muscle may not contract properly, resulting in heavy bleeding and postpartum haemorrhage, events observed approximately 3-5 times more frequently in macrosomic deliveries. Also, if the mother has had a previous caesarean section, the chance of uterine tear along the scar line of the previous surgery is higher.

For the newborn, macrosomia increases the risk of shoulder dystocia, clavicle fractures, and brachial plexus injury, thereby increasing the need for admission to neonatal intensive care units. Strict regulation of maternal blood glucose levels can significantly limit adverse perinatal outcomes. Based on all this evidence, we recently implemented a program (EduGest), which aims to reduce the burden of this disease in our country. Its main objective is to promote the joint action of primary care centres (CAPs) and maternity hospitals in Argentina, to facilitate patients’ access to early consultation, timely diagnosis, and adequate treatment through a structured education program and an integrated multisectoral approach. At this time, we present preliminary data on macrosomia frequency, describe the main indicators of its appearance according to gestational age at the time of the first consultation, and also in the third trimester, and briefly review possible pathogenic mechanisms.

2 | MATERIALS AND METHODS

2.1 | Recruitment and methodology

This observational retrospective research study compared clinical and metabolic data from pregnant women with GD who completed their gestational period and delivered an infant with or without macrosomia. Clinical and metabolic data presented correspond to the baseline data of a prospective study which aims to demonstrate the impact of health care team members and patient education on diagnosis and successful treatment of gestational diabetes. Pregnant women with GD were recruited in CAPs and participating maternity hospitals between 2017 and 2019 and referred for specialized medical attention. For this purpose, we previously established a network, including the following institutions: the J.R. Vidal Hospital, A.I Llano and Camilo Muníagurria in Goya, Irastorza in Curuzu Cuatiá, CAPs and SAFs in Corrientes Province; the Perrando Hospital in Chaco Province; the Argerich Hospital in Ramos Mejía and the Santojanni Hospital in the City of Buenos Aires (CABA), the Maternity Hospital in San Isidro, and the Diego Thompson Hospital in San Martin, Buenos Aires Province, Argentina.

We recruited 1870 pregnant women with GD of whom 1088 completed their gestational period and delivered an infant. Body weights of 137 of the latter were ≥ 4.0 kg, whereas the remaining 951 babies were born weighing ≤ 4.0 kg (Figure 1).

We collected individual clinical and metabolic data using the QualidiabGest form, designed especially for the EduGest study; this form includes personal data and obstetric history, body mass index (BMI), blood pressure, cardiovascular risk factors (CVRF), fasting blood glucose (FBG), serum total cholesterol, and triglycerides. It also includes obstetric history, characteristics of delivery, preeclampsia, gestation-induced hypertension, and newborn’s body weight.

Laboratory assays were run using commercial kits. We classified obesity in non-pregnant and pregnant women using the WHO and Mardones-Rosso criteria, respectively. Regarding dyslipidaemia, we used the ATPIII and Ywaskewycz Benítez et al criteria for non-pregnant and pregnant women, respectively.

We show data on the whole population regarding presence/absence of macrosomia, followed by the same results separated by the trimester of the woman’s first consultation.

2.2 | Statistical analyses

Statistical analyses used the Statistical Package for Social Sciences version 15 (SPSS Inc, Chicago, IL, USA). Descriptive statistics are presented as percentages and mean ± SD. Group comparisons for continuous variables used Student t-test and Mann-Whitney U test depending on the data distribution profile. Chi-squared statistic was used to test differences between proportions. Significance was P ≤ .05.

![Figure 1](image-url)
### 2.3 Ethical considerations

All study procedures are complied with the ethical standards of the institutional research committee, the Helsinki Declaration of 1964 and its subsequent modifications, or comparable ethical standards. The study protocol was analysed and approved by the Ethics Committee of the Universidad Nacional del Nordeste (UNNE) and approved by all participating institutions. All subjects in the study signed an informed consent.

### 3 RESULTS

In the entire population of women with GD having completed the gestational period, macrosomia was found in 12.9% of newborns (Table 1). In these cases, significantly more caesarean sections were performed than in deliveries with normal newborn body weight: 50% vs 35%, respectively (Table 2).

Obesity, the largest CVRF recorded in this population, was present in all mothers, although the difference (34% vs 27% compared to macrosomia) was not statistically significant (Table 1).

Preeclampsia in a small percentage of cases had no significant differences between women that delivered a baby with normal body weight vs those with macrosomia.

Overall, the main and significant indicators of macrosomia were a history of dyslipidaemia (5.6% vs 1.2%, respectively) (patient self-report) and macrosomia in previous pregnancies (27% vs 13%, respectively, Table 1).

We sought markers of macrosomia in the different trimesters of gestation, finding a combination of significantly higher values for BMI, FBG, and triglycerides only in the third trimester of gestation (Table 3) considered late markers of macrosomia.

### 4 DISCUSSION

Our current data showed a prevalence of macrosomia of 12.9%, a figure lower than that of the reports by other authors for women with GD: 16.4% vs 11.2% in their control group.16

Most of the women with GD analysed were obese, but we found no significant difference between women that delivered a baby with normal weight or with macrosomia. This lack of significance could perhaps be ascribed to the small number of cases and to data dispersion. Other authors have reported a positive correlation between mothers’ and offspring's body weight in women with treated GD and women with normal glucose tolerance17: by logistic regression analysis, they found that the mother's body weight was a robust predictor of macrosomia in offspring in both conditions. In our study, however, obesity only became a significant macrosomia predictor in the third trimester, associated with higher serum triglyceride levels. Similarly, Olmos PR et al concluded that in overweight and obese GDM mothers, maternal triglycerides are partially responsible for

### Table 1 General characteristics of all the pregnant women recruited

<table>
<thead>
<tr>
<th>Data recorded</th>
<th>All together</th>
<th>Offspring weight ≤ 4 kg</th>
<th>Offspring weight &gt; 4 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>n</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Mother's age at pregnancy outset (years)</td>
<td>30.7 ± 6.7</td>
<td>1075</td>
<td>30.7 ± 6.7</td>
</tr>
<tr>
<td>Number of previous pregnancies</td>
<td>2.2 ± 2.0</td>
<td>1052</td>
<td>2.1 ± 2.0</td>
</tr>
<tr>
<td>Gestational age at the first consultation (weeks)</td>
<td>29.3 ± 5.8</td>
<td>926</td>
<td>29.4 ± 5.7</td>
</tr>
<tr>
<td><strong>Background</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVRF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>5.1</td>
<td>1088</td>
<td>4.7</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>28.0</td>
<td>1088</td>
<td>27.2</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>5.1</td>
<td>1088</td>
<td>4.9</td>
</tr>
<tr>
<td>Dyslipidaemia (%)</td>
<td>2.1</td>
<td>1088</td>
<td>1.6</td>
</tr>
<tr>
<td>Obstetric background</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DG in previous gestations (%)</td>
<td>12.4</td>
<td>935</td>
<td>12.2</td>
</tr>
<tr>
<td>Premature newborns (%)</td>
<td>7.3</td>
<td>1021</td>
<td>7.6</td>
</tr>
<tr>
<td>Preeclampsia (%)</td>
<td>4.5</td>
<td>1024</td>
<td>4.2</td>
</tr>
<tr>
<td>Family DM background (%)</td>
<td>53.4</td>
<td>1045</td>
<td>52.3</td>
</tr>
<tr>
<td>Offspring with &gt; 4 kg (%)</td>
<td>15.1</td>
<td>1038</td>
<td>13.4</td>
</tr>
<tr>
<td>HIG in previous gestations (%)</td>
<td>9.2</td>
<td>1029</td>
<td>9.4</td>
</tr>
<tr>
<td>Eclampsia (%)</td>
<td>1.1</td>
<td>1025</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Abbreviation: HIG, hypertension induced by gestation.
macrosomic infants despite good maternal glucose control during pregnancy.\textsuperscript{18}

In our study, macrosomia in the obstetric history of women with GD was another good marker of its reappearance in subsequent pregnancies. Intergenerational transmission of obesity-induced macrosomia via epigenetic alterations of different genes of the foetus in utero of a mother with GDM could explain this phenomenon.\textsuperscript{17}

Data analysis according to gestational age showed a clear macrosomia marker in the third trimester of gestation: a combination of high BMI, fasting blood glucose, and triglycerides. This association of clinical and metabolic abnormalities strongly suggests that macrosomia might be the consequence of multifactorial impairments rather than only high glucose levels as originally proposed by Pedersen.\textsuperscript{19} This author ascribed the pathogenesis of macrosomia in offspring of women with GDM to maternal hyperglycaemia crossing the placenta, inducing foetal hyperinsulinemia which by increasing glucose utilization promotes an increase in foetal adipose tissue. This single factor hypothesis has been seriously challenged, since evidence shows that other factors participate in this process, as also occurred in our women with GD.\textsuperscript{10}

Although BMI was not a significant marker of macrosomia in our overall data analysis, it became significant in the third trimester of gestation. We assume that this change was a consequence of the combination of the women’s high BMI when they became pregnant plus weight gained during gestation. Supporting our interpretation is the report that gestational weight gain greater than or less than guideline recommendations, compared to gestational weight gain within recommended levels, is associated with higher risk of adverse maternal and infant outcome.\textsuperscript{20,21}

Maternal hypertriglyceridemia was the other significant marker of macrosomia recorded in our study in the third trimester of gestation; comparable results were reported by Son et al who suggested that after adjusting for several confounding variables, maternal hypertriglyceridemia at 24-32 weeks’ gestation remained an independent parameter for identifying term macrosomic newborns.\textsuperscript{22} To explain this phenomenon, we must remember that since during early

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Type of delivery and maternal complications during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data recorded</td>
<td>All</td>
</tr>
<tr>
<td>Delivery by Caesarean (%)</td>
<td></td>
</tr>
<tr>
<td>Offspring (number)</td>
<td>1.1 ± 0.6</td>
</tr>
<tr>
<td>Offspring weight (g)</td>
<td>3.39 ± 58</td>
</tr>
<tr>
<td>Capurro index (weeks)</td>
<td>38.3 ± 1.7</td>
</tr>
</tbody>
</table>

Maternal Complications

| HIG (%) | 4.9 | 5.3 | 2.2 |
| Preeclampsia (%) | 2.0 | 1.8 | 3.6 |

Abbreviation: HIG, hypertension induced by gestation.

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Characteristics of pregnant women recruited according to gestational age during the consultation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>First trimester</td>
</tr>
<tr>
<td></td>
<td>NB weight &lt; 4 kg</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.2 ± 6.5 (13)</td>
</tr>
<tr>
<td>Weight (kg.)</td>
<td>82.1 ± 22.4 (13)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.8 ± 7.7 (13)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>104.6 ± 11.3 (13)</td>
</tr>
<tr>
<td>TAD (mmHg)</td>
<td>65.4 ± 6.6 (13)</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td>106.0 ± 36.9 (13)</td>
</tr>
<tr>
<td>Fructosamine</td>
<td>314.7 ± 74.6 (3)</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>122.9 ± 40.4 (11)</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>166.0 ± 32.4 (9)</td>
</tr>
</tbody>
</table>

\*Statistically significant; BMI, Body mass index; DBP, diastolic blood pressure; NB, Newborn; SBP, Systolic blood pressure.

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pregnancy the combination of hyperphagia and increased lipogenesis promotes body fat accumulation, during its late stages, an accelerated breakdown of fat depots plays a key role in foetal development.\textsuperscript{25} In fact, during pregnancy an increase in serum triglyceride occurs as a compensatory mechanism to cope with increased demand for metabolic substrates.\textsuperscript{24} Although triglycerides do not cross the placental barrier, lipoprotein receptors in the placenta together with lipoprotein lipase, phospholipase A2, and intracellular lipase activities allow release to the foetus of polyunsaturated fatty acids transported as triacylglycerol in maternal very-low-density, low-, and high-density lipoproteins. Although glycerol crosses the placenta in small proportions, it is a preferential substrate for maternal gluconeogenesis, allowing maternal glucose provision to the foetus by crossing the placenta barrier.

Within such a complex context, the role of adipose tissue in GD and macrosomia development becomes important due to the production/release of adipokines, including leptin, adiponectin, tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), interleukin-6, resistin, visfatin, and apelin\textsuperscript{25,26} in pregnant women.\textsuperscript{27}

Although not measured in our study, other new factors have further increased the complexity of macrosomia pathogenesis: recent studies have demonstrated that foetal growth can be regulated by noncoding RNAs.\textsuperscript{28,29} These studies, attempting to develop biomarkers for prevention and early diagnosis of macrosomia, were described in a recent review.\textsuperscript{30} These authors draw attention to a new aspect of macrosomia predictors: paternal effects on offspring and miRNAs, developmental origins of health and disease.\textsuperscript{31} Furthermore, a recent meta-analysis revealed that deficient periconceptional paternal nutrition affects offspring weight similar to maternal nutrition, epigenetic components being involved in its production mechanism.\textsuperscript{32} Although miRNA participation is supported only by results obtained in rodents,\textsuperscript{33,34} paternal nutrition and metabolic status have a proven effect on macrosomia development.

Additional complexity to the macrosomic issue was recently provided by Hu et al with their retrospective cohort study of 1292 women with NGT and 1155 with GD. They reported that male foetuses had higher risks of large gestational age and macrosomia than female foetuses in NGT pregnancies. These newborns with higher risks of preterm premature rupture of membranes, neonatal infection, acute respiratory disorders, and abnormal neonatal central nervous system development only resulted from GD pregnancies. Therefore, they suggested that particular attention might be paid to male newborns when glycaemia in GD pregnancies was poorly controlled to ensure that these foetuses receive appropriate postpartum care to prevent neonatal infections.\textsuperscript{35}

In view of the current evidence/pathogenic interpretation of macrosomia, we consider that this adverse effect of GD can be prevented/treated by using what is now the most effective tool: early adoption of healthy habits, namely, a healthy meal plan and physical activity.\textsuperscript{36,37} These dietary interventions favourably affect outcomes related to maternal glycaemia and birth weight, thereby suggesting them as an effective strategy to prevent undesirable outcomes associated with GD.\textsuperscript{7,38}

Although our data are clear, they must be considered with caution since: (i) they refer to a relatively small number of cases, particularly in the initial trimesters, (ii) data interpretation is based on many cases using reported evidence rather than our own data, and (iii) since this field is constantly evolving, new reported evidence may possibly modify the current pathogenic explanation of macrosomia.

Despite all these concerns, our data provide useful information for health authorities and decision makers, namely: macrosomia of offspring of women with GD is present in 12.9% of cases, and our data showing its early and late indicators may facilitate early diagnosis and effective prevention/treatment.

ACKNOWLEDGEMENTS
The EduGest implementation was partially funded by the World Diabetes Foundation (WDF 15-1314). The authors are grateful for the efficient and generous cooperation of all the staff of the Facultad de Medicina of the UNNE and the Municipality of the City of Corrientes. Also for the cooperation provided by the Dean of the Faculty of Medicine UNNE, Professor Mag. Omar Larroza and Accountants Dana Zimmerman and Analía Falcón of the same Faculty. Finally, we appreciate the valuable collaboration of Dr. Enzo Rucci for the development of the software that manages the loading and analysis of the database as well as Mrs. Susan Rogers for the manuscript edition. JFE and JJG are members of the CONICET Research Career.

AUTHOR CONTRIBUTIONS
S.G.L. contributed the overall general coordination, data collection, educational group monitoring, interpretation of findings, and critical revision of the manuscript. J.A. and S.S. contributed in the coordination of working groups, data collection, and manuscript revision. J.F.E. contributed to data analysis, interpretation of findings, and manuscript writing. J.J.G. contributed to the coordination of educational groups, data analysis, interpretation of findings, and drafting of the manuscript.

CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

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How to cite this article: Gorban de Lapertosa S, Alvariñas J, Elgart JF, Salzberg S, Gagliardino JJ, on behalf of the EduGest group. The triad macrosomia, obesity, and hypertriglyceridemia in gestational diabetes. *Diabetes Metab Res Rev*. 2020:e03302. [https://doi.org/10.1002/dmrr.3302](https://doi.org/10.1002/dmrr.3302)