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ORIGINAL ARTICLE

Frequency of chromosomal syndromes in the Brazilian population between 2017 and 2021

Frequência de síndromes cromossômicas na população brasileira entre 2017 e 2021

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KEYWORDS

Brazil
Congenital anomaly
Epidemiology

ABSTRACT

Objective: To evaluate the frequency of chromosomal syndromes in the Brazilian population between 2017 and 2021.
Methods: This is an active search of open access databases of the Information System on Live Births (SINASC) from the Brazilian Ministry of Health from 2017 to 2021. For statistical analysis, Analysis of Variance (One-way ANOVA) was followed by the Bonferroni post-test, considering a significant level of $p < 0.05$. The chi-square test was used for correlation analysis.
Results: The underreporting of congenital anomalies in Brazil has decreased over the last few years, showing significant values; however, those numbers varied between regions. The chromosomal syndromes with the highest incidence were Down Syndrome (76.15%), Edwards and Patau Syndromes (14.59%) grouped in the same ICD-10, with the South and Southeast regions, with an average frequency of 0.07%, as the leader in notifications. The maternal variables with a higher incidence of chromosomal syndromes were women over 35 years of age, with 8 to 11 years of schooling, and married.
Conclusion: There was a decrease in the value related to underreporting over the years. The data show a disparity in the notification of chromosomal syndromes between regions and outline the maternal profile of a higher incidence of chromosomal syndromes.

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PALAVRAS-CHAVE

Anomalia congênita
Brasil
Epidemiologia

RESUMO

Objetivo: Avaliar a frequência das síndromes cromossômicas na população brasileira entre os anos de 2017 e 2021.
Métodos: Trata-se de uma busca ativa de bancos de dados de saúde de acesso livre, do Sistema de Informação sobre Nascidos Vivos (SINASC) do Ministério da Saúde do Brasil entre 2017 e 2021. Foi realizada a Análise de Variância (*One-way* ANOVA) seguido do pós-teste Bonferroni, considerando $p < 0,05$. O teste qui-quadrado foi usado para análise de correlação entre as variáveis maternas e risco para o desenvolvimento de síndromes cromossômicas.
Resultados: A subnotificação das anomalias congênitas no Brasil diminuiu ao longo dos últimos apresentando valores estatisticamente significativos, porém apresentou variação entre as regiões. As síndromes cromossômicas de maior incidência foram a Síndrome de Down (76,15%) e Síndrome de Edwards e Patau (14,59%) conjuntas na mesma CID-10, tendo as regiões Sul e Sudeste, com 0,07% de frequência média dos casos, como líderes em notificações. As variáveis maternas nas quais se viu maior incidência de síndromes cromossômicas foram de mulheres acima de 35 anos, com 8 a 11 anos de escolaridade e casadas.
Conclusão: Houve uma diminuição no valor relativo à subnotificação no decorrer dos anos. Os dados evidenciam disparidade na notificação das síndromes cromossômicas entre as regiões e traça o perfil materno de maior incidência de síndromes cromossômicas.

INTRODUCTION

Chromosomal alterations are classified numerically (of the most common incidence) and structural. Both can affect one or more autosomal or sex chromosomes and represent one of the leading causes of miscarriages[1].

Experts state that the ideal age group for conception is between 18 and 35 years, after which the probability of chromosomal errors increases significantly. This relationship is remarkable since pregnant women under 25 years are at less than 2% risk of having a baby with a chromosomal syndrome. In women over 40 years, this risk can reach 35%[2]. Genetic diseases are responsible for many hospital admissions, mental deficits, neurodegenerative diseases, and infertility, significantly influencing health and quality of life. Thus, they are considered a public health problem and need special attention[3].

It is estimated that about 3% of live births worldwide have congenital anomalies, and at least 3.3 million children under 5 years die yearly because of diseases related to these anomalies[4,5]. In Brazil, chromosomal syndromes are grouped within the large group of congenital anomalies, the second leading cause of death among children under five years. Officially, about 24,000 newborns are registered with some anomaly annually[6].

The Live Births Information System (SINASC) is the primary source for notification of live births with congenital anomalies in Brazil through the filling of the field named "Declaration of Live Births" (DNV, in the Portuguese acronym). DNV presents field number 34 of SINASC and is specific for the notification of these diseases, enabling the recording of multiple anomalies[7]. Filling in the field for congenital anomalies is not mandatory in Brazil, but its creation aims to generate a careful record of abnormalities if filled out correctly[8].

The Brazilian Ministry of Health, through Ordinance GM/MS nr. 199 of 01/30/2014 states that the specialized care service is responsible for offering specific diagnostic and therapeutic care for one or more rare diseases on a multidisciplinary basis. The implemented system allows the notification of congenital anomalies, but the lack of filling in the appropriate DNV field makes the typical rates of underreporting cases possible. This scenario leads to failure to identify, direct, treat and monitor patients with these syndromes, and also failure to comply with the ordinance that guarantees diagnosis and treatment, making it difficult to understand the dimension of their demand[9].

In 2017, the Ordinance GM/MS nr. 3,502 of 12/19/2017 was published, establishing the strategy for strengthening surveillance and care actions for children diagnosed or suspected of having congenital syndromes associated with infection by the Zika virus (SCZ) and other syndromes caused by syphilis, toxoplasmosis, rubella, cytomegalovirus, and herpes virus, of national character. In this, children affected by the Zika virus are included in the notification of congenital anomalies in a specific way[10].

The notification of chromosomal syndromes presents great importance within the health surveillance program in Brazil, as it contributes to the prevention and care of these malformations. Given this scenario, this work identifies, through an active search in a public health database, the frequency of chromosomal syndromes in the Brazilian population between 2017 and 2021, the panorama of notifications and the main risk factors related to maternal-gestational behavior for its development.

METHODS

Free access data from the SINASC was used through the website available on the Monitoring Panel for Congenital Malformations, Deformities, and Chromosomal Anomalies from the Brazilian Ministry of Health (http://svs.aids.gov.br/dantps/centrais-de-conteudos/paineis-de-monitoramento/natalidade/anomalias-congenitas) between 2017 and 2021[11].

The collected epidemiological data were filtered by year (2017, 2018, 2019, 2020, and 2021) in the

available tab for selecting the reference year. The filter "(Q90-Q99) Chromosomal anomalies not classified elsewhere" was added in the indicator tab. In the Visualization tabs, filters were added by geographic location (North, Northeast, Midwest, Southeast, and South), maternal age group (0 to 14, 15 to 19, 20 to 24, 25 to 29, 30 to 34, 35 to 39, 40 a + and Blank/Unknown), mother's education (None, 1 to 3 years, 4 to 7 years, 8 to 11 years, 12 years and over and Blank/Unknown) and mother's marital status (Single, Married, Widow, Legally Separated/Divorced, Stable Union and Blank/Unknown).

Data were categorized according to the International Classification of Diseases (ICD-10), limiting the indicators " (Q90-Q99) Chromosomal anomalies not classified elsewhere", location, and maternal variables[12]. There was no need to exclude any data during the collection process.

The value for underreporting is the result of the relationship between the number of fields left in "blank/unknown" and the total number of live births per Brazilian region. The value relative to the frequency concerns the relationship between the number of congenital anomalies reported and the total number of live births per region.

For statistical analysis, tests were performed to compare two or more different groups using analysis of variance (one-way ANOVA) followed by the Bonferroni post-test. The chi-square test was used for the association test between the categorical variables. Significant differences were determined considering the significance level at $p < 0.05$ (95% confidence interval). The graphs and the data obtained were analyzed using GraphPad Prism software version 5.0.

RESULTS

Table 1 contains the number of live births in Brazil in the last 5 years and their respective situations regarding filling in the notification field of congenital anomalies in the DNV. There was a decreasing variation in the value related to underreporting, with statistical significance comparing 2017 with the other years.

Figure 1A shows an underreporting variation rate, showing statistical significance over the last 5 years. In the Southeast region, the values between 2017 and 2019 did not show significance; in the South region, there was no significance between 2017 and 2018. The South and Northeast regions showed an increase ($p < 0.001$) in underreporting over the years when referred to 2017, while the North and Midwest regions showed a decrease ($p < 0.001$). The Southeast region was the only one to show the maintenance of values related to underreporting over the years mentioned.

Figure 1B shows data on the notification frequency of chromosomal syndromes in Brazil; statistical significance ($p < 0.001$) was observed only between 2017 and 2021. It is possible to observe that, in the Northeast region, there was no statistical difference between the mentioned years. In the Southeast region, there was no significance between 2017 and 2018, and there was a significant decrease ($p < 0.01$) in the reported frequency over the years. The years that did not show statistical significance compared to 2017 are in black on the graph. In the North region, there was no significant statistical difference in the total number accumulated between 2017 and 2021. The other years alone presented a significant result ($p < 0.001$) compared to 2017, showing a frequency increase in the North and Midwest regions. The South region only showed statistical significance ($p < 0.01$) between 2017 and 2021.

Table 2 shows the frequency of chromosomal syndromes by region, corresponding to the number of cases reported in each region concerning the total number of cases in Brazil. Thus, it is possible to observe that the Brazilian region with the highest incidence of cases of chromosomal syndromes was the South, with an average frequency of 0.070% cases, followed by the Southeast with 0.066%. The Northeast region appears as the third region with the highest notification of these syndromes, with an average of 0.038%, followed by the Midwest (0.037%) and the North (0.031%).

According to Table 3, the most frequent chromosomal syndrome reported in Brazil is Down syndrome (Q90), corresponding to 76.15% cases, followed by Edwards syndrome and Patau syndrome (Q91) under the same ICD-10, with an incidence of 14.59%. Other chromosomal anomalies not classified elsewhere (Q99) corresponded to the third most reported ICD-10, followed by partial and other trisomies of the autosomes not classified elsewhere (Q92), with 1.25% of notifications. In comparison, Turner syndrome (Q96) was the fifth most reported ICD-10, with an incidence of 1.18% of reported cases.

The data presented in Figure 2 highlight the reported frequency of ICD-10 referring to chromosomal anomalies not classified elsewhere (Q90-Q99) and the most recurrent syndromes corresponding to Down syndrome (Q90), and Edwards and Patau syndromes (Q91). In Brazil's overall panorama, there was a notification variation of these syndromes between the years, with statistical significance ($p < 0.001$).

Table 1 — Number of live births with or without congenital anomalies in Brazil, between 2017 and 2021.

Congenital anomaly	2017	2018	2019	2020	2021	p-value*
Yes	25,287	25,932	24,838	23,320	16,447	
No	2,832,634	2,854,738	2,770,603	2,651,944	1,974,346	
Blank/Unknown	65,614	64,262	53,705	50,761	33,010	
Total	2,923,535	2,944,932	2,849,146	2,726,025	2,023,803	**p < 0.05**
Value related to underreporting	2.24%	2.18%	1.88%	1.86%	1.63%	
Frequency-related value	0.86%	0.88%	0.87%	0.86%	0.81%	

***chi-square test.

	2017	2018	2019	2020	2021
Midwest	7.90%	6.80%	5.05%	2.88%	2.10%
South	0.75%	0.76%	0.91%	1.21%	1.04%
Southeast	1.67%	1.78%	1.65%	1.78%	1.60%
Northeast	2.52%	2.38%	1.92%	1.81%	1.68%
North	1.13%	1.30%	1.40%	2.30%	2.00%
Brazil	2.24%	2.18%	1.88%	1.86%	1.63%

	2017	2018	2019	2020	2021
Midwest	0.65%	0.71%	0.72%	0.70%	0.71%
South	0.82%	0.82%	0.83%	0.83%	0.78%
Southeast	1.06%	1.07%	1.00%	0.99%	0.92%
Northeast	0.79%	0.79%	0.82%	0.81%	0.81%
North	0.59%	0.65%	0.70%	0.64%	0.59%
Brazil	0.86%	0.88%	0.87%	0.86%	0.81%

Figure 1 — Chromosomal Syndromes notification in Brazil from 2017-2021. A) Underreporting of Chromosomal syndromes by Brazilian region show a decrease between 2017 and 2021. There was no significant decrease in the Southeast region between 2017 and 2019 and in the South region between 2017 and 2018. B) Values related to the frequency of notification of chromosomal syndromes by Brazilian region, with statistical significance only between 2017 and 2021. The elements marked in black correspond to the years that did not show significance ($p > 0.05$). *P*-value by the One-way ANOVA test followed by the Bonferroni post-test.

Table 2 — Frequency of notification of chromosomal syndrome in relation to the total number of live births by region.

Brazilian Regions	2017	2018	2019	2020	2021
North					
Live births	312,682	319,228	313,696	300,532	225,982
Chromosomal syndromes	81	109	102	91	76
Frequency (%)	0.026	0.034	0.033	0.030	0.034
Northeast					
Live births	817,311	836,850	805,275	769,732	578,302
Chromosomal syndromes	269	295	324	302	253
Frequency (%)	0.033	0.035	0.040	0.039	0.044
Southeast					
Live births	1,151,832	1,147,006	1,102,997	1,051,138	766,717
Chromosomal syndromes	731	760	744	757	495
Frequency (%)	0.063	0.066	0.067	0.072	0.065
South					
Live births	397,604	395,857	386,097	374,458	280,715
Chromosomal syndromes	237	299	286	280	194
Frequency (%)	0.060	0.076	0.074	0.075	0.069
Midwest					
Live births	244,106	245,991	241,081	230,165	172,087
Chromosomal syndromes	73	100	78	103	63
Frequency (%)	0.030	0.041	0.032	0.045	0.037

Table 4 shows increasing predominance in the number of chromosomal syndromes, proportional to the increase in maternal age, reaching the peak of occurrences between 35 and 39 years ($p < 0.0271$). The same occurred when analyzing the years of maternal schooling and its association with chromosomal syndromes; it was observed an increase in the number of cases, reaching a peak of occurrence between 8 and 11 years of schooling ($p < 0.0021$). When observing the mother's marital status, the highest number of cases concentrated on married women was identified ($p < 0.0487$), followed by single women and women in stable relationships, respectively.

DISCUSSION

Chromosomal syndromes are genetic alterations that correspond to about 5% of all human conceptions, and their aggravations are responsible for a good proportion of all hospital admissions, mental deficits, neurodegenerative diseases, and infertility[13]. This study highlighted an increase in the notification of congenital anomalies between 2017 and 2021 in the Brazilian population, which may represent better attention in the diagnosis/notification of these syndromes or a change in epidemiological behavior in our country population. In primary care, only Down Syndrome is part of the group

Table 3 — Number of cases of chromosomal syndromes distributed per year, according to ICD-10.

Indicator	2017	2019	2018	2020	2021	%
(Q90-Q99) Chromosomal abnormalities not classified elsewhere	1,391	1,563	1,534	1,533	1,081	100
(Q90) Down Syndrome	1,071	1,200	1,162	1,151	824	76.15
(Q91) Edwards and Patau syndromes	199	226	230	228	153	14.59
(Q92) Other trisomies and autosomal partial trisomies, not elsewhere classified	12	13	22	24	18	1.25
(Q93) Monosomies and deletions of autosomes, not elsewhere classified	5	5	7	8	9	0.48
(Q95) Balanced rearrangements and structural markers, not classified elsewhere	1	1	1	0	0	0.04
(Q96) Turner Syndrome	12	21	20	17	14	1.18
(Q97) Other sex chromosome abnormalities, female phenotype, not classified elsewhere	3	2	7	6	4	0.31
(Q98) Other sex chromosome anomalies, male phenotype, not classified elsewhere.	11	10	5	10	6	0.59
(Q99) Other chromosomal anomalies, not classified elsewhere	84	93	90	96	58	5.93

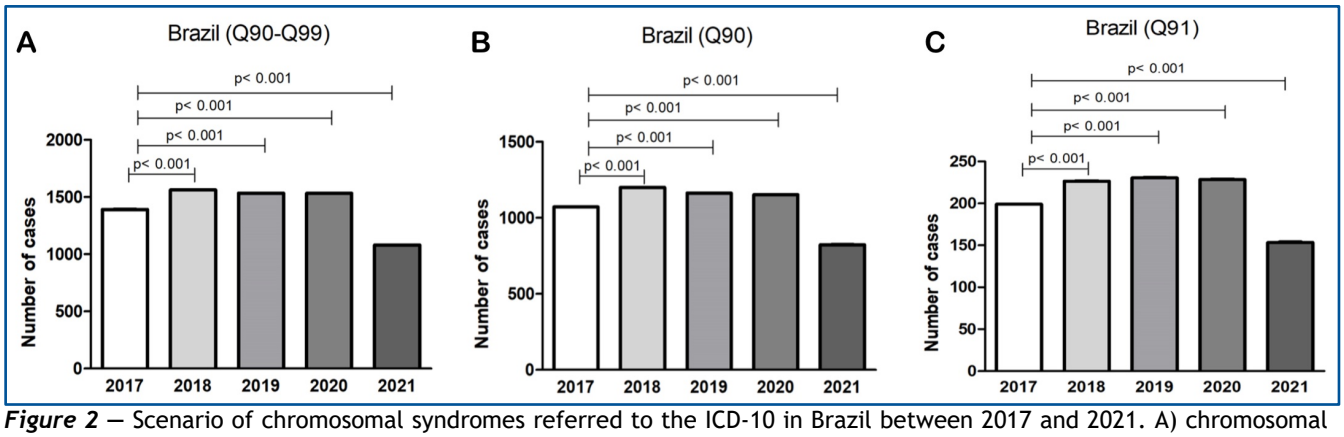

Figure 2 — Scenario of chromosomal syndromes referred to the ICD-10 in Brazil between 2017 and 2021. A) chromosomal anomalies not classified elsewhere (Q90-Q99). B) Down syndrome (Q90) number of cases; and C) Edwards and Patau syndromes (Q91) number of cases notification. *P*-value by the One-way ANOVA test followed by the Bonferroni post-test.

of priority congenital anomalies because of its higher frequency, which can be associated with greater ease of diagnosis[14].

The DNV field 34 is an essential tool for epidemiological monitoring of congenital anomalies in the country, but birth defects are still underreported due to the non-completion or poor completion of this field[15]. The data described here point to an average of 2% of non-completion of the respective field between the mentioned years (2017–2021). Another study in which SINASC data were evaluated between 2006 and 2010 observed that the absence of filling out the information about congenital malformations was 1.5%[16]. The data collected through the DNV allow characterizing the incidence of specific congenital malformations; thus, they contribute to implementing new public policies that meet the needs of live births with congenital anomalies[17].

The reliability of the information on chromosomal syndromes contributes to the identification of risk factors, frequency, epidemiological profile, and referral to specialized services, improving individuals' quality of life[18,19]. The World Health Organization, to establish prevention and care for congenital anomalies, developed basic actions for creating national health surveillance programs[20].

Guimarães et al.[21], in a study associating the information available in the databases of live births and infant death, highlighted the need for better precision in the diagnosis of chromosomal syndromes by relating the number of deaths to late diagnosis. It is possible to associate the underreporting described in this study as an influence on the accuracy of the diagnosis.

According to information provided in this study, the South and Southeast regions corresponded to the highest notification, with 0.07% of average frequency

Table 4 — Absolute frequency of cases of chromosomal syndromes and their correlation with maternal variables distributed by year. Values in n (%).

Maternal variables	2017 (n†= 1,391)	2018 (n = 1,563)	2019 (n = 1,534)	2020 (n = 1,535)	2021 (n = 1,081)	p-value ‡
Age						
00 a 14	7 (0.5) *	4 (0.3)	3 (0.2)	4 (0.3)	2 (0.2)	0.0271
15 a 19	77 (5.5)	79 (5.1)	88 (5.7)	60 (3.9)	35 (3.2)	
20 a 24	143 (10.3)	165 (10.6)	157 (10.2)	133 (8.7)	98 (9.1)	
25 a 29	152 (10.9)	155 (9.9)	153 (10.0)	145 (9.4)	101 (9.3)	
30 a 34	239 (17.2)	258 (16.5)	248 (16.2)	239 (15.6)	171 (15.8)	
35 a 39	438 (31.5)	505 (32.3)	472 (30.8)	495 (32.2)	339 (31.4)	
40 a +	335 (24.1)	397 (25.4)	413 (26.9)	456 (29.7)	335 (31.0)	
Blank/ Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	
Scholarity						
None	7 (0.5)	13 (0.8)	10 (0.7)	11 (0.7)	5 (0.4)	0.0021
1 to 3 years	29 (2.1)	35 (2.2)	39 (2.5)	42 (2.7)	19 (1.8)	
4 to 7 years	199 (14.3)	201 (12.9)	176 (11.5)	172 (11.2)	99 (9.2)	
8 to 11 years	682 (49.0)	786 (50.3)	744 (48.5)	716 (46.6)	522 (48.3)	
12 or more years	467 (33.6)	523 (33.5)	561 (36.6)	577 (37.6)	429 (39.7)	
Blank/ Unknown	7 (0.5)	5 (0.3)	4 (0.3)	15 (1.0)	7 (0.6)	
Marital Status						
Single	445 (32.0)	497 (31.8)	505 (32.9)	514 (33.5)	358 (33.1)	0.0487
Married	625 (45.0)	727 (46.5)	737 (48.0)	699 (45.5)	477 (44.1)	
Widow	6 (0.4)	2 (0.1)	5 (0.3)	9 (0.6)	12 (1.1)	
Divorced	40 (2.9)	41 (2.6)	33 (2.2)	45(2.9)	32 (3.0)	
Stable Union	259 (18.6)	287 (18.4)	239 (15.6)	258 (16.8)	195 (18.0)	
Blank/ Unknown	16 (1.15)	9 (0.6)	15 (1.0)	8 (0.5)	7 (0.6)	

†Total number of live births with chromosomal syndromes; ‡p-value obtained by the chi-square test; *****Percentage referring to the relationship between the total number of live births with chromosomal syndrome and the reported value for each maternal variable.

related to chromosomal syndromes cases, corroborating with the National Council of Health Secretaries (CONASS), which recorded, in 2007, 156 geneticists distributed unevenly in the country (128 in the South and Southeast regions, 19 in the Northeast, 8 in the Center-West and only 1 in the North)[22]. In a similar study conducted to describe the prevalence of congenital anomalies in five British regions, between 1991 and 1999, Glasgow was the leader in the incidence of congenital anomalies (95% CI 102–116 cases/100 thousand births), followed by the Northern region (95% CI 95.6–103 cases/100 thousand births)[23].

Data related to education in genetics to health professionals indicate that up to 95% of training courses for health professionals in the South region include the subject of genetics in the curriculum. In the case of the Northeast, only 34.74% courses included this subject[24]. This disparity is significant and confirms the CONASS previous reporting. Thus, these data can guide which Brazilian regions demand more significant efforts in genetics training of healthcare professionals.

The results obtained in this study, through the SINASC monitoring panel, indicate Down syndrome as the most frequently reported, followed by Edwards and Patau syndromes, while Turner syndrome does not represent 2% of cases, a result that does not corroborate the literature. Venâncio et al.[25], in a study that analyzed 4,375 karyotypes in Mato Grosso, Brazil, showed that 78.2% of the observed alterations were numerical, 16.5% were structural, and 5.3% presented both structural and numerical alterations. Down Syndrome corresponded for 56.8% of the cases and Turner Syndrome for 16.0%, the second most frequent anomaly. Similar studies reinforce Down syndrome as the most frequent chromosomal syndrome and sex chromosomal anomalies as the second most frequent cause[26-28].

In the present study, the data reported about maternal variables and the chromosomal syndrome notification showed a predominant profile for the incidence of these anomalies, which corresponds to women over 35 years, with more than 8 years of education and married. A review study on risk factors in pregnancy indicated that this profile occurs because of the greater participation of women in society and in the labor market, associated with more accessible resources for control of birth[29].

The ideal age for pregnancy is considered between 18 and 35 years. After that, the chance of segregation errors increases considerably[2]. This relationship can be reinforced since advanced maternal age significantly increases the risk of chromosomal syndromes, other associated comorbidities, and fetal death[30].

A study in Denmark showed that pregnant women aged 40 years and over, compared with women aged 20 to 34 years, had a higher risk of chromosomal abnormalities (3.83% vs. 0.56%, OR 7.44 [CI 99.8 % 5.93–9.34]), miscarriage (1.68% vs. 0.42%, OR 3.10 [99.8% CI

2.19–4.38]), and birth before 34 weeks of pregnancy (2.01% vs. 1.21%, OR 1.66 [CI 99.8% 1.23–2.24]), as suggested by the present study when evaluating relevant maternal variables in the incidence of chromosomal syndromes[31]. In Italy, a study to determine the relationship between maternal age and the prevalence of human embryonic aneuploidy pointed out that the rate of non-euploid embryos was lower (2%-6%) in women aged 26 to 37 years, 33% at 42 years and 53% at 44 years[32].

Given this scenario, it is essential to highlight the need to inform women of reproductive age about the risk factors associated with advancing maternal age. Appropriate professional monitoring in reproductive planning can provide more possibilities and autonomy for decision-making about the appropriate time for pregnancy[33].

Genetic diseases in Brazil are challenging since patients' access to specialized services in public health centers is difficult and, when available, requires a long therapeutic itinerary until a diagnosis is obtained. Additionally, the lack of education of health specialists about these diseases and the scarcity of accredited reference centers make it difficult or impossible for patients to access adequate care, leading them to turn to the private sector[34].

It is necessary to address some limitations of our study. The Birth Monitoring Panels show that the information presented in 2020 and 2021 is preliminary; therefore, the numbers obtained may not reflect the actual scenario for these years[11].Thus, the results found in this study suggest malpractice in the notification of chromosomal syndromes in Brazil since there is a noticeable disparity between the value related to the underreporting of the country's most developed regions and other localities. This may interfere with the frequency of notified and non-reported cases and does not reflect the actual epidemiological situation of the chromosomal syndromes and other comorbidities presented.

CONCLUSION

The data presented in this study show a decreasing variation in the underreporting of cases of congenital anomalies in Brazil between 2017 and 2021, while the frequency of notifications remained stable. The Brazilian region with the highest notification of cases of chromosomal syndromes was the South, followed by the Southeast region. The epidemiological profile related to a higher incidence of chromosomal syndrome cases corresponds to women over 35 years, with more than 8 years of schooling and married, which allows us to mention the need for reproductive counseling and prenatal care for this group. Therefore, it is essential to highlight the importance of adequate case notification of chromosomal syndromes for health surveillance, which dramatically impacts patients' quality of life, their families, and the health system itself.

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