The burden of antenatally undiagnosed major congenital anomalies in live-born babies at a busy secondary level maternity hospital in the Western Cape

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This dissertation is submitted in 'publication-ready' format according to UCT guidelines. The dissertation will be submitted for publication to the South African Journal of Child Health (SAJCH). This manuscript was written in accordance with the journals specifications as per instruction to authors for research submission. The author guidelines recommend a total of three tables or figures- permission will be requested from the editors to include a total of two tables and four figures in this manuscript as they add more precision and understanding.

Conflict of interest

There is no conflict of interest to which to declare.

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KEYWORDS AND ABREVIATIONS:

ART: Antiretroviral treatment

ASD: Atrial septal defect

AVSD: Atrioventricular septal defect = Endocardial cushion defects

CA: Congenital anomalies

DNA: Deoxyribonucleic acid

ELBW: Extremely low birth weight

FAS: Foetal anomaly ultrasound scan

HIC: High income countries

HIV: Human immunodeficiency virus

LBW: Low birth weight

LMIC: Low-and-middle income countries

MCA: Major congenital anomalies

MPLA: Multiplex ligation-dependent probe amplification

Non-syndromic: No known associated genetic/chromosomal abnormalities

NVD: Normal vaginal delivery

OEIS syndrome: Omphalocele, exstrophy of the cloaca, imperforate anus and spina defects

PDA: Patent ductus arteriosus

QF-PCR: Qualitative florescent-polymerase chain reaction

RPR: Rapid plasma reagin

Syndromic: Genetic/ chromosomal abnormalities

TLD: Tenofovir, Lamivudine and Dolutegravir anti-retroviral combination medication

VACTERL: vertebral, anorectal, cardiac, tracheoesophageal, renal and limb abnormalities

VLBW: Very low birth weight

VSD: Ventricular septal defect

TITLE PAGE

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Abstract

Background: Major congenital anomalies (MCA) account for considerable morbidity and disability in South Africa (SA) where there is a predicted birth prevalence of 27.5/1000 live births. There are limited data on MCA prevalence and impact on neonatal services in SA, especially the Western Cape province.

Objective: To determine the prevalence, characteristics, and short-term outcomes of antenatally-undiagnosed neonates with MCA at Mowbray Maternity Hospital (MMH) in 2022.

Methods: A retrospective, cross-sectional study of live-born neonates with MCA admitted to MMH neonatal services between 1 January- 31 December 2022. Stillbirths and antenatally diagnosed MCA neonates were excluded. Cases identified from the ward register and data collected by folder review using a standardized data collection form and analysed using R and Microsoft Excel. Continuous variables, described as medians and interquartile ranges, compared using the Wilcoxon rank sum test. Categorical variables presented as proportions and assessed using chi^2test.

Results: With 73 neonates included, the in-facility MCA prevalence rate was 36 per 1000 neonatal admissions and 6/1000 live MMH in-born infants. Most (82%) had a basic antenatal ultrasound and 29% a fetal anomaly scan. Syndromic MCA was present in 36% and non-syndromic MCA in 64%. Non-syndromic MCA included isolated genitourinary (21%), orofacial (19%), gastrointestinal (17%) and cardiovascular defects (15%). The most prevalent syndromic MCA was Trisomy 21 (58%). Syndromic MCA was significantly associated with advanced maternal age (≥36 years), increased gravidity (≥5) and low birth weight (<2500g), $p < 0.001$. The in-hospital mortality rate was 15%.

Conclusion: In this single hospital-based study, the MCA prevalence was high among in-born and referred neonates. Diagnosis was not made antenatally despite a high proportion of women booking early and receiving antenatal ultrasound. Large collaborative registries and studies are recommended to establish the true impact of CA on children and their outcomes in SA.

Introduction

The World Health Organization (WHO) defines congenital anomalies (CA) as a subset of birth defects which are macroscopic morphological anomalies, excluding functional disorders that are present at birth and of prenatal origin.[1–4] The aetiology is multifactorial with infectious, genetic and environmental contributory factors; however, 50% have no known cause.[1]

The Centres of Disease Control and Prevention (CDC) defines major congenital anomalies (MCA) as structural or functional changes with significant medical, social or cosmetic consequences for the individual, typically requiring medical intervention. MCA account for most deaths, morbidity and disability related to CA and commonly include structural cardiac, neurological, genitourinary, gastrointestinal, and orofacial defects as well as serious chromosomal disorders including Trisomy 21,18 and 13. [1, 5,6]

CA are the 4th leading cause of neonatal mortality globally preceded by preterm birth, birth asphyxia and neonatal infections.[1,7,8] Studies assessing the contribution of CA to perinatal mortality are limited in low-and-middle income countries (LMIC).[8] An annual estimated 7.9 million children, 6% of total birth globally, are born with serious birth defects of genetic or partially genetic origin.[3]

Improvement and motivation by many countries to achieve the sustainable development goals (SDGs) target 3, is reflected by the decreasing global under-5 mortality (U5M) rate from 71.2/1000 livebirths in 2000 to 37.1/1000 in 2019, thought mainly due to improvements in diarrhoeal and infectious diseases. The global neonatal mortality rate is declining more slowly by comparison, from 28/1000 livebirths in 2000 to 17.9/1000 in 2019, with CA recognised as an important cause of U5M.[7,8]

One 2005 study reported the lack of robust data from LMIC and postulated that approximately 10% of neonatal deaths in LMIC may be due to CA citing unavailable or inaccessible prenatal screening, out-of-hospital births, lack of trained professionals to identify and manage CA appropriately, and inadequate resources and referral pathways as potential contributors.[9,10]

The 2006, “March of Dimes”, Global Report on Birth Defects, recognised that approximately 94% of severe CA occurred in LMICs.[1,9] A systematic review by Toobaie *et al.* of the CA prevalence in LMICs found congenital heart defects to have the highest reported incidence globally of 57/10 000 live births. Approximately 9% of CA were found to be surgical defects of which 50% were correctable with early intervention.[9]

The challenges in LMICs are the lack of diagnosing CA, poor documentation and poor notification; reflecting the limited estimates of the true impact of CA being unavailable for most countries, including South Africa (SA).

The South African National Department of Health (NDoH) guidelines for the management and prevention of genetic disorders, birth defects and disabilities were published in 2001. This revised the congenital defects surveillance system with the introduction of the Birth Defect Notification Tool form.[6] The aim was to consolidate data on CA from each of the nine provinces into a national database. Despite this, reporting is poor and SA data lacking.

A systemic review on the effectiveness of this surveillance system showed that only 1.8% of the expected total CA were reported, with the highest annual notification being KwaZulu Natal, 54% and the least being in Western Cape, 2.5%.[6] This emphasized common challenges seen in LMIC, including SA; besides the lack of diagnosing CA, poor documentation and poor notification is a reality therefore limiting estimates of the true impact of CA in these countries.

A recent data review emphasized the reality that congenital disorders remain an unprioritized healthcare issue in SA with national surveillance under-reported by >95%. They used modelled epidemiological estimates to predict CA prevalence of 27.5/1000 live births for SA.[11]
Despite health system challenges, SA is one of the leading African countries implementing strategies and surveillance frameworks to reduce childhood and maternal mortality outcomes by means of NDoH audits including the Perinatal Problem Identification Programme (PPIP) and Birth Defect Notification Tool form to improve documentation and notification of CA allowing for equitable resource allocation and implementation of management pathways to improve child healthcare outcomes in SA.[10,12]

WHO and CDC National Centre on Birth Defects and Developmental Disabilities support many programmes and research initiatives to raise global awareness, strengthen surveillance, prevention and better care of CA before and after birth. Early diagnosis and appropriate management are imperative to improve health outcomes. Prenatal education, access to basic antenatal care, antenatal ultrasound scans, skilled sonographers, availability of specialist fetal anomaly scans(FAS), tertiary and paediatric surgical facilities remains a challenge in many LMICs, including SA.[9,13]

In regards to advanced maternal age (AMA), historically >35 years; in SA, antenatal screening for CA is only available for women ≥37 years.[14] The South African Society of Obstetrics and Gynaecology recommends three routine antenatal ultrasonography screening during pregnancy: a basic obstetric dating scan (level 1), basic anatomy scan (level 2) and advance FAS (level 3).[14,15] If clinically identified as a high-risk pregnancy or any CA seen, they can be referred for a formal specialist FAS between 18-22 weeks. If appropriate, further investigations like amniocentesis and/or genetic testing are indicated to formulate a management plan including genetic counselling with the option of termination of pregnancy for severe birth defects.

Effective interventions to prevent and manage children born with CA require investment from health systems by strengthening and expanding newborn screening, early clinical detection, and diagnosis of CA, followed by referral for appropriate treatment.[16] Importantly, MCA not leading to early death, also have a significant impact on quality of life, not only for the child but for their caregivers and communities.

We aimed to determine the prevalence, characteristics, associated factors, and short-term outcomes of antenatally undiagnosed MCA neonates admitted to Mowbray Maternity Hospital (MMH), a secondary-level-obstetric referral hospital in Cape Town, South Africa.

Methods

Study Design

This was a single centre, retrospective cross-sectional study conducted at MMH from 1 January - 31 December 2022.

Study site and population

MMH is a government, regional hospital and a secondary-level obstetric referral centre with most referrals in late pregnancy. It is also the main delivery and referral site for non-tertiary neonates born within the MetroWest district in Cape Town. MMH is a 74-bed neonatal unit, including 12 ICU, 24 high care and 17 special care beds. Total deliveries for the region were 33,506 in 2022; 10,312 of these occurred at MMH and 2,045 required admission to the neonatal unit. A further one third of the regional deliveries occurred at local primary care midwife-obstetric units (MOU), the majority referred to MMH if indicated, including MCA. The total MMH neonatal admissions offered a reasonable representation of the district delivery MCA burden.

Inclusion criteria

All liveborn neonates, delivered or referred to MMH during 2022 for admission, diagnosed postnatally with MCA (using the CDC definition[5]) by means of clinical surface examination, radiological imaging (X-rays, ultrasonography, echocardiography) or laboratory investigations and documented in the MMH MCA Neonatal Register were included.

Exclusion criteria

Stillbirths were excluded due to the potential for incomplete examination and documentation at the delivery facilities. Antenatally diagnosed MCA cases by ultrasonography or laboratory investigations and minor CA, defined as structural changes with only cosmetic, limited social and no medical health consequences for the individual[5] (e.g., postaxial polydactyly type B, newborn cryptorchidism etc) were excluded.

Sample size, Data collection and Tools

We reviewed all neonates recorded in the MMH MCA Neonatal Register in 2022. A total of 78 neonates were reviewed and 73 found eligible. Maternal and neonatal information were collected manually from clinical folder reviews, using a paper-based standardized data collection sheet ***(Appendix 3).*** Maternal data included obstetric history, medical and pregnancy-related conditions, medications and substance use, evidence and timing of antenatal booking, presence or absence of an antenatal ultrasound and FAS. Neonatal data included gestational age, birth weight, birth details, APGAR scores, details of MCA, methods of diagnosis of MCA (clinical surface examination, radiological imaging, laboratory results) and in-facility clinical outcomes. The information was entered into REDCap electronic database, directly transferred onto a Microsoft Excel spreadsheet for data cleaning and statistical analysis.

Data Analysis

Statistical analysis was done using R*(version R-4.4.2)* and Microsoft Excel *(version 16.52, 2021)* and descriptive statistics were used to describe neonatal and maternal demographic characteristics. The hospital based Clinicom and Perinatal Problem Identification (PPIP) databases(12) were used to inform total MMH neonatal admissions, inborn live births, and MCA-related deaths over the study period. Total neonatal admissions served as denominator. Prevalence and mortality rates were calculated with simple counts and percentages. Continuous variables were described using medians with interquartile ranges and compared using the Wilcoxon rank sum test. Categorical variables were described as proportions, and comparisons made using the Chi^2 test or Fishers exact test, as appropriate. Post-hoc analyses with adjusted residuals were conducted to determine specific cells contributing significant Chi^2 statistics. Statistical significance was set at $p < 0.05$.

Ethics Approvals were obtained from the University of Cape Town Human Research and Ethics Committee (HREC REF: 365/2022) and permission was obtained from MMH Research Committee. A waiver of informed consent was granted.

Results

Maternal and neonatal demographics

Total neonatal admissions to MMH were 2045 in 2022. Seventy nine percent (79%) inborn and 21% out-born deliveries, referred from surrounding MOUs in the Metro West region of Cape Town ***(Figure 1).***

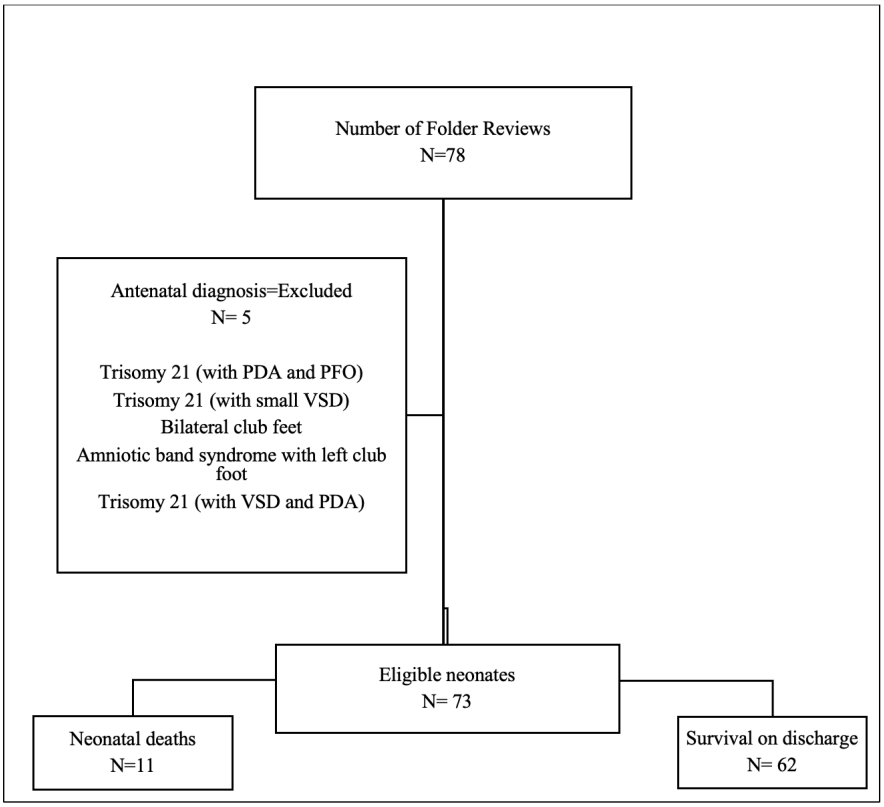


Figure 1: Study population. Graphic illustration of neonates eligible for study.
Over the one-year study period, a total of 78 MCAs were identified, and 73 neonates fulfilled inclusion criteria. Five neonates were excluded with antenatal diagnosis on antenatal ultrasound including one neonate with Trisomy 21 confirmed on chorioamniocentesis.
PDA: Patent Ductus Ateriosus. PFO: Patent Foram Ovale. VSD: Ventricular Septal Defect.

Ninety-six percent of women with neonates affected by MCA received at least one antenatal visit. Of these 51% booked before 20-weeks gestation. Eighty-two percent (82%) had at least one routine antenatal ultrasound scan and 21 (29%) had a FAS in which the MCA were not detected. Most women fell into the age category of 21-30 years (42%) and 26% had AMA (≥36years).

Fifteen percent of women were living with HIV, of whom all were on antiretroviral treatment (ART) and more than 85% were virally supressed (viral load < 50copies/ml) at delivery. Four neonates were syphilis exposed but asymptomatic: two mothers were incompletely treated during pregnancy and two fully treated ***(Table 1).***

Table 1: Maternal and Neonatal characteristics

Maternal characteristics	Frequency, N (%)
Maternal Age (years)	**(n= 73)**
<20	4 (6%)
21-30	31 (42%)
31-35	19 (26%)
36-40	12 (16%)
>40	7 (10%)
Age (years) median (IQR)	31 (25, 36)
Gravidity	
1	13 (18%)
2-3	35 (48%)
4-5	18 (25%)
>5	7 (9%)
Gravidity median (IQR)	3 (2 - 4)
Parity	
1-2	39 (53%)
3-4	26 (36%)
≥5	8 (11%)
Parity median (IQR)	*2 (2 - 3)*
Antenatal visits	
Any (booked)	70 (96%)
None (Unbooked)	3 (4%)
Gestation at first ANC booking (weeks)	
<20	37 (51%)
≥ 20	35 (48%)
Unknown*	1 (1%)
HIV status	
Living with HIV	15 (21%)
Not living with HIV	58 (79%)
Syphilis Rapid plasma Reagin (Syphilis screen)	
Positive+	4 (5%)
Negative	69 (95%)
At least 1 routine Antenatal Scan	
Yes≠	60 (82%)
No:	13 (18%)
Fetal anomaly scan (no anomaly detected)	
Yes	21 (29%)
No	52 (71%)
Pregnancy related illness	13 (18%)
Hypertensive disorder	8 (11%)
Gestational diabetes	1 (1%)
Other§	4 (6%)

Neonatal characteristics	Frequency, (N) %
Total births	
Inborn	58 (79%)
Outborn	15 (21%)
Completed gestational age at delivery (weeks)	
< 37	23 (32%)
≥37 – 41^{+6}	50 (68%)
≥ 42	0
Median gestational age (weeks)(IQR)	38.00 (36.00, 39.00)
Sex	
Male	25 (34%)
Female	48 (66%)
Mode of delivery	
NVD	40 (55%)
Elective caesarean section	16 (22%)
Emergency caesarean section	17 (23%)
Apgars	
1 minute, *Median (IQR)*	9 (8 - 9)
5 minute, *Median (IQR)*	10 (8 - 10)
Birth weight category	
ELBW < 1000g	2 (3%)
VLBW 1000g-1499g	3 (4%)
LBW 1500g- 2499g	23 (32%)
Normal birth weight 2500g-3999g	41 (56%)
Macrosomia (high birth weight) ≥ 4000g	4 (5%)
Birth weight median (IQR)	2800 (1960,3080)

*Missing data
+Maternal RPR reactive: 2 mothers had untreated syphilis, asymptomatic neonates. Two fully treated antenatally.
≠Note: 60 antenatal ultrasounds done did not detect abnormalities: 34 had ultrasounds ≤20 weeks
§ Maternal E Coli UTI, Deep vein thrombosis on warfarin, maternal syphilis (treated)
Denominator = all Mowbray Maternity Hospital neonatal admissions in 2022

More than a third (39%) of the neonates had a birthweight < 2500g (LBW). Just less than a third (32%) of neonates were delivered prematurely (<37 weeks gestation). Two (3%) were extremely low birth weight (ELBW, <1000g), 4% very low birth weight (VLBW, 1000-1499g) and 32% low birth weight (LBW, 1500-2500g), respectively. Fifty-six percent were normal birth weight and 5% macrosomic (≥4000g).

Pregnancy-related illness were present in 13 women (18%) and included gestational hypertension (11%), gestational diabetes (1%) and other conditions (6%). Maternal chronic medication included mostly antiretroviral treatment: Tenofovir, Lamivudine and Dolutegravir (TLD) and antihypertensive agents. One woman with gestational diabetes was on multiple

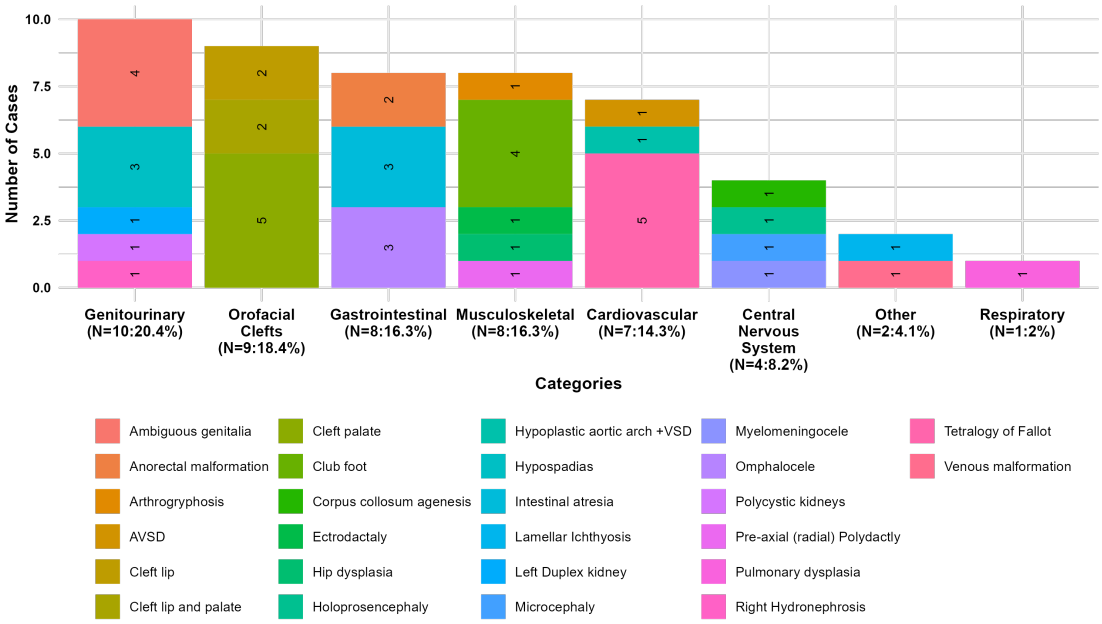
medications, including metformin, antihypertensive agents, anti-retroviral agents, isoniazid prophylaxis, sulfamethoxazole-trimethoprim and pyridoxine. There were no documented use of lithium or sodium valproate. One quarter (n=18) of women acknowledged substance use during pregnancy: cigarette smoking (55%), alcohol (28%), cannabis (6%), and herbal substance use (6%).

Prevalence of major congenital anomalies

The prevalence rate of MCA was 36/1000 neonatal admissions (73/2045) and 6/1000 live births for inborn neonates.

Forty-seven neonates with non-syndromic associated MCA were identified, 64% of the study population ***(Figure 2).*** These included 21% genitourinary, 19% orofacial, 17% musculoskeletal, 17% gastrointestinal, 15% cardiovascular and 9% central nervous system defects. The least common defects were pulmonary defects, venous malformations, and dermatological conditions. Multiple MCA occurred in two neonates particularly in the cardiovascular and genitourinary categories, the remaining were neonates with isolated MCA.

Figure 2: Types of Non-syndromic major congenital anomalies (N=47)

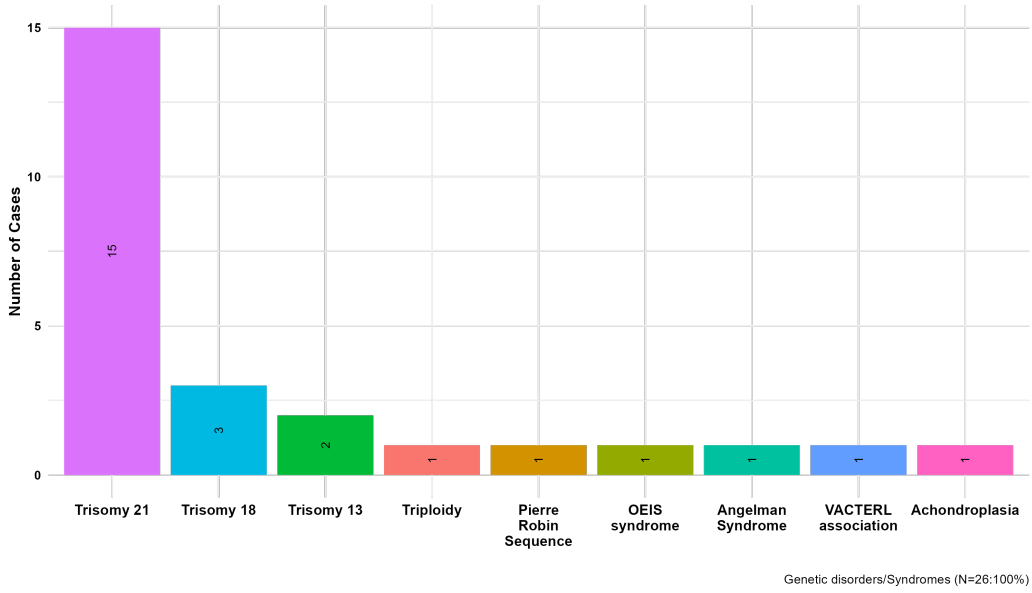


Multiple MCA: (1) Polycystic kidney disease, VSD and hypoplastic aortic arch (2) Bilateral cleft lip and plate with left peripheral pulmonary stenosis.

There were 26 neonates with syndromic-associated MCA, representing 36% of the study population ***(Figure 3).*** Trisomy 21 (58%) was the most prevalent. The other chromosomal disorders included Trisomy 13 (12%), Trisomy 18 (4%) and Triploidy (4%). Amongst these cases, the most common associated defects were isolated cardiovascular (54%) predominantly in neonates with Trisomy 21 (n=11) and orofacial-cleft defects (11%). Two neonates had multiple MCA (VACTERL and OEIS) and two neonates had single gene disorders (Angelman syndrome and Achondroplasia).

Five neonates (7%) had central nervous system defects consisting of two corpus collosum agenesis, microcephaly, myelomeningocele (ruptured), and holoprosencephaly. Genetic studies, including karyotyping, QF-PCR and MLPA, confirmed the diagnosis in 21 of the 26 neonates, with the remaining being by specialist clinical diagnosis.

Figure 3: Types of Syndromic major congenital anomalies (N=26)



Multiple MCA: (1) OEIS syndrome: Omphalocele, exstrophy of the cloaca, imperforate anus and spina defects (2) VACTERL association: Vertebral, anorectal, cardiac, tracheoesophageal, renal and limb abnormalities
Genetic disorders: (1) Angelman Syndrome (2) Achondroplasia

Comparison between syndromic and non-syndromic MCA groups

Median maternal age was significantly higher in the syndromic group (35 years, IQR 31-40) compared to the non-syndromic group (27 years, IQR 25-33), $p < 0.001$. Gravidity of more than 5 was significantly associated with the syndromic group (27% vs 4%), $p < 0.001$. Parity of five or more was commoner in the syndromic group (12% vs 10%), $p = 0.038$ ***(Table 2).***

The mode of delivery also differed significantly by MCA group ($p < 0.001$): Elective caesarean sections were more common in the non-syndromic group (30% vs. 8% respectively). A significant association in the sex distribution was observed ($p = 0.050$), with males more likely to be non-syndromic (47% vs. 12%), and females syndromic (53% vs. 88%). Gestational age at delivery showed significant association ($p < 0.001$) with a higher proportion of premature deliveries (< 37 weeks) in the syndromic group.

Associated factors

Maternal HIV status and syphilis status did not show a significant association within the groups ($p > 0.9$ for both). Pregnancy-related illnesses, medication use, and type of substance use respectively, had no significant group association. There were no significant association in attendance of antenatal care between the groups ($p = 0.484$) or in the receipt of at least one routine antenatal ultrasound, 79% vs 88% respectively ($p = 0.470$).

Proportionally more of the FAS-undetected MCA neonates were syndromic (38%) vs non-syndromic (23%). Most were Trisomy 21 (n=7), where four had associated intracardiac defects: two endocardial cushion defects; one large ventricular septal defect (VSD) and one fenestrated atrio-ventricular septum and branch pulmonary artery stenoses. Other cardiac defects not identified on FAS were a large VSD in a neonate with Trisomy 13; VSD in an omphalocele-exstrophy of the cloaca-imperforate anus-spinal defect (OEIS) syndrome, a hypoplastic left heart syndrome (HLHS) in a vertebral, anorectal, cardiac, tracheoesophageal, renal and limb abnormality (VACTERL) and two Tetralogy of Fallot defects in 2 non-syndromic neonates.

Table 2: Comparison between non-syndromic and syndromic major congenital anomalies

Characteristics	Non-syndromic MCA N= 47 (64 %)	Syndromic MCA N= 26 (36%)	p-value
Maternal Age (years)			< 0.001
<20	4 (9%)	0	
21-30	26 (55%)**	5 (19%)	
31-35	10 (21%)	9 (35%)	
36-40	6 (13%)	6 (23%)	
>40	1 (2%)**	6 (23%)**	
Age median (IQR)	*27 (25, 33)*	*35 (31, 40)*	*<0.001*
Antenatal visits			0.484
Yes (booked)	44 (94%)	26 (100%)	
No (unbooked)	3 (6%)	0	
Gestation at first antenatal clinic booking (weeks)			0.002
< 20	24 (51%)	13 (50%)	
≥ 20	23 (49%)	12 (46%)	
Unknown*	0	1 (4%)	
HIV status			>0.9
Living with HIV	9 (19%)	6 (23%)	
Not living with HIV	38 (81%)	20 (77%)	
Syphilis RPR (syphilis screen)			>0.9
Positive§	2 (4%)	2 (8%)	
Negative	45 (96%)	24 (92%)	
At least one antenatal scan			0.470
Yes	37 (79%)	23 (88%)	
No	10 (21%)	3 (12%)	
Fetal anomaly scan			0.275
Yes (no anomaly detected)	11 (23%)	10 (38%)	
No	36 (77%)	16(62%)	
Gravidity			< 0.001
1	10 (18%)	3 (12%)	
2-3	24 (48%)	11 (42%)	
4-5	11 (25%)	7 (27%)	
>5	2 (9%)**	5(19%)**	
Gravidity median (IQR)	*3.00 (2.00, 4.00)*	*3.00 (2.00, 4.00)*	*0.200*
Parity			0.038
1-2	28 (60%)	11 (42%)	
3-4	14 (30%)	12 (46%)	
≥5	5 (10%)**	3 (12%)**	
Parity median (IQR)	*2.00 (1.00, 3.00)*	*3.00 (2.00, 4.00)*	*0.089*
Pregnancy related illness	11 (23%)	2 (8%)	0.085
Chronic Medication Use‖			>0.9
Yes	12 (26%)	7 (27%)	
No	35 (74%)	19 (73%)	
Type of substance use	14 (30%)	4 (15%)	0.179
Cigarette smoking	8 (17%)	2 (8%)	
Alcohol	5 (11%)	0	
Illicit drugs+	0	1 (4%)	
Unknown	1 (2%)	1 (4%)	
Place of birth			>0.9
Inborn	37 (79%)	21 (81%)	
Outborn	10 (21%)	5 (19%)	

Delivery gestational age (weeks)			<0.001
< 37	14 (26%)	11 (42%)	
37 – 41^{+6}	33 (74%)	15 (58%)	
≥ 42	0**	0**	
Gestational age median (IQR)	*38 (35, 40)*	*38 (36, 39)*	*0.600*
Sex			0.050
Male	22 (47%)**	3 (12%)	
Female	25 (53%)	23(88%)**	
Mode of delivery			<0.001
NVD	20 (42%)	20 (77%)	
Elective caesarean section	14 (30%)**	2 (8%)	
Emergency caesarean section	13 (28%)	4 (15%)	
Apgars: median (IQR)			*>0.9*
1 minute	9 (8 – 9)	9 (6 -9)	0.717
5 minute	10 (8.75 – 10)	10 (8 – 10)	0.849
Birth weight category			<0.001
ELBW: < 1000g	2 (4%)	0	
VLBW 1000g-1499g	2 (4%)	1 (4%)	
LBW 1500g- 2499g	14 (30%)	9 (34%)	
Normal birth weight, 2500g-3999g	27 (57%)	14 (54%)	
Macrosomia ≥4000g	2 (4%)	2 (8%)**	
Birth weight median (IQR)	*2800 (1985, 3060)*	*2665 (2340,3295)*	*0.700*
Transferred for surgical intervention	11 (23%)	5 (19%)	>0.9
Mortality	5 (11%)	6 (23%)	0.279
Survival to hospital discharge	41 (87%)	21 (81%)	0.690

*Missing data
§Maternal RPR reactive: 2 mothers had untreated syphilis, asymptomatic neonates. Two fully treated antenatally.
||Chronic medication use: 1 case of gestational diabetes on metformin, antihypertensives agent, anti-retroviral medication (Tenofovir, Lamivudine, Dolutegravir), Isoniazid, sulfamethoxazole-trimethoprim, pyridoxine; 1 case of a maternal urinary tract infection case on oral antibiotics; the remaining cases included anti-retroviral medication.
+Maternal ingestion of pesticides at 4 months of pregnancy
**Post-hoc analysis results for the variables with significant chi-square tests, identifying which cells contributed significantly to the overall chi-square statistic based on the adjusted residuals

Short-term outcomes

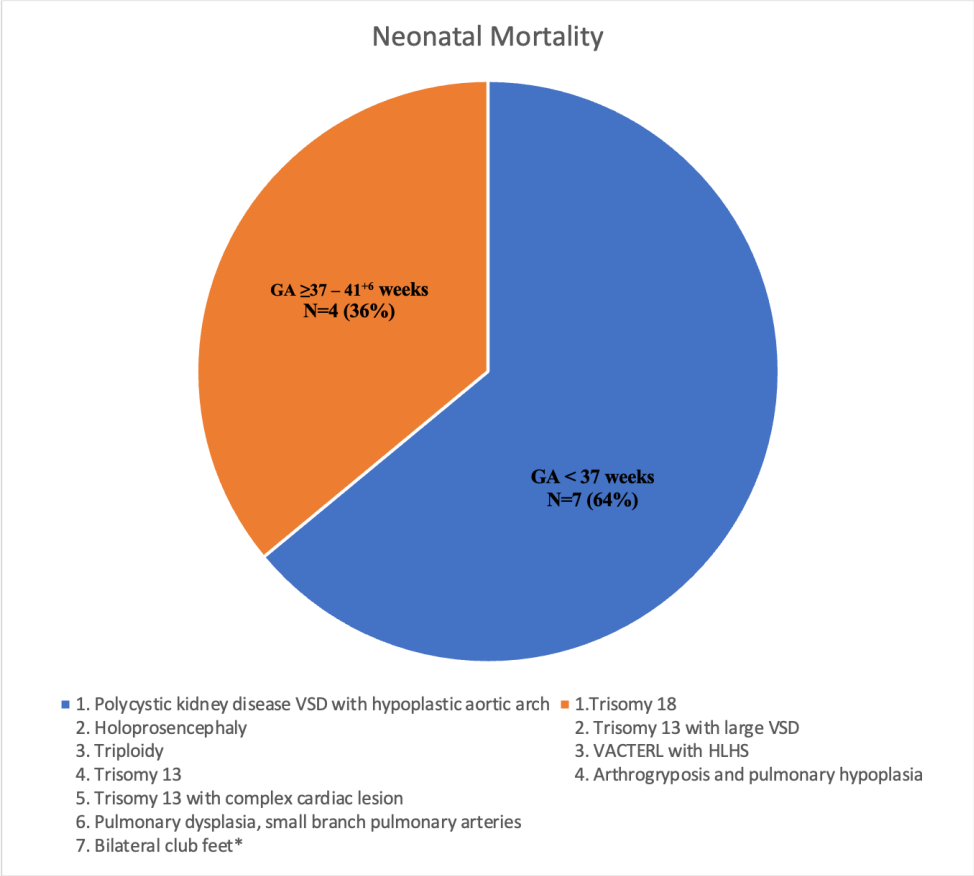
Twenty neonates (27%) with MCA required neonatal intensive critical unit (NICU) admission of whom 10 (14%) required non-invasive ventilation consisting of continuous positive airway pressure (CPAP) or high-flow nasal cannula (HFNC). Only 2 (3%) required invasive ventilatory support. Fifteen neonates (21%) required transfer to tertiary level hospital, 14 (93%) for surgical intervention, predominantly for gastrointestinal and genitourinary defects and two (29%) for urgent cardiological intervention.

More than a third (34%) of neonates had prolonged hospital admission of ≥7 days (range 7-175 days), 76% of these required rehabilitation services for feeding difficulties, poor growth or assistance with social services. These were mostly neonates with syndromic MCA, predominantly Trisomy 21 and orofacial cleft defects. Twenty-seven percent of neonates were clinically well, not requiring immediate medical intervention and were discharged home within 48-72 hours post-delivery with scheduled follow up appointments. The overall survival to in-hospital discharge, including transfers out, were 85% (n=62).

Neonatal Mortality

The overall in-hospital mortality rate was 11 out of 73 neonates (15%), of whom 7 (64%) were preterm, 27% VLBW (<1500g) and 36% LBW (< 2500g). Six deaths (55%) were neonates with syndromic MCA. These included two with Trisomy 13; Trisomy 18; Triploidy and a VACTERL association with a HLHS. Five neonates (46%) had non-syndromic MCA; diagnosed with holoprosencephaly; bilateral polycystic kidneys with a hypoplastic aortic arch and VSD; pulmonary dysplasia and bilateral small pulmonary arteries and one neonate with severe arthrogryposis and pulmonary hypoplasia ***(Figure 4)***.

Figure 4: Neonatal mortality



This graph demonstrates the in-facility causes of neonatal mortality and associated complete gestational age. Nine neonates (82%) were early neonatal deaths (death within the first week of life). Two (18%) were late neonatal death (Neonatal death after the first 7days but before 29days of life) *Not the primary cause of death (neonate died from severe perinatal hypoxia, meconium aspiration syndrome and multiorgan dysfunction).

Discussion

MCA and its relation to neonatal mortality and morbidity has been an area of growing interest due to its significant impact on childhood health outcomes.[9] There are limited studies done in SA and other LMICs to reflect these outcomes. This study aimed to narrow this gap by reflecting on the burden of antenatally undiagnosed MCA in the Western Cape by describing its prevalence, associated factors and short term outcomes within the MetroWest district.

Our study identified an in-facility MCA prevalence rate of 36 per 1000 neonatal admissions and 6 per 1000 live births among in-born neonates, which differs from other local studies: In Johannesburg, Mayer et al, 2021,[17] found an incidence of 2.60 per 1000 live births at a tertiary hospital over a two-year period and Saib et. al. demonstrated a CA prevalence of 15.57 per 1000 live births in 2020 from a regional hospital in Kwa-Zulu Natal (KZN).[18] These prevalence differences may be due to different study population sizes, research methods and case definitions. Both other studies included antenatally and postnatally diagnosed CA and minor and major CA; major CA defined as serious anomalies that may result in death, limited life expectancy or lifelong disability in the absence of care and minor anomalies as having little impact on health or quality of life.[18] In addition, KZN has historically been known for more complete CA documentation and notification and may thus have a more established reporting system, hence their higher prevalence.[6] Another study done in Nigeria showed a CA prevalence of 20.73 per 1000 live births, 2017[19] while a much older study published in 1995 by Venter et al. found a prevalence of 14.97 per 1000 live births in SA.[20]

Accurate CA prevalence data requires comprehensive healthcare systems with efficient surveillance programs, diagnostic capabilities (clinical and laboratory) and national infrastructure which are challenging in most LMIC.[9] Currently, global newborn CA prevalence estimates are 2-3% in most high-income countries (HIC)[18,21] but estimated higher, ~6% in LMIC.[9,18,22] The 2012 Modell Global database method estimated SA predicted birth prevalence of CA, a subset of birth defects to be 27.5 per 1000 live births[11] which is higher compared to a recent systematic review and meta-analysis of 32 African countries, showing a pooled CA prevalence of 2.35% (23.5 per 1000 births) with the range of 2%– 2.69% in Africa, 1.6% for South Africa.[22]

All studies acknowledge the considerable CA prevalence disparity in different LMIC attributed to inadequate surveillance systems, documentation, and notification.

LMIC are estimated to carry near 94% of the CA burden,[1] where poor maternal health and diet, increased teratogen, alcohol and drug exposure, poor antenatal access, screening, and late booking play a significant role. There has been an improvement in women accessing antenatal care since 1998 with 76% of women receiving four or more visits in 2016.[23] This was reflected in our study where 96% of women attended antenatal care services, most before 20weeks gestation and received at least one antenatal visit.

Most of our participants (82%) had at least one routine antenatal scan and 29% a FAS where the MCA were not detected. Amongst the 21 women who had FAS, 90% were done within the recommended ≤22 weeks gestation and 24% were AMA. Most cases where a FAS did not detect the MCA, were neonates with Trisomy 21 and/or significant intracardiac defects. A single FAS ≤22weeks may miss underlying chromosomal disorders and even intracardiac defects. Despite health care system challenges this possibly reflects improved maternal access to health services. This high false negative rate may largely be due to antenatal ultrasonography services being patient, operator, and equipment dependant. Also, NDoH AMA early screening services being limited to women ≥37 years excludes younger women who deliver neonates with chromosomal disorders as identified in our study. Women >35 years who book early should ideally have a basic anatomy scan (level 2) at 10-14 weeks and a detailed FAS. This may be improved by advocating for comprehensive maternal screening and diagnosis of structural and syndromic MCA through adequate clinical training of healthcare professionals and equitable distribution of financial support and human resource allocations especially in government hospitals.[16]

Our study population was analysed into two groups: non-syndromic-associated MCA (64%) and syndromic-associated MCA (36%). Both groups consisted of variations of single and multiple defects occurring in individual cases. In contrast to global estimates[1] our study had a high percentage of MCA associated with chromosomal disorders (27%) even though five dysmorphic babies did not receive genetic testing. A recent African large meta-analysis found 8.94% chromosomal disorders-associated CA, higher than the described 6% in high income countries (HIC)[24] They postulate that, besides the known LMIC risk factors for CA mentioned

above, a higher percentage AMA may be a contributing factor. Their study highlights the large gaps in reported versus expected proportions of chromosomal disorders among CA births in Africa where limited resources, poor screening and testing contribute to under-reporting.[24]

As perinatal care for prematurity, intra-partum hypoxia and infections improve, CA are coming to the forefront as an important contributor to neonatal mortality. The Perinatal Problem Identification Programme (PPIP) data for the Metro West region of Cape Town showed MCA to be the 2nd leading cause of early neonatal death for babies over 1000g in 2022, preceded only by perinatal hypoxia and followed by prematurity and infection.[25] In addition, as maternal health improve, including management of communicable diseases, malnutrition, maternal infections and intrapartum problems, chromosomal disorders contribute an increasing proportion to poor childhood health outcomes.[1] Chromosomal disorders are responsible for a significant proportion of mortality and morbidity, 20% higher in sub-Saharan Africa than in HIC.[24]

The chromosomal CA risk is known to increase with maternal age.[22,24] Our study confirmed a significant association between higher maternal age and syndromic MCA. In the syndromic MCA group, 46% of mothers were 36 years and older.

Our in-facility mortality was higher than the 10% described in previous LMIC studies[9] possibly due to this facility being a regional referral centre. Of our study deaths, 91% were early neonatal deaths reflecting the severity of MCA. Our study outcomes confirmed prematurity, low birth weight and the presence of multiple CA as known predictors of poor survival.[26] Additionally, more than a third (34%) were long-stay cases (>7days) and 21% required transfer to tertiary hospitals, 93% for surgical intervention, mainly for gastrointestinal, genitourinary and critical cardiovascular defects. This confirms the high burden of MCA on neonatal services in the Western Cape.

Limitations of study

This was a retrospective study looking at both in- and out-born neonates admitted to a single centre with a relatively small sample size and inherent limitations of incomplete clinical data documentation in folders and registries. Since MMH is an obstetric referral centre, the sample may have been biased towards more high-risk or complicated pregnancies. This may have resulted in an overestimated MCA prevalence rate. However, it must be acknowledged that many MCA categories are not clinically visible or identified in the newborn period, prior to hospital discharge.

The MMH MCA Neonatal Register (paper-based) was initiated in 2014 but only included MCA from 2022, with data recorded by all medical doctors in the unit for analysis. Thus, many MCA cases and possibly cases assessed after-hours may not have been documented. The exclusion of all minor CA and all stillbirths will also lead to an underestimate of the true MCA prevalence since MCA are common in stillbirths.[24] This may limit interpretation and comparability of observed birth prevalence with other data sources, limiting generalisability.

Conclusion

The prevalence rate of MCA in 2022 at MMH was 36 per 1000 neonatal admissions to a single regional facility and in-born only prevalence of 6 per 1000 live births. The in-hospital early mortality rate was 15%; 21% required referral for further medical/surgical intervention and 34% required long hospital stay. Diagnosis was not made antenatally despite a high proportion of women booking early and receiving at least one basic antenatal ultrasound. We hope this study outcomes encourage better MCA identification and surveillance to improve provincial and national notification, thus advocating for better preventative strategies and appropriate management and referral guidelines. Further collaborative South African studies are needed to strengthen data to accurately reflect the holistic burden of CA and its impact on childhood outcomes in SA.

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UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

22 July 2022

HREC REF: 365/2022

Dr A van Niekerk
Division of Neonatology
Mowbray Maternity Hospital
Email: Anika.vanniekerk@westerncape.gov.za
Student: melvinfelicity@gmail.com

Dear Dr van Niekerk

PROJECT TITLE: THE BURDEN OF 'ANTENATALLY UNDIAGNOSED' MAJOR CONGENITAL ANOMALIES IN LIVE-BORN BABIES AT A BUSY SECONDARY LEVEL MATERNITY HOSPITAL IN THE WESTERN CAPE
(MMED DEGREE – DR MELVIN FELICITY AMANKRAH)

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19. Please refer to guidance letter dated 02 February 2022 on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Approval is granted for one year until the 30 July 2023.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Melvin Amankrah will also be involved in this study.

Please quote the HREC REF 365/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Appendix 1

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/ref 365.2022

Appendix 1

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HUMAN RESEARCH ETHICS COMMITTEE
27 NOV 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.11.2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	27/11/2023

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za. Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	14/11/2023		
HREC REF Number	365/2022	Current Ethics Approval was granted until	30July 2023
Protocol title	The burden of 'antenatally undiagnosed' major congenital anomalies in live-born babies at a busy secondary level maternity hospital in the Western Cape.		
Principal Investigator	Dr AM van Niekerk (=Primary supervisor to MMed student: Purely observational study, record review)		
Department / Office Internal Mail Address	Neonatal Unit, Mowbray Maternity Hospital, 12 Hornsey Road, Mowbray, 7700 anika.vanniekerk@westerncape.gov.za		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☐ No☑

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☐☑	Data collection is complete(2022) , data analysis and write-up only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	
Nil	

3. Protocol summary

Total number of records ~~or specimens~~ collected, reviewed ~~or stored~~ since the original approval		86
Total number of records or specimens collected, reviewed or stored since last progress report		N/A
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	☐ No☑

4. Signature

Signature of PI		Date	14/11/2023

Appendix 2

Appendix 3

ConGenStudy2022: Data Capture Sheet

By: Dr M Amankrah
Supervisors: Dr Anika van Niekerk and Dr Kalk

The burden of antenatally undiagnosed major congenital anomalies in live born babies at a busy secondary level maternity hospital in the Western Cape

Study number:	
Baby's File Sticker **Name** **DOB** **Folder number** **Sex**	
Mother's File sticker	

Variable	Type	Data Entry
Maternal obstetric information		
Date of birth		
Age	Numerical	
ANC booking date	Numerical	
ANC Booking Site	Categorial	
Number of ANC visits	Numerical	
Gestational age at 1st booking (weeks)	Numerical	
Number of antenatal visits	Numerical	
Booking HIV status	Categorical	
Booking RPR status	Categorical	
Antenatal scan	Categorical	
Fetal anomaly scan	Categorical	
Gravidity		
Parity	Numerical	
Diagnosed Pregnancy related illness **Diagnosis:**	Categorical	
Medication use **Type:**	Categorical	
Substance use: **Alcohol:** **Smoking:** **Illicit drug use:** **Toxins:**	Categorical	

Birth Details		
Completed Gestational age at delivery(weeks)	Numerical	
Mode of delivery		
Birth weight	Numerical/Categorical	
Apgars	Numerical/Categorical	
Clinical outcome: **Alive + well** **Alive + sick** **Demised**	Categorical	
Clinical outcome details:		
Referred (yes or no)	Categorical	
Transferred for further care (yes or no)	Categorical	
Type of major congenital anomaly		
Final Diagnosis [ICD-10 code]		
Characteristics of major congenital anomaly	Categorical: Cardiac defect Respiratory tract defect Neurological defect Genitourinary defect Gastrointestinal defects Orofacial defects Genetic disorders with associated CA Others:	
Method of diagnosis:		
Clinical examination: **Radiological:** **Laboratory results:**	Categorical	

Appendix 4 : SAJCH instructions to authors

Author Guidelines

SAJCH Author Guidelines

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

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Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

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Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAJCH* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Protection of rights to privacy

Patient

Information that would enable identification of individual patients should not be published in written descriptions, photographs, radiographs and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAJCH.*

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Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note thatit is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

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SAJCH is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAJCH* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

MANUSCRIPT PREPARATION

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Editorials, Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format – this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAJCH is a Journal on child health, therefore for articles involving genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

- May include up to 3 illustrations or tables.
- A max of 20 - 25references

Structured abstract

- This should be no more than 250words, with the following recommended headings:

- **Background:** why the study is being done and how it relates to other published work.
- **Objectives:** what the study intends to find out
- **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
- **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
- **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

***Scientific letters*/short reports**

These include case reports, side effects of drugs and brief or negative research findings.

Guideline word limit: 1500 words

- Abstract: unstructured, of about 100-150 words
- May include only one illustration or table
- A maximum of 6 references

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

Review articles

Review articlesshould always be discussed with the Editor prior to submission.

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners. They should be aligned to practice in South and/or sub-Saharan Africa and not a precis of reviews published in the international literature

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.

- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 400 words

Letters to the editor should relate either to a paper or article published by the SAJCH or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx/doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

FROM SUBMISSION TO ACCEPTANCE

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the *SAJCH* requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
    - Anonymous manuscript (unless otherwise stated)
    - Author Agreement form [forthcoming]
    - Manuscript
    - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
    - Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer Review Process

All manuscripts are reviewed initially by the Editor-in-Chief and only those that meet the scientific and editorial standards of the journal, and fit within the aims and scope of the journal, will be sent for

external peer review. Each manuscript is reviewed by either one or two reviewers selected on the basis of their expertise in the field. A double blind review process is followed at SAJCH.

Authors are expected to receive feedback from reviewers and an editorial decision within approximately 6 weeks of submission. The time period of the entire review process may vary however depending upon the quality of the manuscript submitted, reviewers' responses and the time taken by the authors to submit the revised manuscript.

Manuscripts from review may be accepted, rejected or returned to the author for revision or resubmission for review. Authors will be directed to submit revised manuscripts within two months of receiving the editor's decision, and are requested to submit a point by point response to the reviewers' comments. Manuscripts which authors are requested to revise and resubmit will be sent for a second round of peer review, often to the original set of reviewers. All final decisions on a manuscript are at the Editor's discretion.

Production process

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Errata and retractions

Errata

Any error or inaccuracy in an author's (co-author's) contribution after it has been published, can be directed to publishing@hmpg.co.za,including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
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We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish anerratum in the next issue. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

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Send an email to publishing@hmpg.co.za, including the following details:

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- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

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