ORIGINAL RESEARCH

Down Syndrome is the Leading Indication for Late-stage Termination of Pregnancy in Mongolia

Jargalsaikhan Badarch[1,2,3,4], Gunjana Kumar[3,5], Budzaya Enkhbayar[6], Terkhen Turbat[1], Tegshjargal Sereenendorj[7], Batbayar Tumurkhuleg[8], Srijan Singh[3,9], Alvaro Dendi[3,10], Amita Singhal[11,12], Akhil Maheshwari[2,3,4,11,12,13,14], On behalf of the Global Newborn Society (GNS) Down Syndrome Foundation

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Abstract

Background: Prenatal sonograms frequently show congenital anomalies in fetuses. As expected, families receiving information about severe or multi-system anomalies experience ceaseless distress and may request for termination of the pregnancy. This study was designed to identify the most frequent indications for termination of pregnancy for fetal anomalies (TOPFAs). These data can help in early detection, which can then facilitate informed decisions either for safe terminations or for well-timed fetal procedures for rehabilitation. This information is also important for appropriate genetic testing and assessment of the risk of recurrence in later pregnancies.

Objective: To investigate the frequency and epidemiological profile of various fetal abnormalities that have evoked requests for late termination of pregnancy in Mongolia.

Materials and methods: This cross-sectional observational study was conducted in a cohort of 45,095 pregnancies. Of these, 156 were terminated because of fetal anomalies. Data pertaining to fetal/congenital anomalies were collected after informed consent from families and compared with 312 healthy controls to evaluate associated maternal risk factors.

Results: In this cohort, 34.5 in 10,000 pregnancies were terminated because of fetal anomalies during the study period 2017–2019. A total of 156 terminations were related to congenital anomalies. Down syndrome (DS) was the most frequent reason (25%). The other leading reasons were multiple congenital anomalies (16%), cleft lip/palate (10.9%), and anomalies of the central nervous system (9.6%) or the musculoskeletal system (9.6%). Maternal age >35 years, higher education, less spacing between successive pregnancies, and previous history of abortion(s) were associated with a higher likelihood of birth defects.

Conclusion: Down syndrome is the leading indication for late-stage TOPFAs in Mongolia. Multi-system congenital anomalies, clefts, and anomalies of the central nervous system and musculoskeletal system were other reasons that led to requests for termination of pregnancy.

Keywords: Birth defect, Chromosomal anomalies, Cleft lip, Cleft palate, Combined defect, Congenital anomalies, Down syndrome, European surveillance of congenital anomalies, International classification of diseases, Termination of pregnancy for fetal anomaly.

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Key Points

- Fetal/congenital anomalies include structural and/or functional defects in various organs or systems that are notable at birth.
- This cross-sectional observational study was conducted in Mongolia. In a cohort of 45,095 pregnancies, 156 were terminated because of fetal anomalies.
- Down syndrome (DS) was the leading reason (25%) for terminations. Multi-system anomalies (16%), cleft lip/palate (10.9%), and anomalies of the central nervous system (9.6%) or the musculoskeletal system (9.6%) were other frequent indications.
- Maternal age >35 years, higher education, less spacing between successive pregnancies, and history of abortion(s) were associated with a higher risk of birth defects. Identification of risk factors can help in designing appropriate interventions.

Introduction

Each year, there are about 133 million births all over the world. Of these, some 7.9 million show chromosomal and organ system defects. The prevalence of these defects typically ranges from 3 to 8% globally across races, ethnicities, and geographical regions.[1] An international survey across 193 countries showed a high prevalence of birth defects in Sudan at 82 per 10,000 live births, followed

[1]Department of Obstetrics and Gynecology, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia

[2]Mongolian Association of Obstetrics, Gynecology and Neonatology-MOGNA, Ulaanbaatar, Mongolia

[3]Global Newborn Society, Clarksville, Maryland, United States of America

[4]Mongolian Chapter of the Global Newborn Society, Ulaanbaatar, Mongolia

[5]Department of Neonatology, National Institute of Medical Sciences and Research, Jaipur, Rajasthan, India

[6]RMC Clinic, Ulaanbaatar, Mongolia

[7]Enkh-Saruul "A" Clinic, Ulaanbaatar, Mongolia

[8]Khuree Maternity Hospital, Ulaanbaatar, Mongolia

[9]Department of Neonatology, Kailash Hospital, Noida, Uttar Pradesh, India

[10]Department of Neonatology, Centro Hospitalario Pereira Rossell, Universidad de la República, Montevideo, Uruguay

[11]GNS Down Syndrome Foundation, Delhi, India

[12]Department of Pediatrics, Louisiana State University, Shreveport, Louisiana, United States of America

[13]GNS Down Syndrome Group, Clarksville, Maryland, United States of America

by Greece at 55, South Korea at 54, the United States (US) and China at 47, and France at 39.[2] The Global Burden of Disease study showed congenital anomalies caused 11% of all infant deaths[3] and considerable long-term impairment.[4] Unfortunately, consistent epidemiological data are not easily available in many regions. In this study, we focused on congenital disorders in Mongolia, both in terms of the spectrum and temporal changes, that have led to requests for termination of pregnancy.

Recent advancements in genetics and medical technologies have enabled early detection of anomalies *in utero* or soon after birth.[5] However, the etiopathogenesis of congenital anomalies remains uncertain in 40–60% of all cases. Single-gene disorders, chromosomal abnormalities, exposure to teratogens, and deficiencies in micronutrients may all be potentially important factors.[6] Maternal age, infections, concurrent chronic disease, *in utero* exposure to medical/recreational drugs, environmental contaminants, and radiation may also increase the risk and severity of anomalies.[7] There is a need for continued efforts to address these issues.

For fetal anomalies, timely identification, classification, and assessment for severity is important. The International Classification of Diseases (ICD) has emphasized severity as a key determinant in the identification of congenital problems.[8,9] Major congenital anomalies affect the infants' life expectancy, health status, or physical and social functioning; minor ones do not affect health or short-/long-term functions.[10–13] In contrast, anomalies classified as "minor" have minimal or no effects on morbidity or mortality.[10] Consistent prenatal monitoring and targeted care can effectively lower perinatal mortality.[11] The 63rd World Health Assembly passed a resolution to urge member countries to establish national programs for surveillance and prevention of congenital anomalies.[7]

In Mongolia, the incidence of anomalies has increased over the past two decades. During the period 1990–1999, 1.48 infants per 1,000 live births were noted to have congenital anomalies in the capital city region, Ulaanbaatar. This incidence increased to 2.15 in 2000–2004.[14] Improved quality and compliance with prenatal testing could be an important factor but other hitherto-unknown causes cannot be excluded. Improved perinatal care and increased fetal survival could also be one because many congenital abnormalities are associated with higher fetal mortality.[15] However, despite all advancements in prenatal care,[16] the medical establishment in Mongolia is not quite ready for *in utero* treatment of major anomalies. Hence, when conditions with the possibility of life-long disabilities are detected, termination of pregnancy is often seen as the most humane option. Similar to the laws in many other countries,[17,18] medical termination is permitted up to 22 weeks' gestation.[19]

Here, we have examined the indications and temporal trends of terminations of pregnancy for fetal anomalies (TOPFAs) in Mongolia. These data are needed for downstream studies to ascertain genetic and/or environmental risk factors/causes and socio-demographic associations. An improved understanding of the epidemiology of birth abnormalities can help design targeted preventive/therapeutic efforts.[20]

Materials and Methods

This cross-sectional observational study was performed between January 2017 and December 2019 in the Capital Hospital and the Amgalan Maternity Hospital, Ulaanbaatar, Mongolia. The ethics review committee approved the study prior to its initiation. Before enrolment for data collection, parental consent was obtained, strict confidentiality was maintained during data processing and the reports were created after removing all personal identifiers. Data were collected from mothers who were citizens of Mongolia and underwent TOPFA after 13 weeks of gestation.

Detailed obstetric and demographic data related to the current and previous pregnancy(-ies) were evaluated in detail. The frequency, pattern, and severity of anomalies of congenital malformations along with the period of termination were noted as outcome variables. All relevant variables were compared with a set of controls (pregnant women who delivered a healthy infant during the study duration). The total number of patients, the number included, the number identified to have congenital anomalies, and the number of healthy mother-baby dyads were evaluated for various risk factors.[21]

Prevalence of the birth defect(s) was estimated per 10,000 births. We used the Statistical Package for the Social Sciences (SPSS) software, version 25.0 for analysis. Socio-demographic information, risk variables, and the frequency of congenital malformations were summarized.[22] Qualitative data are reported as frequency and percentage, whereas quantitative data are presented as mean and standard deviation.[23] Student's *t*-tests and analysis of variance were used to analyze differences between groups.[24] Binary logistic regression was performed to evaluate risk.[25] Non-parametric methods were used as required.[26] Statistical significance was determined as $p < 0.05$ after due consideration.[27]

Results

Out of the 45,095 pregnant mothers seen during the study period, 156 underwent termination of pregnancy because of fetal anomalies. These were compared with 312 control mother-baby dyads to identify the risk factors associated with congenital anomalies. The recorded anomalies encompassed a range of conditions, including cardiovascular, musculoskeletal, chromosomal abnormalities, and neurological anomalies. Overall, congenital anomalies were seen in 0.35% of all patients.

The study included women aged 16–45 years. In the control group, the mean (± standard deviation) age was 27.9 ± 5 years, whereas the group with congenital anomalies was 31.8 ± 6 years. Table 1 shows the demographic characteristics of mothers who underwent TOPFA vs controls. Maternal age and education status were important; mothers who had an age >35 years and had received higher education were at greater risk of having fetuses

[14]Banaras Hindu University Institute of Eminence, Varanasi, Uttar Pradesh, India

Corresponding Author: Jargalsaikhan Badarch, Department of Obstetrics and Gynecology Mongolian National University of Medical Sciences; Mongolian Association of Obstetrics Gynecology and Neonatology, Ulaanbaatar, Mongolia, Phone: +976 99111458, e-mail: jargalsaikhan.b99@gmail.com; president@mogna.org

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Table 1: Maternal demographic profile

Maternal parameter	*Cases (n = 156) n (%)*	*Healthy volunteers (n = 312) n (%)*	*p-value*
Age (years)			
16–20	2 (1.3%)	12 (3.9%)	0.001
21–25	23 (14.7%)	89 (28.5%)	
26–30	51 (32.7%)	122 (39.1%)	
31–35	28 (16.7%)	63 (20.2%)	
36–40	38 (24.4%)	25 (8%)	
>40	14 (9%)	1 (0.3%)	
Education			
Illiterate	0	1 (0.3%)	0.03
Primary	0	1 (0.3%)	
Secondary	41 (26.3%)	106 (34%)	
Professional and technical	0	7 (2.2%)	
Higher	115 (73.7%)	197 (63.1%)	
Working status			
Unemployed	51 (32.7%)	129 (41.3%)	0.96
Employed	99 (63.5%)	149 (47.6%)	
Student	6 (3.8%)	34 (10.9%)	

Table 2: Maternal age-based termination of late pregnancy due to fetal anomalies

Maternal age	*Total births*	*Number of cases of late termination with fetal anomalies*	*Cases of late termination with fetal anomalies per 10,000 births*
<19	5,479	2	3.6
20–29	13,747	74	53.8
30–39	15,996	66	41.2
>40	9,873	16	16.2
Total	45,095	156	34.5

Table 3: Late terminations of pregnancy in the birth cohort by year

Year	*Total births*	*Number of cases of late termination with fetal anomalies*	*Cases of late termination with fetal anomalies per 10,000 births*
2017	20,156	72 (46.2%)	35.7
2018	20,186	68 (43.6%)	33.9
2019 (1st quarter)	4,753	16 (3.8%)	33.7
Total	45,095	156 (100%)	34.6

with birth defects, and consequently, underwent terminations of pregnancy more frequently than healthy controls. When considered individually, mothers with age 20–39 years had the highest number of termination of pregnancy (Table 2). The overall prevalence of birth defects leading to terminations in the defined period (2017–2019) was 34.5 per 10,000 live births. This was distributed as 35.7, 33.6, and 33.4 per 10,000 births in the years 2017, 2018, and 2019, respectively (Table 3).

Table 4 shows the prevalence of the various congenital malformations (Fig. 1). Chromosomal abnormalities were the most frequent (29.5%, 10.2 per 10,000 live births), followed by fetuses with multiple birth defects that were not otherwise specified (16%, 5.5 per 10,000 live births), cleft lip and palate (10.9%, 3.7 per 10,000 live births), and abnormalities of central nervous system and musculoskeletal system (each accounted for 15%, 9.6 per 10,000 live births). Some other less frequently seen malformations involved the urinary tract, cardiovascular system, gastrointestinal system, eye and ear abnormality, genital defects, and respiratory system in the descending order of prevalence. More details of this pattern of congenital abnormalities are provided in Table 5. In the subgroup with chromosomal abnormalities, (DS; 8.6 per 10,000 births) was the most frequent; the other frequently seen abnormalities were cleft lip and palate (3.7 per 10,000 live births). Multi-system anomalies included malformations, where migration defects in the central nervous system were the most frequent (1.6 per 10,000 births); similarly, phocomelia[28] and abdominal wall defects were also noted (1.8 per 10,000 births).

Table 6 shows the relationship between congenital abnormalities and other maternal factors. Pregnancy spacing of less than 2 years or a history of previous miscarriages were noted as important predictor of congenital anomalies. Sixty-seven percent of the anomalies in terminated pregnancies showed defects that might not have been immediately life-threatening; 33% of anomalies in terminated pregnancies were perceived as immediately life-threatening and the other 67% might not have resulted in life-incompatible anomalies. In the subgroup likely to have high mortality, most had combined abnormalities not otherwise specified (n = 21) followed by central nervous system abnormalities (Table 7). These anomalies are listed in Table 8. The occurrence of neonatal life-incompatible abnormalities showed no correlation with any of the maternal risk factors (Table 9).

Discussion

This large population-based study is the first of its kind to enlist the congenital anomalies leading to requests for TOPFA(s) in Mongolia. We also have presented information on maternal risk factors and neonatal outcomes associated with congenital anomalies in Mongolia. During the study period from 2017 to 2019, the prevalence of congenital anomalies leading to late termination of pregnancy in this region was 34.5/10,000 births. The numbers remained similar during the study years, but these data need to be followed closely. The incidence of lethal congenital malformations can vary over time and across regions.[29]

Timely detection of congenital anomalies was influenced not only by specific diagnoses/biological factors but also by socioeconomic status, maternal age/education, and spacing between successive pregnancies.[30] Even though this cohort did not show significant differences in the outcomes of infants who were treated at family, district, or private hospitals, the need for comprehensive and accessible healthcare services for expectant mothers can still not be disregarded. Timely diagnosis is important. Counseling about the availability of treatment modalities, the likelihood of success of intervention, and the predictors of subsequent morbidity and mortality can provide families with emotional support that all decisions were made only after considering all possible options.[31] The importance of this longitudinal panoptic approach cannot be over-emphasized.[32]

In our cohort, DS was the single most important diagnosis (25%) that led to TOPFAs. Down syndrome is characterized by the presence of a full trisomy or some extra genetic material from chromosome 21.[33] It is a well-recognized, serious multisystem condition with

Table 4: Systemic congenital anomalies leading to late termination of pregnancy

Organ system	*Number of cases (n = 156) (%)*	*Per 10,000 births*	*Mean maternal age at diagnosis*
Chromosomal anomalies	46 (29.5%)	10.2	32.6 ± 2.3
Down syndrome	39 (25%)	8.6	35.8 ± 5.8
Multi-system birth defects**	25 (16%)	5.5	30.1 ± 6.5
Cleft lip and palate	17 (10.9%)	3.7	30.8 ± 6.3
Central nervous system	15 (9.6%)	3.3	27.1 ± 6.7
Musculoskeletal system	15 (9.6%)	3.3	30.9 ± 7.1
Urinary tract	8 (5.1%)	1.7	30.6 ± 6.2
Cardiovascular system	6 (3.8%)	1.3	30 ± 2.7
Gastrointestinal tract	5 (3.2%)	1.1	28.7 ± 6.8
Eye and ear defects	2 (1.3%)	0.4	32 ± 4
Genital defects	1 (0.7%)	0.2	35
Respiratory system	1 (0.7%)	0.2	31
Other anomalies*	15 (9.6%)	3.3	30.6 ± 5.3

*Other anomalies include congenital diaphragmatic hernia (2), inguinal hernia (4), cystic hygroma (2), conjoined twins (2), and facial dysmorphism (5).
**Multi-system birth defects were not identified with the most frequent manifestations of any chromosomal abnormalities

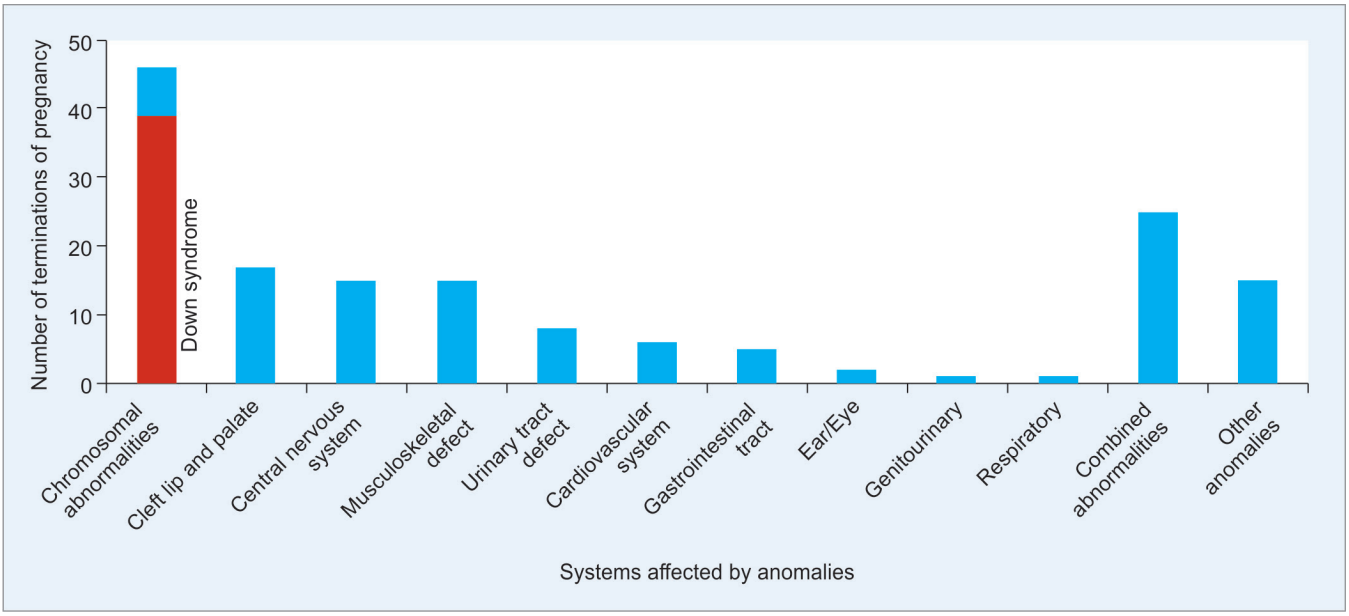

Fig. 1: Number of terminations of pregnancy performed for various systemic/genetic congenital anomalies during the study period. Down syndrome was the most frequently-noted chromosomal anomaly (depicted in red) in the first bar

life-long implications. The incidence is estimated to be somewhere between 1 in 1,000 and 1 in 1,200 live births worldwide,[34] indicating that about 3,000–5,000 infants are born with DS each year.[35] There can be minor temporal and geographical variability in geno-/phenotypic features but the condition has been constantly recorded in all races/ethnicities and economic levels.[36,37] Our understanding of the pathogenesis of DS remains limited. As is evident in our data and other studies, advanced maternal age is a known risk factor. The risk is known to increase with maternal age (1 in 1250 for a 25-year-old mother, 1 in 1,000 at age 31, 1 in 400 at age 35, and about 1 in 100 at age 40).[38,39] The average maternal age in our DS subgroup was 35.8 ± 5.8 years. In a retrospective review of the Asian population, Song et al.[40] highlighted that a maternal age of ≥34 years increased the risk of having an infant with DS. However, age is not the sole determinant; many infants with DS related to trisomy/structural abnormalities of chromosome 21 are born to women of age <35 years.[41]

Nearly 96% of all cases with DS have a supernumerary chromosome 21, resulting from a failure of these chromosomes to separate during gametogenesis.[42] All the cells in the body carry an extra chromosome 21, and consequently, an extra copy of >200 protein-coding genes affects homeostasis in cells, tissues, organs, and systems.[33] In 3–4% of cases, genetic alterations other than a canonical trisomy have been identified, including Robertsonian translocations, an isochromosome, or a ring chromosome.[43] The Robertsonian, or the translocation DS, is an unbalanced anomaly with an extra copy of the long arm of chromosome 21.[44,45] Isochromosomes contain long arms of the chromosome that mirror each other.[46] The ring chromosome 21 is seen less frequently; the ends of chromosome 21 join and form a ring.[44] Finally, 1–2% of infants with DS are mosaics, where some, not all, cells show a chromosome 21 trisomy.[47,48]

There is a need for detailed analysis of the chromosomal abnormalities in DS.[49] Phenotypical features such as the facial

Table 5: Congenital birth defects leading to termination

Anomaly	*Number of cases (n = 156)*	*Per 10,000 births*
Chromosomal (46; 29.4%)		
Down syndrome	39 (25%)	8.6
Edwards syndrome	4 (2.5%)	0.9
Other chromosomal syndromes	3 (1.9%)	0.7
Cleft lip and palate (17; 10.9%)		
Central nervous system (15; 9.6%)		
Brain malformations that are most likely to cause cerebral palsy (migration defect)	7 (4.4%)	1.6
Hydrocephalus	3 (1.9%)	0.7
Microcephaly	2 (1.3%)	0.4
Spinal deformities	2 (1.2%)	0.4
Cerebellar agenesis	1 (0.6%)	0.2
Musculoskeletal defect (15; 9.6%)		
Phocomelia	4 (2.6%)	0.9
Abdominal wall defect	4 (2.6%)	0.9
Foot deformities	3 (1.9%)	0.7
Skeletal dysplasia	2 (1.2%)	0.4
Brachydactyly	1 (0.6%)	0.2
Acromesomelic dysplasia	1 (0.6%)	0.2
Urinary tract defect (8; 5.1%)		
Bilateral polycystic kidney	3 (1.9%)	0.7
Megabladder	2 (1.2%)	0.4
Unilateral kidney cyst	2 (1.2%)	0.4
Unilateral kidney dysplasia	1 (0.6%)	0.2
Cardiovascular system (6; 3.8%)		
Ventricular septal defect	3 (1.9%)	0.7
Malposition of aorta	1 (0.6%)	0.2
Cor triatriatum	1 (0.6%)	0.2
Atrial septal defect	1 (0.6%)	0.2
Gastrointestinal tract (5; 3.2%)		
Tracheoesophageal fistula	2 (1.2%)	0.4
Hepatomegaly	2 (1.2%)	0.4
Esophageal and laryngeal perforation	1 (0.6%)	0.2
Ear/Eye (2; 1.3%)		
Microtia	1 (0.6%)	0.2
Microphthalmia	1 (0.6%)	0.2
Genital (1; 0.6%) Hypospadias	1 (0.6%)	0.2
Respiratory (1; 0.6%) Polycystic lung	1 (0.6%)	0.2
Combined abnormalities	25 (16%)	5.5
Other anomalies	15 (9.6%)	3.3

Table 6: Risk factors associated with congenital anomalies

Toxic	*Cases n (%) (n = 156)*	*Healthy volunteers n (%) n = 312*	*p-value*
Tobacco smoking	5 (3.2%)	5 (1.6%)	0.27
Alcohol	0	0	
Radiation exposure	15 (9.6%)	22 (7.05%)	0.35
Pregnancy spacing			
<2	70 (44.8%)	121 (38.8%)	0.01
3–5	42 (26.9%)	111 (35.6%)	
>5	44 (28.2%)	80 (25.6%)	
Previous miscarriages	63 (40.4%)	53 (17%)	0.001
Parity-primigravida	24 (15.4%)	62 (19.9%)	0.24
Consanguinity	25 (16%%)	65 (12.7%)	0.33
First antenatal care			0.88
<12 week	117 (75.1%)	233 (74.5%)	
13–20 week	20 (12.8%)	63 (20.1%)	
>21 week	9 (5.8%)	8 (2.7%)	
No antenatal care	6 (3.8%)	8 (2.7%)	
BMI			
<18.5	60 (38.5%)	100 (32.1%)	0.17
18.5–24.9	32 (20.5%)	95 (30.4%)	
25–29.9	33 (21.1%)	75 (24%)	
>30	31 (19.9%)	42 (13.5%)	
Type of Hospital			
Family hospital	19 (21.2%)	260 (83.6%)	0.21
District hospital	106 (77.3%)	51 (16.4%)	
Private hospital	2 (1.5%)	0	

Table 7: Anomalies compatible or incompatible with life

Organ system	*Compatible with life n (%)*	*Incompatible with life n (%)*	*Total*
Chromosomal anomalies	42 (91.2%)	4 (8.7%)	46
Combined abnormalities	4 (16%)	21 (84%)	25
Nervous system	1 (6.7%)	14 (93.3%)	15
Eye and ear defect	2 (100%)	0	2
Cardiovascular system	5 (83.3%)	1 (16.7%)	6
Respiratory defect	0	1 (100%)	1
Cleft lip/Palate	17 (100%)	0	17
Gastrointestinal tract	5 (100%)	0	5
Genital defect	1 (100%)	0	1
Urinary tract	5 (62.5%)	3 (37.5%)	8
Bone or musculoskeletal system defect	15 (100%)	0	15
Other anomalies	8 (53)	7 (47%)	15
Total	105 (67.3%)	51 (32.7%)	156

appearance, cardiac anomalies such as the endocardial cushion defect, neurodevelopmental delay, and the dermatoglyphic changes could all be rooted in the long arm of chromosome 21. The gene for the Cu/Zn-superoxide dismutase (SOD1) is located in 21q22.1,[50,51] the amyloid precursor protein (APP) in 21q11.2-21.05,[52] and six probes for single-copy sequences bind in a narrow, contiguous region: D21S46 in 21q11.2-21.05, D21S47 and SF57 in 21q22.1-22.3, and D21S39, D21S42, and D21S43 in 21q22.3.[53,54] The variability in the DS phenotype may result from the variability of gene expression of transcription factors that are encoded on chromosome 21, copy number polymorphisms, microRNA activities, RNA editing, and perhaps epigenetic modulation.[55] Understanding DS is a recognized, universal priority because this is not a universally lethal condition.[56] The United Nations General Assembly has marked 21st March as World Down Syndrome Day (A/RES/66/149)[35] to raise public awareness of DS. The DS International network

Table 8: Details of systemic anomalies perceived as compatible and incompatible with life

Organ/System	*Compatible with life*	*n (%)*	*Incompatible with life*	*n (%)*
Chromosomal abnormalities (46)	Down syndrome	39 (84.8%)	Edward syndrome	4 (8.7%)
	Other syndromes	3 (6.5%)		
Nervous system (15)	Meningocele	1 (6.7%)	Brain malformation	7 (46.7%)
			Hydrocephalus	3 (20%)
			Cerebellar agenesis	1 (6.7%)
			Microcephaly	2 (13.3%)
			Open cervico-dorsal meningomyelocele	1 (6.7%)
Ear defects (1)	Microtia	1 (100%)	–	
Eye defects (1)	Microphthalmia	1 (100%)	–	
Cardiovascular system (6)	Atrial septal defect	1 (16.7%)	Cor-triatriatum	1 (16.7%)
	Aorta malposition	1 (16.7%)	–	
	Ventricular septal defect	3 (50%)	–	
Cleft lip and palate (17)	Cleft lip—bilateral	12 (70.6%)	–	
	Unilateral cleft lip and palate	5 (29.4%)	–	
Gastrointestinal tract (5)	Tracheal-esophageal fistula	2 (40%)	–	
	Hepatomegaly	2 (40%)	–	
	Esophageal and laryngeal perforation	1 (20%)	–	
Genital tract (1)	Hypospadias	1 (100%)	–	
Urinary abnormality (8)	Megabladder	2 (25%)	Bilateral polycystic kidney	3 (37.5%)
	Unilateral kidney dysplasia	1 (12.5%)	–	
	Unilateral kidney cyst	2 (25%)	–	
Bone defect or musculoskeletal system defect (15)	Phocomelia	4 (26.7%)	–	
	Brachydactyly	2 (13.3%)	–	
	Skeletal dysplasia	2 (13.3%)	–	
	Foot deformities	3 (2.8%)	–	
	Abdominal wall defect	4 (26.7%)	–	
	Acromesomelic dysplasia	1 (6.7%)		
Respiratory system (1)	–	–	Polycystic lung disease	1 (100%)
Combined abnormalities (25)	–	4 (16%)	–	21 (84%)
Other anomalies	–	8 (53%)	–	7 (47%)

Table 9: Correlation of compatibility of fetal anomalies with maternal age mother's age

	Mother's age						
	Less than 30 years old		*31–40 years old*		*Older than 41 years old*		
Compatibility with life	*n*	%	*n*	%	*n*	%	*p-value*
Compatible with life	49	31.4%	45	28.8%	11	7%	0.626
Incompatible with life	27	17.3%	20	12.8%	4	2.6%	
Total	76	48.7%	65	41.7%	15	3.2%	

hosted the 13th World Down Syndrome Day Conference at the UN headquarters on 21–22 March 2024 in New York.[57]

The World Health Organization (WHO) records show that 17–42% of infant mortality all over the world can be attributed to congenital anomalies.[58] This is a major, distressing area that every obstetrician/perinatologist has to deal with in her/his everyday clinical practice.[32] In 11 European Surveillance of Congenital Anomalies (EUROCAT) countries,[59] the average infant mortality rate associated with congenital anomalies was 1.1 per 1,000 births.[60] Notably, countries where TOPFA is not permitted, such as Malta and Ireland, reported higher rates of infant mortality due to congenital anomalies, with rates of 3 and 2.1 per 1,000 births, respectively. The rate of stillbirths associated with congenital anomalies was reported as 0.6 per 1,000 births. The average number of TOPFAs, at 4.6 per 1,000 births, was nearly three times more than the combined rates of stillbirths and infant deaths. Termination of pregnancy for fetal anomalies have also been seen to impact the prevalence of post-neonatal survivors with non-lethal congenital anomalies.[61] Since deaths due to congenital anomalies tend to occur during infancy or in early childhood,[62] the burden in years of life lost is higher—congenital anomalies ranked 14th among all causes of death.[63] Moreover, it is more tedious to get the prevalence pertaining to low-middle-income countries which either do not have a national registry or the termination is illegal and hence, not

documented. A study conducted in Southeast Asia revealed that out of 640 women who underwent medical termination of pregnancy, 245 cases were attributed to congenital fetal malformations, accounting for 38.2% of the total cases.[64]

In addition to DS, early or advanced maternal age is also associated with an enhanced risk of other congenital anomalies.[65] The higher incidence of these anomalies among educated mothers could be attributed to better awareness of newer diagnostic modalities, but biological factors are likely important. Decreased spacing (less than 2 years) among the subsequent pregnancies with previous abortion were certain other contributory factors in the current study. Paternal consanguinity, maternal malnutrition, obesity, inadequate prenatal care, smoking, prior abortion, past congenital abnormality in their fetus, prematurity, and low birth weight are some factors studied.[6,21,66] Public education on risk factors, maternal health, and early prenatal care is crucial. A better understanding of these issues can help with timely and improved intervention, with better maternal and infant outcomes.[67]

In our cohort, we also recorded a high frequency of multi-system anomalies that could not be classified into known syndromes (16%), cleft palate and lip (10.9%), central nervous system (9.6%), and musculoskeletal defect (9.6%). Other common malformations were related to the urinary tract, cardiovascular, and gastrointestinal systems. Among the anomalies of the CNS, migration defects (4.5%) with a high likelihood of future cerebral palsy form a major cohort. Phocomelia and abdominal wall defects are among the most common anomalies in the musculoskeletal system leading to TOPFA. In a retrospective study from the African Gulf registry assessing the incidence and risk factors of congenital anomalies, the highest incidence was observed in CVS (35%), followed by multiple congenital anomalies (21%), chromosomal/genetic anomalies (15%), renal anomalies (12%), CNS anomalies (n = 20; 6%), facial anomalies (14.4%), and other anomalies affecting the GIT, respiratory system, urogenital system, and skeletal system (7%). Additionally, multivariable regression analysis revealed associations between various specific congenital anomalies and factors such as multiple pregnancies, parity ≥1, maternal body mass index (BMI), and demographic factors including the mother's age, ethnicity, and infant's gender.[68] In another cohort, the circulatory system was most frequently implicated, followed by the neurological and musculoskeletal systems.[12] Between 1990 and 2019 in China, there was an increasing trend in the age-standardized incidence rate for congenital anomalies, with an average annual percentage change (AAPC) of 0.26% (0.11–0.41%). By 2019, this rate reached 148.12 per 105 person-years (124.03–176.33). Most of these congenital anomalies were heart defects, which showed an AAPC of 0.12% (−0.08% to 0.32%). Conversely, the age-standardized mortality rate for congenital anomalies exhibited a decreasing trend, with an AAPC of −4.57% (−4.97% to −4.17%), reaching 4.62 per 105 person-years (3.88–5.57) in 2019. Most mortality cases were associated with congenital heart anomalies, which had an AAPC of −3.77% (−4.35% to −3.19%). Additionally, the age-standardized disability-adjusted life years (DALYs) rate for congenital anomalies also showed a decreasing trend, with an AAPC of −3.74% (−3.95% to −3.52%), reaching 480.95 per 105 person-years (407.69–570.04) in 2019.[30] With the variations across various sites, a cross-sectional study from Bangladesh also showed a higher incidence of CNS and musculoskeletal/gastrointestinal defects.[66]

In countries where termination of pregnancy is legal, there is some variation in the definitions of types of anomalies for which termination of pregnancy is permitted. For instance, in the United Kingdom (UK), the law allows termination if the anomaly poses a 'substantial risk' that the child would be "seriously handicapped."[31] Conversely, in the Republic of Ireland, 2 medical practitioners must agree that the baby will die during pregnancy, labor, or within 28 days after birth before permitting TOPFA.[69] In the United States, access to TOPFA varies by state due to differences in governments, healthcare providers, and medical insurance restrictions.[70] Six states entirely prohibit TOPFA, while an additional four requires mandatory counseling on available perinatal hospice services before it can be performed.[71]

In Mongolia, TOPFA during late pregnancy is permitted by law.[72] However, currently, there is no standardized registration and reporting system for these cases. There is awareness that infant mortality can be reduced through prevention, early diagnosis, and surgical care of birth defects. However, with these established laws, many fetuses who could have survived might have also got terminated; possible reasons could have been rooted in the lengthy process of evaluation, parental wishes, and financial difficulties. In the current study, 67.3% of fetuses were terminated despite the condition(s) being compatible with life, such as DS and cleft lip/palate. There is an urgent necessity for a comprehensive, legally-supported requirement for mandatory counseling for parents prior to any decision regarding termination. Such a system should provide parents with information about both antenatal and postnatal treatment options available along with financial support. This approach will likely reduce the termination in conditions that are potentially salvageable.

In a cross-sectional study involving over 3.3 million infants in the Czech Republic,[73] the combined incidence of major congenital heart defects during both prenatal and postnatal periods remained more or less the same over the three decades studied. Of these cases, 43% were born, 54.1% resulted in termination of pregnancy, and 2.9% ended in prenatal death. However, there were significant changes in the rates of detection and termination practices over time. Prenatal detection increased substantially from 6.2% in 1991 to 82.8% in 2021. Conversely, the rate of terminations decreased from 70% in 1991 to 43% in 2021. Most terminations were performed in the first trimester (73.3%) followed by a significant decline in the second (42.6%). Furthermore, there was also a decline in the postnatal prevalence of major CHDs from 0.21 to 0.14%. An individualized approach to healthcare can be helpful. Importantly, this indicates a degree of consensus about how appropriately trained health professionals, compassionate and person-centered care, good information and communication, and a thoughtful and integrated care pathway, can help make parents feel supported and cared for through what is an emotionally traumatic experience.[74]

We need standardized systems such as the ICD-9 or ICD-10 for categorizing birth defects.[8] These can enable data comparison across different geographical regions and over time. According to the Global Burden of Disease Study and WHO reviews, congenital anomalies may contribute to up to 17–42% of infant mortality.[61] Given the substantial variability in the incidence of congenital abnormalities across regions, efforts should be directed toward more precise targeting and intervention strategies.[75]

Conclusion

Chromosomal abnormalities such as DS and multiple congenital defects are the most common reasons for requests for TOPFA.

Congenital anomalies are noted more frequently in mothers with higher age, less pregnancy spacing, and a history of previous abortion. These congenital defects carry an emotional, financial, and social burden with a need for prolonged medical care and possible long-term disabilities; the effect is noticeable not only on a child's health and development, but also on families, healthcare systems, and the whole society.[76] Appropriate prenatal, intrapartum, or postnatal evaluation could be helpful in prevention, counseling, and management. Better understanding could help design studies aiming for genetic understanding, clinical amelioration, and even cure.

Orcid

Akhil Maheshwari https://orcid.org/0000-0003-3613-4054

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