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Birth prevalence of Down syndrome by maternal age in Costa Rica, 1996-2016

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Abstract: Justification: Down syndrome is the most frequent chromosomopathy in Costa Rica and the world, as well as the main cause of intellectual disability. Advanced maternal age is the main known risk factor for this condition. The objective was to know the trend of Down syndrome in live births according to maternal age in Costa Rica. Methods: A prevalence study was made of all Down syndrome cases, born alive in Costa Rica from 1996 to 2016 and reported to the Costa Rican Births Defects Register Center, a national program for the monitoring of congenital defects. The trend and prevalence in live births was determined, according to maternal age: <20, 20-34 and 35 years or more, and according to period: 1996-2007 and 2008-2016. A Poisson regression was carried out, taking as references the group 20-34 years and the period 1996-2002 and the results were compared Wald's chi-square. The prevalence ratio in mothers ⩾35 years and the population attributable fraction was calculated for this stratum. Finally, the trend of Down syndrome was compared with the trend of the specific fertility rate in mothers ⩾35 years. Results: For 1996-2016 the prevalence of Down syndrome in live births was 1.02 x 1000 (95% CI: 0.97-1.07). There was a significant increase from 0.91 (1996-2007) to 1.16 x 1000 (2008-2016), at the expense of the prevalence in mothers ⩾35 years, which increased from 4.27 to 5.44 x 1000; while the fertility rate in these mothers fell significantly from 20.15 x 1000 (95% CI: 20.02-20.28) in 1996-2007, to 15.58 x 1000 (95% CI 15.46-15.70) in 2008-2016. Maternal age mean MS in SD was 32.2 years, versus 25.5 years in the general population (p⩽0.001). The prevalence ratio adjusted by period, in mothers of ⩾35 years, against mothers of 20-34 years was of 8.05 (95% CI 7.25-8.95) and the population attributable fraction was 41.22%. Conclusions: The livebirth`s prevalence of Down syndrome in Costa Rica increased for the study period, at the expense of prevalence in mothers ⩾35 years, although the specific fertility rate in these women fell significantly. The inclusion of the National Children's Hospital - as a national reference institution for this syndrome - within the surveillance network of congenital defects, could be a determining factor in prevalence rise.

Key words: Down syndrome; epidemiology; maternal age; prevalence

1 Justification

Down syndrome (DS) is a clinical disorder caused by trisomy of chromosome 21, the most common of the autosomal aneuploidies, as well as the most common genetic cause of intellectual disability [1]. It is estimated that at least 43% of pregnancies with a confirmed diagnosis result in spontaneous fetal loss or abortion [2].

The global prevalence of DS among live births (LB) is approximately 1 in 700 [1], which varies from 1 per 600 to 2 per 1,000 live births [1,3-6], depending on population characteristics, distribution by maternal age (MA), and fertility rates specific to each MA, the availability of prenatal diagnosis and elective termination of pregnancy (ETP) [4], as well as the characteristics of the surveillance systems themselves [7].

In Costa Rica, the Congenital Disease Registry Center (CREC) analyzed the prevalence of Down syndrome at birth, reporting a rate of 1.03 per 1,000 births (95% CI 0.92-1.13) for 1996-2000, a rate that has remained stable since the CREC's inception in 1987 [8]. Barboza et al.[9] reported a prevalence of DS for 1996-2005 of 0.92 per 1,000 live births and 1.71 per 1,000 stillbirths (fetal death after 20 weeks of gestation). According to the CREC's epidemiological reports (2014-2016) [10-12], DS is the eighth most common congenital defect in the country, with a prevalence ranging from 1.16 to 1.49 per 1,000 births.

Causes of DS include non-disjunction (95%), translocation (2-4%), and mosaicism (2-4%) of chromosome 21 [13,14]. The vast majority of cases are not inherited and result from errors in cell division during the development of the egg, sperm, or embryo; non-disjunction during maternal meiosis accounts for approximately 88% of cases [15,16], while less than 10% of conceptions with trisomy 21 (T21) are of paternal origin [15]. Advanced maternal age (≥35 years) at the time of conception is by far the most significant risk factor associated with the occurrence of DS, a finding that has been confirmed in various populations of different ethnicities and socioeconomic statuses [6,13-17].

In Costa Rica, a country where congenital defects are not listed among the causes of ETP and access to prenatal diagnostic techniques is very limited, there is no up-to-date study determining the prevalence of DS. The aim of this study is to analyze trends in the prevalence of DS at birth in our country in relation to maternal age from 1996 to 2016.

2 Methods

An observational prevalence study was conducted. Cases of DS born between 1996 and 2016, reported to the CREC—the national surveillance system for birth defects—were analyzed congenital conditions, with population coverage of more than 95% of births in the country. The denominators used to calculate prevalence rates (total live births in the country, 1996-2016) were obtained from the online database of the National Institute of Statistics and Censuses [a].

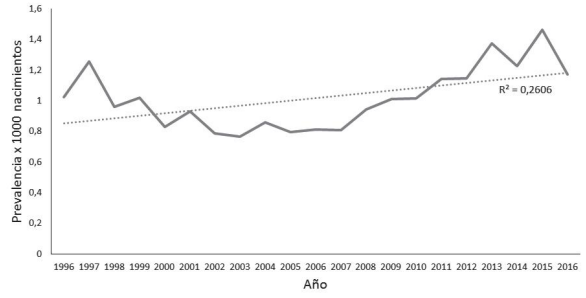

Figure 1. Trend in the prevalence of Down syndrome at birth, by year. Costa Rica, 1996-2016

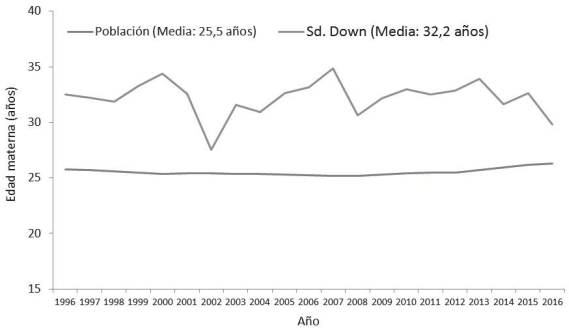

Figure 2. Mean maternal age at birth for cases of Down syndrome and the general population, by year. Costa Rica, 1996-2016

The trend in Down syndrome for 1996-2016 and its prevalence at birth by sex were determined. Two subperiods were used, 1996-2007 and 2008-2016, since in 2008 the reporting period was extended to the first year of life (previously, cases were reported only at the time of birth), and the National Children's Hospital (the national referral center for all cases of DS)

was included in the registry, which increased the registry's sensitivity.

A linear Poisson regression (module: generalized linear models; software: SPSS Statistics version 23) was performed, which is represented as follows:

log (prevalence) = β0 + β1 (period) + β2 (mother's age group)

Based on this regression, the marginal means for DS prevalence were obtained, as well as the relative risks (RR) corresponding to the two subperiods (1996-2007 and 2008-2016) and groupings by maternal age (under 20 years, 20-34 years, and 35 years or older), with their respective confidence intervals (95% CI). The estimates were compared using Wald's chi-square tests, with the first subperiod and the MA group of 20-34 years serving as the reference. A significance level of 0.05 was set.

The proportional distribution of births with DS by maternal age was calculated, as well as the specific fertility rate for mothers aged 35 to 49 years. The average maternal age for total births and births with DS was calculated. Finally, the impact of maternal age on the prevalence of DS was evaluated using the etiological fraction and the population attributable fraction.

This analysis is based on aggregated, non-identifiable epidemiological surveillance data in accordance with Costa Rica's Congenital Malformations Surveillance Protocol.

3 Results

Between 1996 and 2016, 1,589 cases of DS were registered in the CREC among 1,551,676 live births, for a prevalence of 1.02 per 1,000 live births (95% CI: 0.97–1.07). The prevalence by sex showed no significant differences, with a rate of 1.01 per 10,000 live births (95% CI: 0.93–1.07) among boys and 10.11 per 1,000 live births (95% CI: 0.94–1.08) in girls, for a male-to-female prevalence ratio of 0.99.

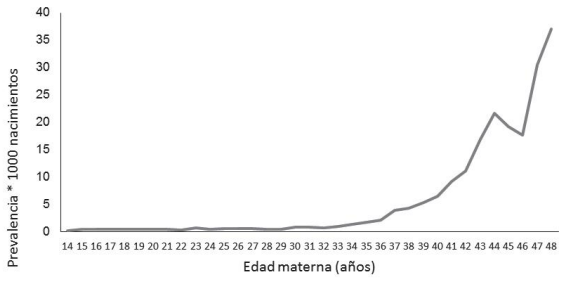

Figure 3. Risk of Down syndrome at birth, by maternal age in years. Costa Rica, 1996-2016

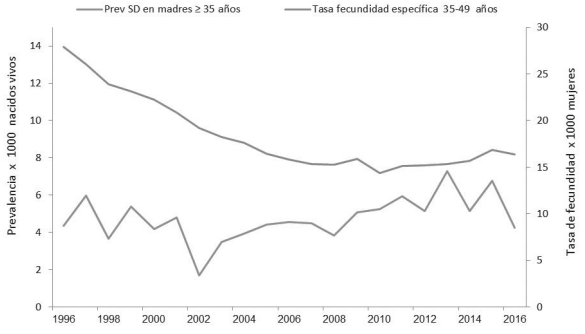

Figure 4. Trend in the prevalence of Down syndrome among mothers aged ≥35 years and the age-specific fertility rate among mothers aged 35-49 years. Costa Rica, 1996-2016

Table 1. Prevalence and percentage distribution of Down syndrome by maternal age group and period, Costa Rica, 1996-2016

Maternal age	1996-2007				2008-2016			
	N	Live births	%	Prevalence per 1000 (95% CI)	N	Live births	%	Prevalence per 1000 (95% CI)
≤19	73	180507	9	0.40 (0.31-0.50)	61	119132	8	0.51 (0.38-0.64)
20–34	333	621569	41	0.54 (0.48-0.59)	311	465894	40	0.67 (0.59-0.74)
≥35	398	93209	49	4.27 (3.85-4.69)	352	64753	46	5.44 (4.87-6.00)
Unknown	13	4331	2	3.00 (1.37-4.63)	48	2281	6	21.04 (15.15-26.93)
Total	817	899616	100	0.91 (0.85-0.97)	772	652060	100	1.18 (1.10-1.27)

A significant increase in SD at birth was observed, from 0.91 per 1,000 live births (95% CI 0.85–0.97) during 1996-2007, to 1.16 per 1,000 live births (95% CI: 1.08-1.25) in 2008-2016.

Figure 1 shows the trend in prevalence rates throughout the analyzed period. The increase in prevalence is primarily driven by children of mothers ≥ 35 years of age. Table 1 shows an increase across all maternal age groups, with the increase being significant only in this group of mothers, which accounted for 47.2% of cases, with no significant changes in their percentage contribution across the different subperiods.

The mean maternal age in the general population was 25.5 years (SD: 0.3; 95% CI: 25.36–25.64), while among mothers of children with DS it was 32.2 years (SD: 1.6; 95% CI: 31.47–32.92) (Figure 2).

The crude and adjusted prevalence ratios by age at first birth and study period are presented in Table 2. The prevalence ratio for mothers over 35 was 8.05 compared to mothers aged 20 to 24.

Figure 3 shows that, starting at 33 years of maternal age, the prevalence of SD begins an exponential increase up to age 49.

When analyzing the trend in prevalence among mothers aged ≥35 and comparing it with the fertility rate in this same maternal age group (Figure 4), it is observed that although the fertility rate has decreased over time, the prevalence of SD in this maternal age group has shown a slight increase in recent years. The fertility rate among mothers aged 35 to 49, by subperiod, showed a highly significant decrease ($p \leq 0.001$), from 20.15 per 1,000 (95% CI: 20.02–20.28) in 1996–2007 to 15.58 per 1,000 (95% CI: 15.46–15.70) for 2008–2016[b].

Finally, taking into account a prevalence of DS in mothers aged ≥35 years of 4.75 per 1,000 live births, compared with a prevalence of 0.60 per 1,000 live births in mothers under 35 years of age, an attributable fraction among exposed individuals of 87.32% was calculated (the percentage of DS cases attributable to maternal age ≥ 35). The population attributable fraction was 41.22% (the percentage of DS cases that could have been prevented if there had been no mothers aged ≥35).

4 Discussion

The prevalence found in the analysis was 1.02 × 1,000 live births (95% CI: 0.97-1.07), which falls within the range reported by the major congenital defect surveillance networks [3-7]. A 26% upward trend was observed, which is statistically significant ($p \leq 0.05$) when comparing the periods before and after the National Children's Hospital (the national referral center for Down syndrome) was incorporated into the CREC in 2008. A significant increase in the specific prevalence was observed only among mothers aged ≥35 years, which impacts the overall rate. There was a slight decrease in the percentage of mothers aged ≥35 years; however, given that there was an increase in the percentage of mothers of

unknown age, it cannot be concluded that this percentage decrease is real (Table 1). All of the above suggests that in Costa Rica, the increase in the prevalence of DS at birth is likely due primarily to an increase in case detection (following the inclusion of the National Children's Hospital).

Several reports worldwide have demonstrated an increase in the total prevalence (including stillbirths, fetal deaths, and live births) of DS that correlates with a percentage increase in pregnancies among mothers aged ≥35 years; this increase may or may not be reflected in the prevalence of DS among live births, depending on access to prenatal diagnosis and fetal echocardiography in each country [3-5,7]. However, our study showed a significant decrease in the fertility rate among mothers over 35 years of age.

In the United States, the prevalence among live births had been showing an increase in two national studies covering subsequent periods, 1979-2003 [18] and 2004-2006 [7]. By 2010, the United States reported a decrease in the prevalence of Down syndrome at birth (1.12 per 1,000 live births); the author concludes that this rate is 39% lower than would be expected in the absence of ETP [19].

The European Registration of Congenital Anomalies (EUROCAT) recorded a prevalence of DS among live births of 0.98 per 1,000 live births for 2012-2016 [20], which is very similar to that reported by the study in Costa Rica. In Europe, the observed prevalence at birth is significantly lower than expected, due to the implementation of prenatal screening for DS and subsequent ETP [20,21]. Similarly, a trend analysis of DS from 1993 to 2004 across 20 population-based registries of the International Clearinghouse for Birth Defects Surveillance and Research [4], showed that, despite an increase in the prevalence of pregnancies with DS (from 1.31 to 1.82 per 1,000 pregnancies), the prevalence at birth remained stable at 0.83 per 1,000 live births. This study also demonstrated a proportional increase in mothers aged ≥35 years from 10.8% to 18.8%, as well as an increase in the ETP for DS, rising from 4.8 to 9.9 per 10,000 pregnancies.

This scenario, in which the prevalence at birth has decreased as a result of advances in prenatal diagnosis and an increase in the incidence rate, has been observed in several countries over the past decade: Spain [22,23], Singapore [24], Thailand [25], and Taiwan [26]. In Taiwan, the prevalence of DS at birth fell from 0.22 per 1,000 live births in 2001 to 0.078 per 1,000 live births in 2010, and the percentage of live-born children with DS dropped to 20.64% after 2008, when second-trimester screening was universally implemented [27].

Studies show that developing countries experience a greater impact on the prevalence at birth when there is limited access to prenatal diagnosis and subsequent ETP, coupled with a percentage increase in mothers aged 35 or older. A study published by Nazer et al.[5] using data from the Latin American Collaborative Study on Congenital Malformations (ECLAMC) shows that the prevalence of DS in South America has been trending upward. For 2005-2008, the ECLAMC reported a prevalence of 1.88 per 1,000 live births for nine South American countries (Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Paraguay, Uruguay, and Venezuela), ranging from 1.32 per 1,000 in Uruguay—similar to the figure reported in our study—up to 2.47 per 1,000 in Chile [28]. On the other hand, Cuba [29] shows a significant downward trend in the prevalence of pregnancies with DS, estimated at 0.98 per 1,000 births, which is not reflected in the prevalence of live birth (0.78 per 1,000), due to a slight decrease in the overall fertility rate, but mainly due to the existence of the National Program for Prenatal Cytogenetic Diagnosis, which includes subsequent ETP in confirmed cases.

In our study, 47.2% of cases occurred in mothers aged ≥35 years (while this group accounts for 10% of all births), and there was a relative risk of 8 in mothers aged ≥35 years compared with mothers aged 20-34 years. These data are consistent with a EUROCAT study [3] covering 1990-2009, which demonstrated a percentage increase in Down syndrome among mothers over 35 years of age, as well as in the mean age of mothers, with a prevalence ratio of 5.5 (95% CI 5.2-5.8) for DS in mothers aged 35-39 compared to mothers aged 25-29, which increased to 17.3 (95% CI 16.3-18.4) in mothers over 40

years of age.

In this analysis of Costa Rica, Figure 3 shows how the risk of DS increases as maternal age increases. This is also demonstrated by Morris et al.[30], who compared several published models of DS risk by specific maternal age and concluded that all models predict a risk that rises exponentially starting at age 35. However, it is likely that the risk does not continue to increase exponentially in women over the age of 45, where the results are inconsistent, given the small number of cases of women with pregnancies at those ages.

The main weakness of our study is that, since the data are derived from epidemiological surveillance, specific information on karyotypes is not available, as this is not part of the country's surveillance protocol.

The prevalence of Down syndrome at birth in Costa Rica increased due to the prevalence among mothers aged ≥35 years, even though the specific fertility rate among these women fell significantly. The inclusion of the National Children's Hospital as the national referral center for this syndrome, within the congenital anomalies surveillance network, may have been a determining factor in the increase in prevalence.

Given this evidence, women who wish to become pregnant should be encouraged to do so during their fertile years, when the risk of Down syndrome is lower.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Note:

[a]: http://www.inec.go.cr/poblacion/nacimientos.

[b]: Data from the Central American Population Center (www.ccp.ucr.ac.cr) and INEC (www.inec.go.cr).