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ORIGINAL ARTICLE

Postnatal effects of metformin on growth in children of mothers with gestational diabetes mellitus

Efectos postnatales de la metformina en el crecimiento en hijos de madres con diabetes mellitus gestacional

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What do we know about the subject matter of this study?

Gestational diabetes is known to be on the rise and both insulin and metformin are used in its treatment, but there is uncertainty about the long-term effects of metformin on the offspring of women treated during pregnancy.

What does this study contribute to what is already known?

This study evaluates the postnatal growth of children of mothers who received metformin during pregnancy, compared to those treated with insulin. It provides a deeper understanding of the postnatal effects of metformin, offering crucial information on its safety and efficacy up to six years of life, in the context of the treatment of gestational diabetes.

Abstract

Gestational diabetes mellitus (GDM) has an incidence of 7.6%. Insulin is the standard treatment but metformin, which crosses the placental barrier, has become an easy-to-administer alternative, although its long-term effects remain uncertain. **Objective:** To evaluate weight and height development up to 6 years of age of children born to mothers with GDM treated with metformin and compare them with those treated with insulin. **Patients and Method**: A retrospective cohort study was conducted at the *Hospital Italiano de Buenos Aires* (2015-2018), including children born to mothers with GDM treated with metformin or insulin. Newborns of mothers without pharmacological treatment were excluded. Maternal characteristics such as age, body mass index (BMI) at the beginning of pregnancy, weight gain, first pregnancy, pregnancy outcome, and treatment were evaluated, as well as the newborn characteristics such as large for gestational age (LGA), small for gestational age (SGA), and preterm. Weight and height development controls were conducted at 6, 12, 24, 48, and 72 months, standardized in Z-scores. Inverse Probability of Treatment Weighting (IPTW) and Generalized Estimating Equations (GEE) were used. **Results**: A total of 187 newborns were included; with IPTW showing good covariate balance between groups. No significant differences were observed in the Z-scores of BMI, weight, and height between the groups. **Conclusions**: Both insulin and metformin have similar effects on the weight and height development of children during the first 6 years from birth, born to mothers with GDM. Further research is needed to confirm these results.

Keywords:
Gestational Diabetes Mellitus;
Insulin;
Metformin;
Growth;
Cohort Study

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Introduction

The high prevalence of diabetes globally, and its increasing incidence in pregnant women, has prompted new research data on the relationship between blood glucose and pregnancy[1]. An increase in the incidence of gestational diabetes mellitus (GDM)[2] has been observed, currently reaching 7.6%[3].

Regarding the treatment, insulin remains the standard of reference for cases that do not respond to non-pharmacological measures, since it does not cross the placental barrier.[4] However, in recent decades, there has been an increase in the prescription of other drugs, such as metformin, which is recommended for patients with GDM according to the guidelines of the National Institute for Health and Care Excellence (NICE)[5] and the American College of Obstetricians and Gynecologists (ACOG)[6]. Metformin is presented as an easier alternative to insulin in pregnancy; however, unlike insulin, metformin does cross the placental barrier[7].

Recent evidence shows that metformin reduces placental energy production, an essential factor for adequate fetal growth[8]. As a result, offspring exposed to metformin during gestation are at a higher risk of being born small for gestational age (SGA) and of showing signs of catch-up growth and obesity in childhood, which increases their risk of developing cardiometabolic diseases in the future[9]. The exact mechanisms by which metformin affects fetal growth and the long-term health of the offspring are not yet fully clarified[7].

Publications addressing postnatal growth trajectories, based on anthropometric measurements such as weight, length, and body mass index are limited[10-15]. Furthermore, the results are variable, with some studies observing no differences and others suggesting that children treated with metformin may have a higher weight[10-14]. Besides, few studies evaluate these data longitudinally[15]. All available publications come from studies conducted in other countries, and there are currently no specific data for Latin America.

The objective of this study is to evaluate the postnatal growth during the first 6 years of life of the children of mothers with GDM who received metformin during pregnancy and to compare it with the growth of those whose mothers were treated with insulin in two hospitals in Argentina.

Patients and Method

Analytical retrospective cohort study of children who survived up to 72 months of age, born to mothers diagnosed with GDM who required pharmacological treatment with metformin or insulin, evaluated at the *Hospital Italiano de Buenos Aires* between 2015 and 2018. Newborns of mothers with GDM who did not require any pharmacological treatment for metabolic control during pregnancy were excluded.

Data were obtained from the electronic health record (EHR). The *Hospital Italiano de Buenos Aires* is a high-complexity university hospital in the Autonomous City of Buenos Aires. It operates as an integrated health network: it has 18 outpatient centers and two high-complexity hospitals. Care in all its settings is recorded in a single EHR per patient[16,17]. It contains all clinical information (health issues, clinical diagnoses, medical progress notes, laboratory results, and studies, among others).

Maternal characteristics assessed included: age at delivery, body mass index (BMI) category at early gestation (normal weight, overweight, and obese)[18], weight gain during pregnancy defined as the difference between the final pregnancy weight and the weight at the date of the last menstrual period in kilograms, whether it was the first pregnancy, route of delivery (cesarean section or vaginal birth), year of delivery (2015 to 2018 cohort), whether the pregnancy was the result of fertility treatment, whether health coverage was provided by a medical plan associated with the institution or another provider, and pharmacological treatment.

In relation to the newborns, it was recorded whether they were large for gestational age (LGA), defined as those with a birth weight greater than the 90th percentile for gestational age and sex[19], or small for gestational age (SGA), with a birth weight less than the 10th percentile for gestational age and sex[20]. For this classification, the Argentine population references for birth weight according to sex and gestational age were used[21]. It was also included whether the birth was preterm, that is, occurred between 22 and 36.6 weeks of gestation[22].

Weight and length/height and BMI measurements were made at five specific time points: at 6, 12, 24, 24, 48, and 72 months of life and were obtained from routine check-ups performed on children by pediatric service physicians following the standards established by the Argentine National Ministry of Health[23]. The 3 measures were standardized into Z scores using the World Health Organization data tables with Argentine Data with the LMS growth method from 0 to 19 years[24,25].

The study protocol was approved by the Ethics Committee for Research Protocols of the *Hospital Italiano de Buenos Aires*.

Statistical analysis

A study conducted at this institution identified 582 women with GDM between 2015 and 2018, of whom 229 received pharmacological treatment[3], and of these, 111 had children with pediatric follow-up at the *Hospital Italiano* after birth. From these data, it was estimated that at least 100 children could be included in the study. Quantitative data were expressed as mean and standard deviation and qualitative data as absolute and relative frequency in percentages.

Due to the observational character of this study, the non-random assignment of drug treatment (metformin or insulin) administered to pregnant women may introduce biases, since there are systematic differences between the groups compared. To control these differences and to estimate more precisely the effect of drug treatment, the Inverse Probability of Treatment Weighting (IPTW)[26] was used. We estimated the propensity score for each participant and assessed the overlap of covariates between treatment groups using a common support plot (Figure 1) and a Love Plot to assess the effectiveness of IPTW in balancing covariates between treatment groups (Figure 2). Subsequently, inverse probability weights of treatment were calculated for each individual. Finally, these weights were used in a logistic regression to estimate the treatment effect on the outcome of interest. The STATA 13 software (StataCorp LLC, Texas, USA) was used for the analysis.

Generalized Estimating Equations (GEE) analysis[27] was used to assess the change in age- and sex-adjusted BMI (Z- BMI), age- and sex-adjusted weight (Z-weight), and age- and sex-adjusted length/height (Z-length/height) scores over time in offspring of women with GDM treated with insulin or metformin. The model was constructed with an exchangeable correlation structure, using an identity link for the outcome variables. Treatment group (insulin or metformin), IPTW, time (6, 12, 24, 48, and 72 months), and the interaction between treatment group and time were included as covariates. Interactions were assessed using the ANOVA F test for repeated measures. In addition, we adjusted for other potentially confounding variables, such as having been an LGA or SGA newborn and exclusive breastfeeding. A statistical significance level of less than 0.05 was considered. The analysis of the GEE model was performed with R software version 4.3.3.

Results

A total of 459 healthy living newborns of mothers with GDM were evaluated. Finally, 187 newborns of women with GDM who were treated with insulin or metformin in addition to diet were included. Table 1 describes maternal and newborn characteristics, and conditions in the first six years of life according to metformin or insulin treatment received.

The IPTW showed a good overlap over most of the range of propensity scores, indicating adequate common support (Figure 1). The adjustment showed that the covariates were well balanced and the IPTW was effective (Figure 2).

Considering BMI, weight, and length/height Z-scores, GEE analysis revealed that there was no significant difference in the change in Z-BMI, Z-weight, and Z-length/height scores between sons and daughters of women treated with insulin or metformin (treatment and time interaction for Z-BMI F 0.602 p = 0.661, for Z-weight F 0.47816 p = 0.7518, and for Z-length/height F 1.771 p = 0.13197) (Figure 3A, 3B, and 3C).

Discussion

This study evaluated newborns born to mothers with GDM, who received pharmacological treatment with insulin or metformin. In several studies, metformin appears to be safe for use in pregnancy and to reduce the incidence of some maternal complications such as preeclampsia and cesarean section and fetal/

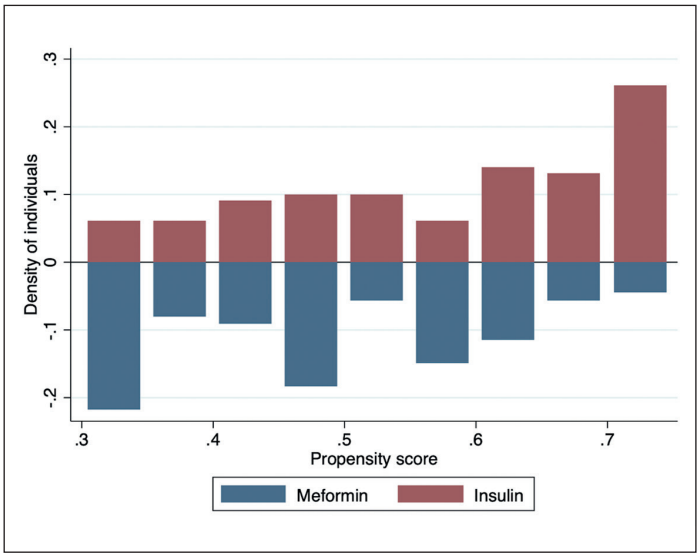

Figure 1. Distribution of propensity scores for the groups treated with metformin and insulin. There is substantial overlap across most of the range of propensity scores, indicating adequate common support. The X-axis shows the estimated propensity scores for each individual in the study, while the Y-axis represents the density of individuals with each propensity score in the metformin and insulin groups.

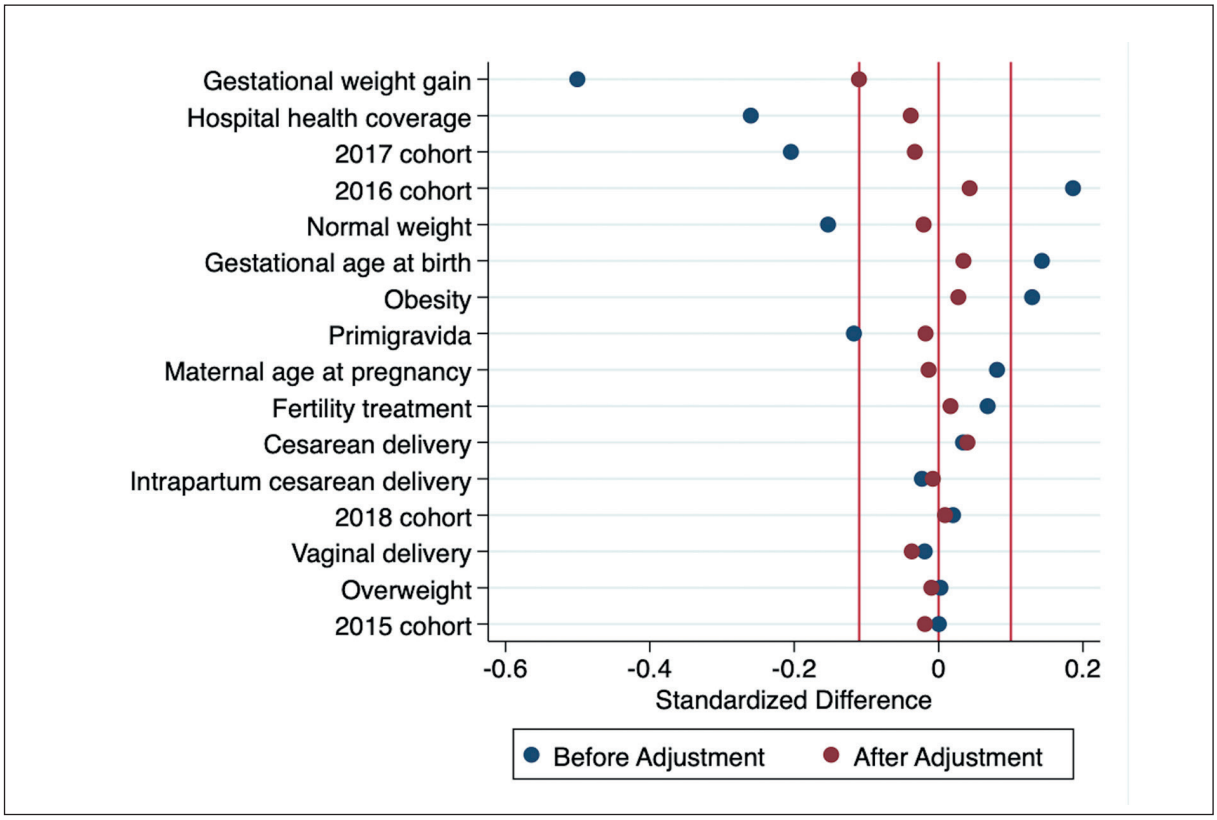

Figure 2. Love Plot: Standardized differences of covariates between treatment groups before and after applying IPTW weights. Standardized differences are calculated as the difference in covariate means divided by the pooled standard deviation of both groups. The X-axis represents the magnitude of the standardized differences in covariates between treatment groups. A standardized difference of less than 0.1 (10%) is considered indicative of good balance. The Y-axis lists the covariates adjusted for in the analysis. Blue dots (Before weighting): represent the standardized differences between treatment groups prior to applying IPTW weights. Red dots (After weighting): represent the standardized differences after applying IPTW. Dots should move closer to zero, indicating that covariates are balanced between groups. The red vertical lines at ±0.1 represent the acceptable threshold for standardized differences. The adjustment suggests that covariates are well balanced and that IPTW was effective.

neonatal complications such as macrosomia or LGA newborns, neonatal hypoglycemia, and hospitalization in neonatal intensive care units[28,29]. The longitudinal analysis found no significant differences in the change in Z-BMI, Z-weight, and Z-length/height scores between the offspring of women treated with insulin or metformin, indicating that both treatments have similar effects on postnatal growth. This has been demonstrated in other studies[11,12,15].

In contrast, other research observed that children whose mothers received metformin had greater weight and length/height without differences in BMI[10], and a meta-analysis of 2 clinical trials demonstrated differences in BMI in children aged 5-9 years, and no difference in absolute weight and length/height[14]. It should be noted that all the studies found in the literature did not adjust for factors that could have influenced growth, such as diet and physical activity; the only adjustment made was for the type of pharmacological treatment received by the pregnant woman, randomizing such treatment in clinical trials or adjusting for maternal characteristics in observational trials.

This study has some limitations. First, the observational nature of the study may introduce biases, and the relatively small sample and concentration in a single center limit the generalizability of the results. Second, it was not possible to evaluate other measures of body composition; only one study performed these measurements[14]. Finally, adjustments for factors inherent to the children that might have influenced their growth were also not performed. In this sense, no study in the literature performed this type of adjustment[10-14].

In addition, this research has strengths. It is one of the first in our country and Latin America to use longitudinal data, that is, a design that allows the evaluation of variations over time, in contrast to previous studies that only analyze data at a single time point[10-14].

Table 1. Maternal and newborn characteristics and conditions during the first six years by type of gestational diabetes treatment

	Insulin n = 87	Metformin n = 100
Maternal characteristics		
Mean age at delivery (SD)	34.6 (5.3)	35.1 (5.5)
HIBA health plan (n %)	53 (60.9)	48 (48.0)
Year of cohort entry (n %)		
2015	20 (23.0)	23 (23.0)
2016	19 (21.8)	30 (30.0)
2017	27 (31.0)	22 (22.0)
2018	21 (24.1)	25 (25.0)
Primigravida (n %)	30 (34.5)	29 (29.0)
Fertility treatment (n %)	7 (8.0)	10 (10.0)
Pre-pregnancy BMI (n %)		
Normal weight	24 (27.6)	21 (21.0)
Overweight	26 (29.9)	30 (30.0)
Obesity	37 (42.5)	49 (49.0)
Mean weight gain (SD)	8.1 (5.5)	5.3 (5.6)
Delivery outcome (n %)		
Cesarean section	49 (56.3)	58 (58.0)
Intrapartum cesarean section	12 (13.8)	13 (13.0)
Vaginal delivery	26 (29.9)	29 (29.0)
Mean gestational age (SD)	37.8 (2.0)	38.03(1.6)
Newborn characteristics		
Mean birth weight (SD)	3173.2 (639.2)	3214.9 (515.3)
Neonatal complications		
LGA (n %)	19 (21.8)	19 (19.0)
SGA (n %)	6 (6.9)	3 (3.0)
NICU admission (n %)	24 (27.6)	14 (14.0)
Exclusive breastfeeding (n %)	19 (21.8)	27 (27.0)
Conditions in first six years		
At least one condition (n %)	11 (12.6)	11 (11)
Chronic corticosteroid use (n %)	1 (1.1)	(1.0)
Cardiac[b] (n %)	0 (0)	1 (1.0)
Respiratory c (n %)	0 (0)	1 (1.0)
Neurological d (n %)	2 (2.3)	3 (3.0)
Another[f] (n %)	11(12.6)	8 (8.0)

[a]Exclusive breastfeeding or formula feeding during the first 6 months after birth. [b]Kawasaki. [c]Cystic fibrosis. [d]Epilepsy of various etiologies. SD: Standard deviation. HIBA: Women with health insurance provided by a medical plan associated with the Italian Hospital of Buenos Aires (HIBA)). n: Absolute frequency. LGA: Large for gestational age. SGE: Small for gestational age. NICU: Neonatal intensive care unit.

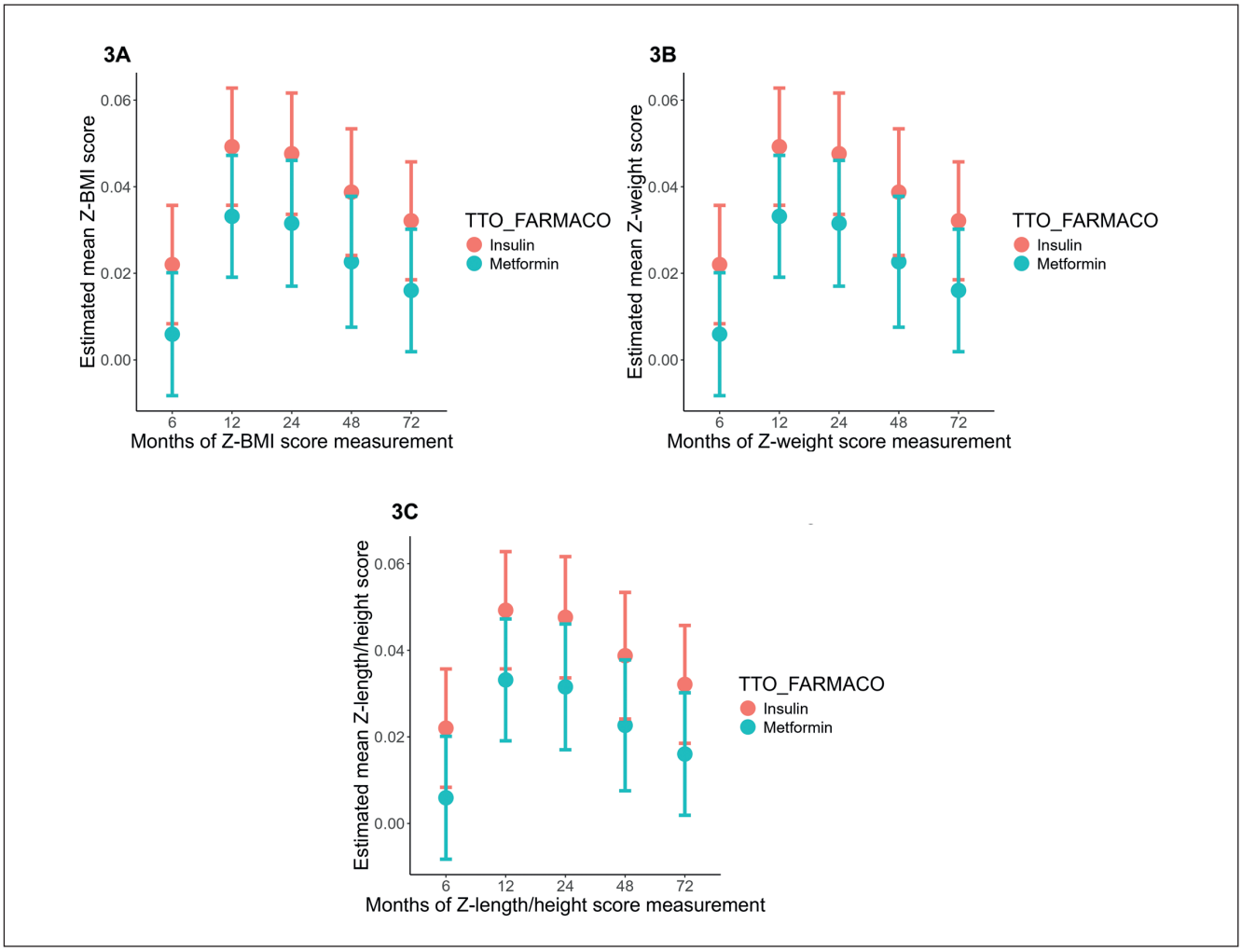

Figure 3. 3A. Longitudinal assessment of body mass index (BMI) Z-score changes according to whether the mother received metformin or insulin during pregnancy; 3B. Longitudinal assessment of weight Z-score changes according to whether the mother received metformin or insulin during pregnancy; 3C. Longitudinal assessment of length/height Z-score changes according to whether the mother received metformin or insulin during pregnancy. The figures show the standardized mean of each anthropometric measurement over time, according to the type of pharmacological treatment received by the mother during pregnancy. Circles represent means, and bars represent standard errors. The model is adjusted for large-for-gestational-age and small-for-gestational-age at birth, exclusive breastfeeding, and IPTW (generated using maternal age at pregnancy, BMI at the time of pregnancy, gestational weight gain, year of pregnancy, whether the pregnancy was achieved through fertility treatment, primigravidity, mode of delivery, gestational age at delivery, and type of health coverage). The parallel trends over time suggest no interaction between time and maternal treatment, meaning there were no significant differences in changes in BMI Z-scores, weight Z-scores, or length/height Z-scores among children born to mothers treated with insulin or metformin.

While some studies have demonstrated significant differences in these point-in-time measures, the longitudinal approach found no such differences. Differences observed in studies comparing a single point in time may not be adequate, as they do not consider previous measurements. This can result in greater statistical power, increasing the ability to detect differences that might not be significant in a longitudinal analysis, which reduces between-subject variability by assessing the same individuals on multiple occasions, providing a more complete picture of trends. In addition, the use of the IPTW method allowed us to emulate a clinical trial, controlling for drug treatment indication bias, and adjusting for other confounding factors.

In conclusion, the findings of this study suggest that both treatments could have a similar impact on offspring's weight and length/height growth up to 6 years from birth. However, further research at other institutions and prospectively is needed to confirm these results.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee, which, according to the study's characteristics, has accepted the non-use of Informed Consent.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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