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Rare Chromosomal Diseases: A Challenge of Preventive Genomic Medicine in the Low-Middle Income Countries

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Abstract

Background: A rare disease is any disease that affects a small part of the population. All chromosomal diseases accompany a person throughout life, even if the symptoms do not appear immediately. Many chromosomal abnormalities appear early in life. Thirty per cent of children with rare diseases will die before their fifth birthday. The prevalence of rare diseases may vary between populations, so a disease that is missed in some populations may be common in others. Prevalence, by definition, ranges from 1/1,000 to 1/20,000. Objective: To report the incidence of chromosome abnormalities after establishing a Birth Defects Integrated Center and birth defects surveillance at Harapan Kita NWCHC. Method: Data were collected retrospectively from a cytogenetic laboratory, Harapan Kita NWCHC, between 2010 and 2021. Inclusion criteria were peripheral blood samples sent to the cytogenetic laboratory. Culture failure samples were excluded. Result: We obtained samples from infants in 1042 with clinical suspicion of genetic abnormalities, 98% of whom were successful for analysis. 183 of 392 inborn infants were diagnosed as abnormal, whereas in the group of referred outpatients, 381 of 650 abnormalities were found. In 9% of the cases, a rare chromosomal abnormality was found. Conclusion: It is advisable to perform on an infant with suspected chromosomal abnormalities chromosomal investigations.

Keywords: *Clinical suspected genetic disorders, common and rare chromosomal abnormalities, mortality, low middle-income country*

Introduction

Knowing the presence of a severe congenital abnormality might help to decide on intensive treatment after birth. Preventive genomic diagnosis plays a crucial role in identifying genetic predispositions to diseases, facilitating early intervention and personalized treatment.(Galli 2016; Newson 2022) Genomic literacy and awareness are essential for managing genetic diseases, encompassing diagnosis, the prevention of complications, and therapy.(Hood 2013) Genomic testing enables risk-based long-term planning for more effective disease prevention, reducing diagnostic uncertainty and guiding treatment selection for improved patient outcomes.

The multifaceted challenge of bioethics in low-income and low-setting countries for

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diagnosing chromosomal disorders encompasses various obstacles. Access to quality-assured laboratory diagnosis presents a significant hurdle, leading to delayed or inaccurate diagnoses and ineffective treatments, thereby jeopardizing patient safety.(Olivier et al. 2019; Newson 2022) The absence of local epidemiological data on the birth prevalence and outcomes of chromosomal disorders impedes policy and service development across numerous countries and continents. Additionally, the diagnostic process faces hindrances due to the scarcity of resources in child and adolescent mental health within low-income countries, compounded by the essential role of detailed clinical examinations and inherent difficulties in this context.(Hood 2013; Cho 2015; Lázaro-Muñoz et al. 2015) Inequitable healthcare access and the need for improved case identification techniques further challenge the diagnostic process in low- to middle-income countries.

Historically, the issue of chromosomal abnormalities may not have been a primary concern in a country as populous as Indonesia, with a population exceeding 275 million.(Queremel Milani and Tadi 2023) Healthcare services focused primarily on addressing visibly apparent congenital structural abnormalities. However, data from regional, provincial, and national health offices in Indonesia have revealed that congenital abnormalities constitute a substantial portion of neonatal mortality.(Queremel Milani and Tadi 2023) While significant efforts and resources have been devoted to tackling issues such as prematurity, low birth weight, sepsis, and asphyxia, the hidden problem of congenital abnormalities has taken center stage in neonatal mortality statistics.

Globally, there has been a decline in infant and post-neonatal under-five mortality that is surpassing the reduction in neonatal mortality.(Cordero and Ashley 2012) In recent years, Indonesia has made slow progress in reducing infant and under-five mortality rates, with no improvement in neonatal mortality rates. In 2021, the neonatal mortality rate in Indonesia is expected to reach 11.3 deaths per 1,000 live births, while the under-five mortality rate will be 22.2 deaths per 1,000 live births. This means that the proportion of neonatal deaths compared to under-five deaths has increased from 30% in 1991 to 51% in 2021. (IHDS 1991-2021) Experts believe that this change may be due to congenital abnormalities.

In 2016, a survey conducted in hospitals in Indonesia showed that approximately 15% of newborns in the country were affected by congenital abnormalities. However, the actual number of chromosomal abnormalities is still unknown. (IHS, 2016) Considering this trend, this paper underscores the importance of addressing genetic diseases associated with chromosomal abnormalities as a significant healthcare challenge in Indonesia. Harapan Kita Hospital stands as a model for integrated services catering to congenital disorders, including genetic disorders and chromosomal anomalies. By highlighting this issue, we hope to stimulate further attention, research, and action in addressing genetic disorders and chromosomal abnormalities to benefit our nation's health and well-being.

Method

Data were collected retrospectively from our cytogenetic laboratory and neonatology ward between 2010-2021. Our lab can analyze samples taken from peripheral blood, amniotic fluid, cord blood or other tissues such as products of conception. However, the inclusion

criteria for this paper were peripheral blood samples from within and other referral hospitals in cases of suspected genetic or chromosomal abnormalities or where the cause of the congenital abnormality could not be explained. Chromosomal karyotype analysis and/or chromosomal microarrays were examined in this case. Culture failure samples were excluded.

Result

We received 1042 samples of infants with suspected genetic disorders from 2010-2021. We performed a karyotyping analysis with a success rate of 98% to detect chromosomal abnormalities by looking for genetic causes that might be the background cause of the case. Fifty-four per cent of infants were found to have chromosomal abnormalities – 9% of the group had rare chromosomal diseases (**Figure 1**)

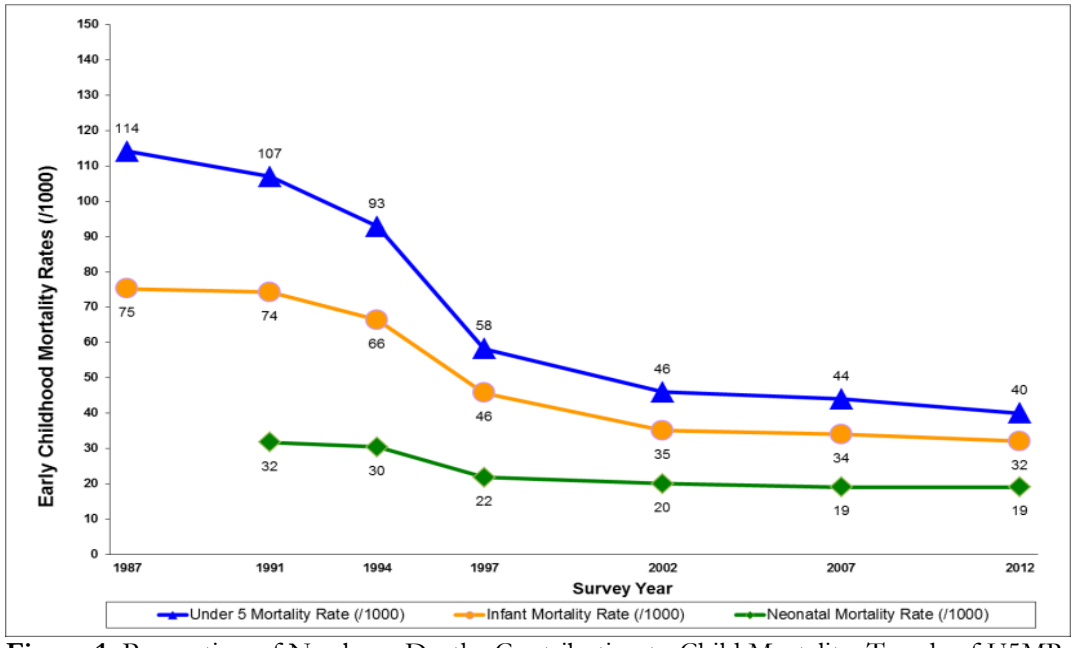

Figure 1: Proportion of Newborn Deaths Contributing to Child Mortality: Trends of U5MR, IMR And NMR, 1991-2015.

Based on the results of our karyotyping analysis, we tried to sort out the disease or group of diseases with a chromosomal background. Ninety-eight per cent of the samples were successfully analyzed. In 46 % of cases, we did not find chromosomal abnormalities. Non-chromosomal abnormalities might cause some of these cases. In some cases with a strong suspicion of genetic abnormalities, we performed a CMA (chromosomal microarray) examination or DNA testing to look for the suspected cause of the accompanying disorder. According to several references we explore, some cases are classified as rare chromosomal abnormalities because these disorders are rarely found (Figures 2 and 3).

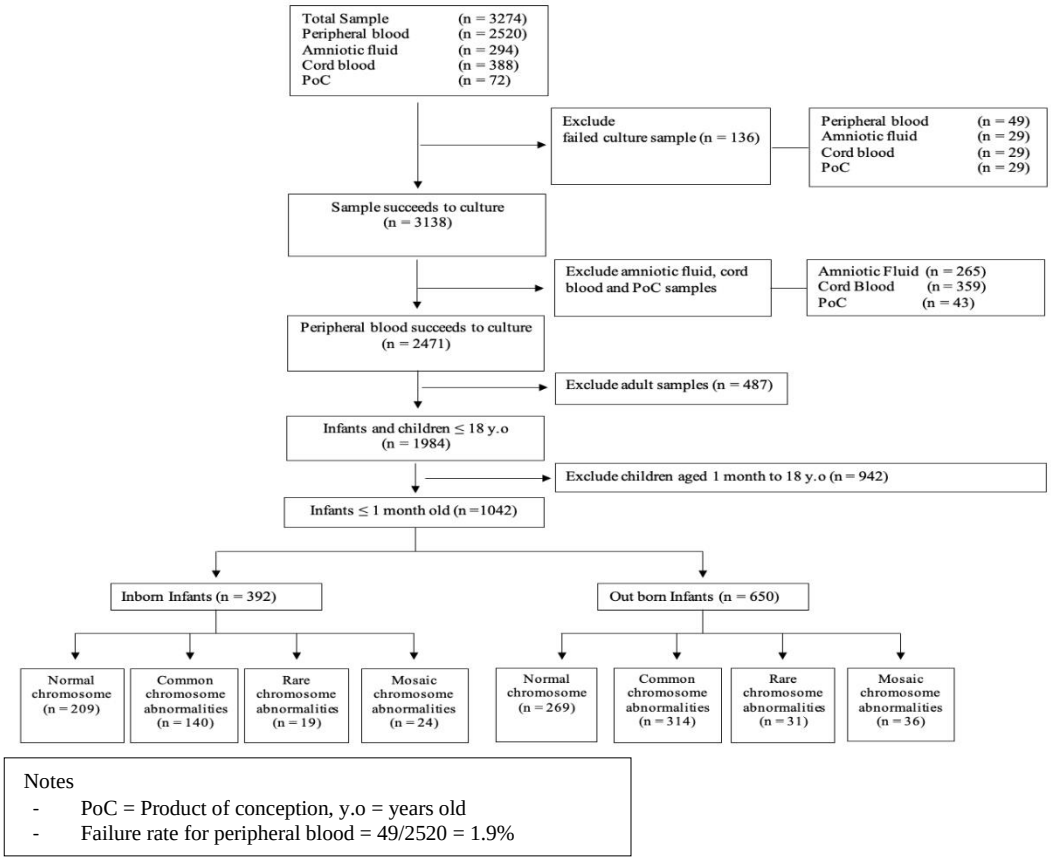

Figure 2: Schematic of Eligible Samples.

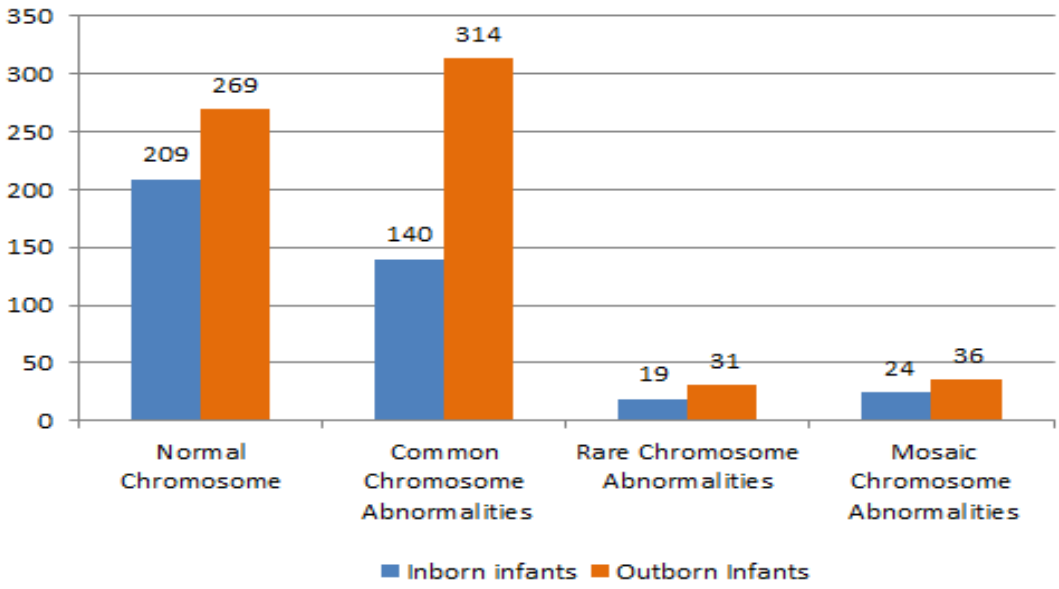

Figure 3: Karyotyping Analysis of Peripheral Blood Sample Based on Clinical Suspicion of Genetic Disorders in Cytogenetic Laboratory Harapan Kita NCWCH 2010-2020 (N= 936).

Table 1 shows the number of cases of chromosomal abnormalities compared with the global prevalence reference. We divide them into common and rare chromosomal abnormalities. Of the 9% of rare disorders encountered, we divided them based on structural abnormalities, uncommon aneuploidy and mosaic disorders.

Table 1: List The Total Number of Patients of Chromosomal Diseases in Indonesian Inborn Babies.

	Disease or group disease based on chromosome karyotyping	Inborn infants (n=392)	Out born infant (n=650)	Global prevalence (/100,000 LB)	Description
	Common chromosome abnormality				
1	Patau Syndrome	10	19	3.7 (1: 27000)	
2	Edwards' Syndrome	46	49	16.7 (1: 6000)	
3	Down Syndrome	80	242	95 (1: 1000)	
4	Turner Syndrome	4	1	5.5 (1: 18.000)	
5	Klinefelter's Syndrome	0	3		
	Rare chromosome abnormality				
1	Structural Abnormality	16	31	-	2 Insertion, 16 deletion, 7 duplication, 1 ring chromosome, 11 translocation, 3 isochromosome, 3 inversion, 4 addition
2	Uncommon Aneuploidy	3	2	-	3 trisomy 9, 1 trisomy 15, 1 marker chromosome
	Mosaic Chromosomal abnormality				
*	Mosaic	24	36	-	

Note: Total Live Birth 2010-2020 Is 20.412/21717 Infants.

*Based on one of the tertiary care hospitals in Indonesia - Harapan Kita National center for women and child's health)

Figure 4**:** shows a significant increase in the number of cases recorded during the second era (2015-2019) compared to the first era (2010-2014). This can be attributed to the establishment of Birth Defects Integrated Center (BIDIC) and the implementation of organized Hospital birth defects surveillance, as well as the strengthening of National Health Insurance at National Women and Children's Health Center (NCWCH) Harapan Kita. Notably, the number of fetomaternal case referrals during this period positively impacted the incidence of congenital abnormalities in newborns, which can greatly improve a fetus' chances of survival. However, the decrease in cases observed during the last era is primarily due to the COVID-19 pandemic, which has understandably shifted healthcare priorities towards treating those affected by the virus.

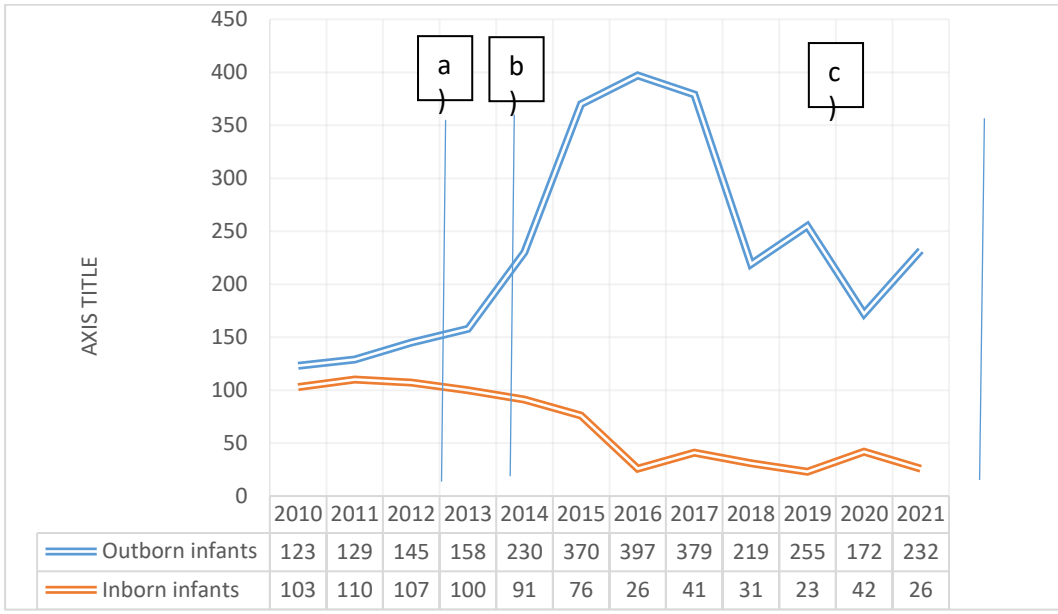

Figure 4 a): The Establishment of BIDIC (Birth Defects Integrated Center) and National Health Insurance **B)** Moh (Minister of Health)/Hospital Surveillance **C)** the Era of the COVID Pandemic.

Table 2. at Harapan Kita NWCHC illustrates the prevalence of birth defects and chromosomal abnormalities. Three eras were analyzed, showing variations among inborn and outborn infants. The latest era had a 2.3% birth defects prevalence, and a 57.3% chromosomal/birth defects case rate surge. There was a sequential increase in rare/chromosomal abnormality rates from 8.5% to 15.3%. These findings indicate dynamic trends in infant health, requiring ongoing monitoring and research.

Table 2: The Common and Rare Chromosomal Abnormalities After the Establishment of BIDIC (Birth Defects Integrated Center) and Birth Defect Surveillance in Harapan Kita NCWCH.

Variable	**First era of 2010 — 2014**		**Second era of 2015 — 2019**		**Third era of 2020 — 2021**	
	Inborn infants	Out born infants	Inborn infants	Out born infants	Inborn infants	Out born infants
Live birth (n)	10411	-	8338	-	2968	-
Birth defect cases (n)	420	785	197	1620	68	404
Normal chromosomal (normal karyotype)	39	97	126	136	44	36
Chromosomal Abnormalities (n)	47	163	98	143	39	72
Rare chromosomal anomalies (n)	4	16	9	11	6	4
Mosaic chromosomal abnormalities	2	12	15	15	7	6
Birth defects prevalence	4.0%	-	2.4%	-	2.3%	-
Rare/chromosomal abnormalities rate	8.5%	9.8%	9.1%	7.6%	15.3%	5.5%
Chromosomal/birth defects case rate	11.2%		49.7%		57.3%	

Discussion

The results of our study revealed a significant number of infants with clinical suspicions of genetic disorders. Out of the total number of suspected inborn infants (392), 183 were diagnosed as abnormal. Similarly, in the group of referred outpatients, 381 out of 650 abnormalities were found. These findings underscore the importance of early detection and diagnosis of genetic disorders in infants. Interestingly, our study found that 54% (1042 samples) of the infants with clinical suspicion of genetic disorders had chromosomal abnormalities, indicating the substantial role of chromosomal anomalies in genetic disorders in infants. Furthermore, 9% of the chromosomal abnormalities identified were rare chromosomal diseases, emphasizing the need for comprehensive genetic testing and evaluation to identify and diagnose these less common conditions.

Challenges in Low- and Middle-Income Countries (LMICs) encompass the implementation of national healthcare insurance programs, where obstacles like extreme poverty, limited knowledge, superstitious beliefs, inefficient payment methods, and drug shortages need addressing for the successful integration of genomic diagnosis. The effectiveness of low and mid-level health workers in primary prevention and control in LMICs is limited, emphasizing the necessity for focused attention. Considering the impact of national health insurance programs on access, utilization, and service quality is crucial, with Health Maintenance Organizations (HMOs) playing a role in providing healthcare benefits and reducing financial burdens. Simultaneously, challenges related to the availability of sufficient medical equipment and capacity for essential surgical care persist in LMICs, necessitating improvements in infrastructure and equipment tailored to specific needs. The implementation of genomic medicine in LMICs requires advancements in health care policy and the adoption of the Personalized Health Care (PHC) model, expected to promote genomic medicine through personalized approaches. Additionally, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative supports the development of an evidence-based process for evaluating genetic tests, offering a adaptable framework for LMICs.

Detecting chromosomal abnormalities in prenatal and newborn screening is critical to ensuring infants' health and well-being. However, one of the barriers to effective detection is the lack of understanding of birth defects and awareness, as well as inadequate availability of services. This barrier can have significant implications for the timely and accurate identification of chromosomal abnormalities, potentially leading to delayed interventions and management. The lack of understanding of birth defects and awareness among healthcare professionals, parents, and the general public can hinder the early recognition of potential signs and symptoms of chromosomal abnormalities. This can result in missed early screening and diagnosis opportunities, leading to delays in accessing appropriate medical care and support services. Additionally, the stigma and misconceptions surrounding birth defects may contribute to a reluctance to seek screening and diagnostic testing, further exacerbating the problem. Furthermore, the inadequate availability of prenatal and newborn screening services for chromosomal abnormalities can pose a significant barrier to effective detection. Limited access to specialized healthcare facilities, trained personnel, and diagnostic technologies can impede the timely and accurate assessment of at-risk infants. In some regions, healthcare resources and infrastructure disparities may further exacerbate the challenges in accessing screening and diagnostic services, particularly for underserved populations. Addressing these barriers requires a multi-faceted approach that encompasses public health education, healthcare provider training, and improvements in healthcare

infrastructure and resource allocation. Efforts to enhance awareness and understanding of birth defects and chromosomal abnormalities should be targeted at both healthcare professionals and the general public, emphasizing the importance of early detection and intervention. Additionally, investments in expanding access to prenatal and newborn screening services, particularly in underserved areas, are essential to ensure equitable access to care for all infants.

The detection of chromosomal abnormalities in prenatal and newborn screening is crucial for infant health. Yet, barriers like a lack of understanding and awareness, coupled with inadequate service availability, hinder effective detection. (Swanson et al. 2022) This can lead to delayed interventions and management, with stigma and misconceptions impeding early recognition. Inadequate availability of services poses a significant barrier, hindering effective detection, especially in regions with disparities in healthcare resources.(Williams et al. 2002; Swanson et al. 2022) Addressing these challenges requires a multi-faceted approach, including public health education, healthcare provider training, and infrastructure improvements.

These challenges exacerbate the decrease in infant mortality rates attributed to congenital anomalies, as highlighted by the World Health Organization and the Ministry of Health of the Republic of Indonesia. Harapan Kita NWCHC is actively involved in surveillance, early detection, and comprehensive management of congenital anomalies, contributing to a concerted effort alongside the establishment of the Harapan Kita BIDIC program. The BIDIC program at Harapan Kita Hospital in Jakarta has significant implications for Indonesia's national health insurance program, *Badan Penyelenggara Jaminan Sosial* (BPJS). As a comprehensive initiative dedicated to preventing, diagnosing, and managing birth defects, BIDIC plays a crucial role in impacting the overall landscape of healthcare delivery, especially concerning birth-related complications. Emphasizing preventive measures like pre-pregnancy care, genetic testing, and environmental factors, BIDIC aligns with BPJS's goals of promoting preventive healthcare and reducing the long-term financial burden on the healthcare system. Harapan Kita Hospital Collaborations between specialized centers like BIDIC and national insurance programs are integral for achieving comprehensive, efficient, and accessible healthcare services for the Indonesian population. Additionally, BIDIC aims to set an example in Indonesia and strives to be a model for other low and middle-income countries, demonstrating its commitment to advancing healthcare practices on a global scale.

Despite uncovering that 54% of infants exhibited chromosomal abnormalities, with 9% having rare chromosomal diseases, it is important to note that the COVID-19 pandemic appears to have impacted our findings. The pandemic has presented substantial challenges in diagnosing and managing these abnormalities, with a noticeable decline in rare disease diagnoses and heightened concerns among affected individuals.(Golbasi et al. 2022) Additionally, the underrepresentation of those with chromosomal abnormalities in COVID-19 research underscores the necessity for targeted strategies to address the pandemic's impact on this vulnerable population.(Golbasi et al. 2022) Our study reveals a declining trend in total outborn infants screened for chromosomal abnormalities.

Study Limitations

The study exhibits potential biases that could impact the validity and generalizability of its findings. The retrospective design, coupled with the inclusion criteria requiring peripheral

blood samples from infants with clinical suspicion of genetic disorders, introduces a potential selection bias, emphasizing cases where such disorders are suspected.(Song and Chung 2010) This might skew prevalence rates, as the study may disproportionately represent more severe or clinically apparent cases.(Song and Chung 2010) The focus on infants with clinical suspicion introduces ascertainment bias, favoring individuals with overt symptoms and potentially neglecting those with milder or less visible indications. The study's location at Harapan Kita NWCHC raises concerns about referral bias, as the population seeking care at this center may not represent the broader population.(Grimes and Schulz 2002) Excluding samples due to failure to culture can cause bias by creating systematic differences between included and excluded samples, affecting the representativeness of the study. (Grimes and Schulz 2002) However, in our investigation, only 2% of samples failed to culture. Readers should approach the study's findings with caution, recognizing and addressing these potential biases in the interpretation of prevalence rates and implications for broader populations.

Clinical Applicability

This study provides valuable insights into the incidence of chromosomal abnormalities in infants with suspected genetic disorders, offering a foundation for future research directions. To deepen our understanding, a prospective study design is recommended to track the development and long-term outcomes of infants diagnosed with chromosomal abnormalities, providing a comprehensive view of the impact on health and quality of life over time.(Blue et al. 2019) Further investigations into rare chromosomal diseases' specific types and patterns are essential for enhancing knowledge of their genetic basis and potential therapeutic interventions. Exploring the genetic underpinnings of rare conditions could contribute to the development of targeted treatments.(Blue et al. 2019) Additionally, future research should focus on assessing the effectiveness of the integrated center and surveillance system in facilitating early detection and intervention for genetic disorders, examining the impact of early diagnosis on treatment outcomes and overall well-being.(Suzumori and Sugiura-Ogasawara 2010; Scriven 2020) Finally, considering the variability in the prevalence of rare diseases across populations, a comparative approach exploring genetic and environmental factors influencing these variations could uncover novel insights into the epidemiology of rare chromosomal diseases and guide the implementation of more targeted screening and intervention strategies based on population-specific risk factors.(Scriven 2020)

Conclusion

Our cytogenetic laboratory has made impressive strides in analyzing patients' chromosomes exhibiting signs of genetic disorders. Our dedicated efforts have resulted in a success rate of 98%, enabling us to identify a significant number of abnormalities and provide optimal patient care. We report that nearly half of the infants with suspected inborn conditions were diagnosed with abnormal chromosomes, which is crucial to improving outcomes for affected infants. Additionally, our team's expertise and commitment is evidenced by the detection of abnormalities in nearly 60% of referred outpatients. Furthermore, we identified rare chromosomal abnormalities in 9% of all infant samples, which is valuable knowledge for accurate diagnosis and treatment. We remain steadfast in our mission to uncover chromosomal abnormalities and improve patient outcomes.

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