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ORIGINAL ARTICLE

Congenital anomalies and comorbidities in neonates with Down Syndrome

Anomalías congénitas y comorbilidad en neonatos con Síndrome de Down

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

Down Syndrome is associated with multiple congenital abnormalities and morbidities. Newborns with Down Syndrome often have lower weight and weeks of gestational age at birth, increasing their risk of neonatal comorbidities.

What does this study contribute to what is already known?

We present the first report of a Chilean neonatal series with Down Syndrome since 2009. The information in this work demonstrates the need for multidisciplinary care guided by comprehensive and standardized management protocols.

Abstract

In Chile, Down syndrome has a prevalence of 2.5 in 1,000 live births. These patients present more congenital anomalies and comorbidities than the general population, increasing their hospitalization rate. **Objective**: To describe congenital anomalies and comorbidities of neonates with Down syndrome born and/or hospitalized between 2008 and 2018. **Patients and Method**: We conducted a retrospective review of patient's medical records born and/or hospitalized during their first 28

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days of life between January 1st, 2008, and December 31st, 2018. For each patient, we recorded maternal age, familiar cases of Down Syndrome, pre and perinatal history, genetic study result, as well as age at admission, reason for hospitalization, comorbidities, length of stay, and death. Two patients that had more than 50% of incomplete medical records were excluded. We studied the associations between comorbidities, congenital anomalies, and death. **Results**: 140 in 79,506 newborns (0.2%) were diagnosed at our center with Down Syndrome in their neonatal period. 24.7% were born preterm and 26.4% had low birth weight for gestational age. Morbidities and hospitalizations were present in 83.6% and 90%, of the study population, respectively. The main reason for hospitalization was polycythemia and the most frequent was hyperbilirubinemia. Four patients died (2.9%) and 70.7% presented at least one congenital anomaly, mainly heart disease. Median maternal age was 36 years and 57.1% of mothers were aged 35 or older. **Conclusions**: This cohort of patients with Down Syndrome provides important information for the optimization of their perinatal management and follow-up.

Introduction

Down Syndrome (DS) is a common chromosomal disease, occurring in 1 per 1,000 live births[1]. According to the Latin American Collaborative Study of Congenital Malformations (ECLAMC) for the period 2001-2010, the estimated rate in Chile is 2.5 per 1,000 live births[2]. Considering the national birth rate, approximately 600 patients with DS would be born in Chile each year[3]. Its frequency has been increasing in our country, something that would not be explained only by the increase in maternal age, but until now there are no other proven causes[4].

Patients with DS have higher rates of congenital anomalies (CA) than the general population, specifically heart (54-66%) and digestive ones (3-13%). At birth, they may weigh less than healthy newborns (NBs) and present hyperbilirubinemia, hypoglycemia, and respiratory distress. All of the above, raise hospitalization rates in relation to the general population by 2 to 5 times, particularly in the first year and month of life[5-11]. Early detection of CA (especially heart disease) significantly improves the prognosis of these patients[9,12].

Between 2008 and 2018, the Clínica Dávila in Santiago, attended an average of 7,200 births per year, representing 3% of national births[3]. The consulting population includes Chilean and immigrant populations, from both the public and private health systems.

Few studies are describing Chilean newborns with DS, and there have been no new reports for over 10 years[2,4,6,13,14]. Since an important number of patients are seen at our center, this cohort represents an opportunity to describe the clinical manifestations of this syndrome and to offer them adequate and timely care.

The objective of this study is to describe the morbidity and CA in infants with DS born and/or hospitalized at our center between 2008-2018.

Patients and Method

Type and population of study

We retrospectively reviewed the electronic and paper-based medical records of patients diagnosed with DS during their postpartum or neonatal discharge, born in the clinic, and/or hospitalized in the Neonatology Service, Clínica Dávila in Santiago, Chile, between January 1, 2008, and December 31, 2018. Information on the first 28 days of life was recorded of each patient, considering re-admissions in that period. Two cases were excluded due to their records were more than 50% incomplete. Patients were not followed up after discharge.

For the calculation of the DS birth rate, all live newborns in our center were considered, including those who were subsequently transferred and excluding those who arrived for hospitalization from other institutions. For the analysis of CA and morbidity, all cases were considered (born with or without subsequent referral, and those admitted from other centers).

Variables

Epidemiological

Family history of DS, suspected prenatal ultrasound, prenatal cytological diagnosis, gestational age (GA), and weight gain adequacy according to Alarcón-Pittaluga curves were included[15]. The result of the requested genetic study and information related to hospitalization, including in-hospital death and its cause, were also recorded.

Morbidity

The diagnosis of polyglobulia was established with central venous hematocrit higher than or equal to 65%[16]. Hyperbilirubinemia was diagnosed with capillary bilirubinemia values according to the American Academy of Pediatrics risk curve for NBs over

35 weeks, and for NBs under 35 weeks, we used the curves of the British NICE guidelines[17,18]. Hypoglycemia was confirmed with glycemia levels under 47 mg/dL (2.6 mmol/L) measured with a hemoglucotest strip[19,20]. Congenital hypothyroidism was diagnosed with two consecutive measurements of plasma TSH higher than or equal to 10 mU/L and with a low free T4 level[21]. Respiratory Distress Syndrome was diagnosed by compatible clinical symptoms and oxygen requirements; pulmonary hypertension according to clinical definition and echocardiography[22]; and thrombocytopenia was considered with platelet count less than 150 per 10^9 [23].

Congenital Anomalies

They were recorded in all systems. In heart anomalies, all echocardiographic findings, which included structural anomalies, were considered. The patent ductus arteriosus (PDA) was included since the follow-up time did not allow knowing its outcome. The following were not included: a) PDA in NB younger than 32 weeks or in process of closure, b) minimal atrial septal defect (ASD) or atrial septal defect (VSD), or in process of closure, and c) isolated non-specific findings. Atrioventricular canal (AVC) defect and patients with coexisting VSD and ASD were grouped as "atrioventricular defects" (AVD) since they are considered late stages of atrioventricular canal closure. When there were the four echocardiographic findings together, quantifying them as a single heart defect, they were classified as "Tetralogy of Fallot", otherwise the defects were recorded individually[24].

The data were reviewed by a Neonatologist, Pediatric Cardiologist, Pediatric Resident, and Clinical Geneticist.

Statistical analysis

Categorical variables were expressed as total number and percentages and the continuous ones as mean, median, p25-p75, and range.

The association between total morbidity/CA and death was calculated using logistic regression models, as well as the association between the presence of CA and death. The association between systems affected by CA was analyzed with Fisher's exact test. An alpha value of 0.05 was considered significant. All analyses were performed with Stata software, version 14.2 (StataCorp LLC).

Ethical considerations

This work was approved by the Ethics Committee of Clínica Dávila de Santiago for the review of paper-based and electronic medical records.

The authors declare no conflict of interest.

Results

Between 2008 and 2018, 79,506 live births occured in our center. Out of them, 140 were diagnosed with DS during the neonatal period. The annual rates per 1,000 live births ranged from 1.4 to 2.4 (in the years 2009 and 2018, respectively). During the period studied, there was no tendency towards a rate increase or decrease; the highest rates occur in 2008 and 2018 (2.2 and 2.4, respectively). The rate for the entire period was 1.8 per 1,000 live births.

Two patients (one of each sex) born in our center were excluded from the sample due to incomplete medical records. Two patients were transferred to the Neonatology Service (at 7 and 10 days of age) and were considered for CA and morbidity analysis.

Table 1 shows the general description of the population. There was a 24.7% prevalence of prematurity and 26.4% of low weight for the gestational age. 18 patients (12.9%) met both conditions. Almost all cases showed a normal Apgar score at 5 minutes. The median morbidity in full-term NB was 1, and in premature infants, it was 2. The median CA in both groups was 1.

The median (p25-75) maternal age was 36 years (31-39) with 57.1% of age higher than or equal to 35 years. The percentage of mothers aged 40 and over was 24.3%.

The hospitalization rate was 90%, with a median age at admission of 1 day of life and 6 days of stay. Table 2 shows the main reasons for admission.

83.6% of patients (117/140) presented morbidity and except for one case, all were hospitalized. The main reason for admission was polyglobulia (26/126 hospitalized) (see Table 2), but the most prevalent morbidity during the first month was hyperbilirubinemia (see Table 3).

Four patients died before the first month of life (2.9%) during neonatal hospitalization in our center. The first one (36 weeks of GA) due to severe AVC and sepsis, the second one (32 weeks) due to sepsis, the third one (34 weeks) due to multiple heart CA, laryngotracheomalacia, and respiratory infection, and the last one due to extreme prematurity (24 weeks), heart malformation, and hematological complications. Two of them were small for gestational age (SGA).

70.7 % of the NBs with DS had some CA detected. Cardiac involvement was observed in 64.3% of the population and the most frequent coexisting echocardiographic finding was the patent foramen ovale in 18.6%. A CA was observed in the gastrointestinal, genitourinary, and abdominal wall systems in 9.3%, 6%, and 3.3% of the sample, respectively (Table 4). The median (p25-75) of CA per patient was 1 (0-2). Our popula-

Table 1. General description of the sample population

Total	140
Gender	
Male N (%)	83 (59.3)
Female N (%)	56 (40)
Undefined N (%)	1 (0.7)
Weeks of gestational age	
Median (p25-75)	38 (37-39)
l < 37 weeks of gestational age N (%)	35 (24.7)
Birth weight	
According to gestational age N (%)	
Appropriate	96 (68.6)
Small	37 (26.4)
Large	7 (5)
Weight in grams: median (p25-75)	3015 (2510-3360)
Apgar Score	
1 minute ≤ 6: N(%)	12 (8.6)
5 minutes ≤6: N(%)	2 (1.4)
Prenatal ultrasonografic suspicion of DS	
Yes N (%)	28 (20)
No N (%)	54 (38.6)
Unknown N (%)	58 (41.4)
Maternal age in years	
Median (p25-75)	36 (31-39)
≥ 35 years N (%)	80 (56.3)
≥ 40 years N (%)	34 (23.9)
Hospitalized in Neonatology Unit	
N (%)	126/140 (90)

Table 2. Data on patients with Down syndrome hospitalized in Neonatology, main reason for admission and death rate

Hospitalized patients	N = 126
Age at admission , in days	
Median (p25-75)	1 (1-2)
Range	0-27
Length of stay in days: median a (p25-75)	6 (4-11)
Main reason for admission	N (%)
Polyglobulia	26 (18.6)
Respiratory distress	22 (15.7)
Hyierbilirubinemia	17 (12.1)
Hypoglycemia	14 (10)
Congenital heart disease	13 (9.3)
Digestive tract malformation	11 (7.9)
Low birthweight	7 (5)
Prematurity	6 (4.3)
Pulmonary hypertension	4 (2.9)
Others:	6 (4.3)
Cyanosis	1 (0.7)
Omphalitis	1 (0.7)
Feeding difficulties	1 (0.7)
Study of fetal hydrops	1 (0.7)
Hypothermia, suspicion of connatal infection	1 (0.7)
Not specified	1 (0.7)
Patients deceased during hospitalization N (%)	4 (2.9)
Non- hospitalized patients N (%)	14/140 (10)

tion presented none (29.3%), two (40.7%), and three (22.1%) or more (7.9%) CA.

28 patients (19.9%) had prenatal ultrasound suspicion of DS, two of them (7.1%) were confirmed with prenatal karyotype testing.

A genetic study was performed on 127 patients (90% of the sample). One study was an in situ immunofluorescence analysis (FISH) with probes for chromosome 21 in blood and without subsequent confirmation through a conventional karyotype; therefore, it was not included in the cytogenetic characterization in Table 5.

Association analysis

There was no significant association between neonatal mortality and number of morbidities

Table 3. Prevalence of morbidity at hospital discharge in patients with Down syndrome

Morbidity	N (%)
Hyperbilirubinemia	68 (48.6)
Due to blood group incompatibility	9 (6.4)
Polygobulia	43 (30.7)
Respiratory distress	35 (25)
Transient tachypnea	15 (10.7)
Persistent pulmonary hypertensionn	10 (7.1)
Hyaline membrane disease	4 (2.9)
Cardiopathy	3 (2.1)
Polyglobulia	1 (0.7)
Congenital bilateral quilothorax	1 (0.7)
Not specified	1 (0.7)
Hypoglycemia	27 (19.3)
Thrombocytopenia	18 (12.9)
Anemia	7 (5)
Hypothyroidism	5 (3.6)
Respiratory infection	5 (3.6)
Ophthalmic infection	5 (3.6)
Hypocalcemia	4 (2.9)
Septic shock	4 (2.9)
Urinary tract infection	2 (1.4)
Other	6
Transient myeloproliferative disorder	1 (0.7)
Omphalitis	1 (0.7)
Rectal bleeding	1 (0.7)
Hemolytic disease	1 (0.7)
Congenital Syphilis	1 (0.7)
Hipokalemia	1 (0.7)
Morbities per patient: median (p25-75)	2 (1-2)
Total without morbidityN(%)	23 (16.4)

Table 4. Congenital anomalies detected in the neonatal period according to system involved

N = 140	N (%)
Cardiovascular System	
Total of affected patients	90 (64.3)
Auriculo-ventricular defects	28 (20)
ASD	22 (15.3)
VSD	17 (11.3)
Fallot Tetralogy	3 (2)
Valvular dysplasia	2 (1.3)
Overriding Aorta	1 (0.7)
Tricuspid insufficiency and Pulmonary stenosis	1 (0.7)
PDA	47 (31.3)
Gastrointestinal System I	
Total	13 (9.3)
Imperforate anus	4 (2.7)
Esophageal atresia	3 (2)
Duodenal atresia	3 (2)
Hirschprung's disease	2 (1.3)
Duodenal stenosis	1 (0.7)
Genitourinary System	
Total	9 (6)
Unilateral cryptorchidism	5 (3.3)
Bilateral cryptorchidism	3 (2)
Renal dysplasia	1 (0.7)
Abdominal wall	
Total	5 (3.3)
Umbilical hernia	3 (2)
Inguinal hernia	2 (1.3)
Respiratory system	
Total	1 (0.7)
Laringotraqueomalacia	1 (0.7)

ASD: atrial septal defect. VSD: ventricular septal defect. PDA: persistent ductus arteriosus.

Table 5. Cytogenetic description of patients born in our center with Down syndrome

Total = 140	N (%)
Family history records	
Previous cases of DS in family	4 (2.9)
No previous cases of DS in family	60 (42.9)
Not specified	76 (54.3)
Conventional karyotype testing	
Lymphocytes (post birth)	124/140 (88.6)
Amniocytes (pre natal)	1/140 (0.7)
Chorionic villi (pre natal)	1/140 (0.7)
Available results: s:	125/126
Free trisomy 21	119/125 (95.2)
Trisomy 21 due to translocation	4/125 (3.2)
Mosaic trisomy 21	2/125 (1.6)
Other genetic studies	
FISH for chromosome 21 in lymphocytes (post natal)	1/140 (0.7)
No information available on records	12/140 (8.6)

FISH: Fluorescent in-situ hybridization, with probes for chromosome 21.

(OR 1.8; p = 0.1; CI 95% 1-3.5) or number of CA (OR 1.2; p = 0.7; CI 95% 0.4-3.5).

Premature NBs presented a median of two morbidities and full-term NBs presented one, with no significant difference: OR 1.4 (p = 0.1; 95%CI 1 - 1.9). There was no significant difference in the number of CA between both groups.

It was not possible to analyze associations between the two cases with mosaic DS diagnosis and other variables since there were only two cases that differed widely from each other.

Out of the patients with cardiac involvement, 8/90 (8.9%) also had involvement of the gastrointestinal system. Of the total of patients with gastrointestinal abnormalities, 8/13 (61.5%) showed concomitant cardiac involvement. There was no significant association between the presence of cardiac and gastrointestinal CA (OR 1.2; p = 0.7; 95%CI 0.4 - 3.5).

Discussion

We described a population of patients with DS born or hospitalized during their first month of life at a clinic between 2008 and 2018, where we observed a birth rate of 1.8 patients with DS per 1,000 live births, with a stable trend over that period. This rate was lower than that reported in Chilean series in previous years and is slightly higher than the latest rates in Latin America[2,4,25].

Most patients were male, with an appropriate weight to their GA and an adequate Apgar score at 5 minutes. Most of the patients were full-term NBs and 24.7% were premature, far exceeding the 8% reported in Chilean NBs[26]. This trend presents the same rates as another national series, where 21.2% of 33 patients were premature and would be consistent with the 9-30% of prematurity in international series[5,7,27-30]. It is not clear why NBs with DS present a higher rate of prematurity. An association has been described between congenital defects and shorter pregnancies in the general population, which could explain a percentage of our cases[31,32]. We observed a 74.3% of CA prevalence in preterm births and 67.6% in full-term births, which is a non-significant difference. We suppose that there may also be elements in the population with DS that cause more premature labor such as the detection of CAs, early rupture of membranes, or intrauterine growth retardation, which would be worth exploring in the future[33,34].

NBs with DS are also associated with lower birth weight than the general population[28,30,35]. Our 26.4% was lower than the 30% described in another Chilean cohort and higher than another one with 12% of patients weighing less than 2,000 grams and mean GA of

37.3 weeks[6,13]. This would be explained by the genetic constitution of the individual, CA, and placental and uterine factors[31-34].

The main risk factor for DS is older maternal age, and in our population we found a median maternal age of 36 years. At birth, more than half of patients with DS had mothers aged 35 years or older, and a significant group was 40 or older (23.9%). Only one other Chilean study reports 51.5% of cases with DS and mothers aged 35 or older, contrasting with others in which the percentage of mothers over 35 is significantly lower[4,6,36]. The percentage of children with DS with mothers over 35 years old has increased, which could be due to the postponement of maternity in Chile or an eventual increase in the age of the patients seen in our center[37,38]. The second risk factor for DS is the presence of a chromosomal translocation in a parent that would segregate during the formation of the gametes causing a trisomy 21, family history of DS, or reproductive losses. This type of trisomy was found in four patients with no family history.

Internationally, the option of pregnancy termination influences the birth rate of NBs with DS. This does not affect our figures, since in Chile there is no termination of pregnancy due to DS[36,37].

Neonatal hospitalizations differed from national and international series in their rate and reasons for admission. 90% of the sample was admitted to the Neonatal Service, mostly on their first day of life. This would be similar to 84.8% of another Chilean series with 33 cases[6]. Our hospitalization rate would be similar to the highest rates reported in European countries[27]. The median length of hospital stay was 6 days. The main reason for admission was polyglobulia (18.6%), which contrasts with other series where the main cause of admission was respiratory distress. This was our second reason for admission (15.7%) and in three cases was secondary to congenital heart disease. In the Chilean series of Retamales et al, respiratory distress represents 7% and the main reason for admission, apart from congenital heart diseases, and in international series, it is reported in 32-72% of cases. This percentage probably varies according to the design of each study. Hyperbilirubinemia is usually the second cause of admission in these patients after CAs and its prevalence varies between 23-14%, similar to what was observed in our series[6,28].

83.6% of our population presented at least one neonatal morbidity and most corresponded to frequent pathology of NBs without DS. Reasons for this figure include a) a high percentage of these patients was hospitalized (82.9%), which could be an overestimation of morbidity, and b) a high prevalence of SGA and premature patients, which increase the risk of concomitant pathologies.

An important cause of neonatal hospitalization in patients with DS are CA, and in our series, it is the second most frequent reason for admission overall (17.1%)[10]. During their hospital stay, 70.7% of patients had at least one CA, and 64.3% presented at least one cardiac anomaly, consistent with the 54-66% prevalence of NBs with DS[8]. Those significant PDAs in NBs older than 32 weeks were included since they are frequently associated with DS[36-38]. Although this could overestimate heart disease, only six patients presented PDA as the only heart abnormality, of which three presented it as the only CA, thus we believe that this does not alter our rates significantly. AVCs are the most frequent heart CA in DS (about 42% prevalence)[8,27,41,42]. As with other Chilean series, we observed a lower frequency of AVCs than in international ones (25% and 20%, respectively)[6]. However, and unlike national and international reports, we observe more ASD than VSD[6,8]. The types of anomalies observed in the digestive tract and their presentation rate (7.9%) were in line with what was described in other series[6,28,43].

There are difficulties in comparing our CA types and frequencies with other studies. Firstly, there are few national series that report the same neonatal data in an NB population with DS, except for Retamales et al (6). Secondly, there are large methodological differences between series in the checking method for CA, follow-up time, inclusion/exclusion criteria, and number of cases (43). Finally, there are different criteria for pregnancy termination in other countries. This can lead to all kinds of discrepancies in results, especially in CA. For example, the incidence and type of heart disease - especially complex heart disease - are more frequent in countries without prenatal detection or access to legal termination of pregnancy, reaching up to 60%[8,27,41]. In addition, in countries with prenatal screening and pregnancy termination, the prevalence of VSD and atrioventricular canal begin to resemble each other (30% to 31%, respectively)[41].

There was no statistical significance in the association between systems with CA. This has been reported for cardiac and gastrointestinal systems in a population without chromosomal diseases, but not yet significantly so in DS[41]. However, a heart CA was detected in 63.6% of patients with some gastrointestinal abnormality.

Our neonatal mortality rate was 2.6%, slightly lower than the 3.7-6% described (27.28). During this period, four patients died; two had low birth weight, three had congenital heart disease, and all were premature, in line with the main risk factors for neonatal mortality in DS. Other factors include ethnicity, socioeconomic aspects, and maternal education level[7,10,12]. Chilean data show that the highest mortality rate of patients with DS is in the post-neonatal period[6,44].

In the prenatal period, we can suspect DS by ultrasonographic markers of aneuploidy with or without cytological testing, CA, and/or screening of cell-free fetal DNA in maternal plasma (45). Diagnostic confirmation is made through a karyotype testing in fetal tissue. Out of the total medical records with prenatal information available (N=82), most did not have ultrasound suspicion of DS, and only two were confirmed by prenatal karyotype testing. It should be noted that within that 41% with no history, there could be cases with and without suspicion. We do not know where the patients carried out their prenatal follow-up and what factors influenced the absence of this data in the Neonatal/Perinatal records. Although it is not one of our objectives, we believe it would be interesting to complete this information and analyze these and other aspects of prenatal detection in another study.

Despite having only 125 karyotype test results, the expected distribution of types of cytogenetic abnormalities in DS was maintained: 95% free trisomy 21 (95.2%), 3% by Robertsonian translocation or another chromosomal rearrangement (3.2%), and 2% mosaic DS (1.6%) (46). The karyotype test with lymphocytes helps to establish the diagnosis and risk of recurrence of DS. In a free trisomy, the risk of recurrence depends on the previous number of pregnancies with DS parents and the maternal age. This risk is considered to be lower than 1% but increases with age. In the presence of trisomy 21 by translocation, the risk of recurrence can vary from 1 to 100%, depending on the type of translocation and the parent carrying it, so in these cases, the parents should always be studied (46). The FISH study does not help to distinguish between a free trisomy and a translocation, and despite being a faster test, it does not allow adequate counseling if it is not complemented with karyotype testing.

The sample size did not provide adequate statistical power to explore other associations between neonatal mortality, morbidity, CA and other variables. The lack of information from the prenatal ultrasound control did not allow the establishment of significant associations with prenatal variables. Other weaknesses of this work are its retrospective nature and bias in the selection and categorization of admission diagnoses, morbidities, and CA by our team. In addition, the follow-up time prevents an adequate estimation of congenital cardiopathies by not filtering those non-physiological PDAs and not adequately reporting other CAs and morbidities detectable later on.

Among its strengths is a 10-year follow-up, in a center with numerous annual deliveries and a few loss of cases.

Given the high incidence of patients with DS in our country, in centers with a large number of deliveries, it would eventually be beneficial to establish a multidisciplinary protocol that accompanies the pregnant mother and then the mother-child pair during the suspicion, diagnosis, and monitoring of this syndrome. This group should be made up of specialists in Obstetrics, Midwifery, Neonatology, Pediatrics, Genetics, Kinesiology, and others according to the needs of each patient.

Conclusions

This series describes the main characteristics of Chilean patients with DS in the neonatal period from 2009 to 2018. The birth rate was 1.8 per 1,000 live births, lower than other Chilean series. The patients presented a higher rate of prematurity and low weight, comorbidity, and CA types than the general population. There was a high rate of morbidity and neonatal hospitalization, mostly due to frequent pathology of NB without DS. The second cause of hospitalization were CA, mainly cardiac, followed by gastrointestinal ones. The information from this study is relevant for a better organization of the perinatal management of these patients and their multiple complications.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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