CONGENITAL ABNORMALITIES DIAGNOSED ANTENATALLY AT CHBAH: A RETROSPECTIVE DESCRIPTIVE STUDY 2016-2018

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Faculty of Health Science

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DECLARATION

I, Neliswa Sibongile Ngubane, declare that this research is original and contains no section copied in entirety or in part from any other source, unless specifically identified in quotation marks and with appropriate referencing. I declare that this work has not been submitted to any other university for the purposes of a postgraduate degree.

NGUBANE

19 May 2021

DEDICATION

To Gordon Keane, this journey would never have been the same without your wit.

PRESENTATIONS

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ABSTRACT

Background

Information on trends and prevalence of congenital abnormalities (CAs) in South Africa remains limited despite adverse associated perinatal and lifelong outcomes. Multiple factors have been shown to contribute to development of CAs. An understanding of our at-risk population will assist us in appropriately and timeously managing our patients.

Objectives

To describe the patterns and trends of CA diagnosed antenatally in our setting, in terms of: chromosomal and structural abnormalities; maternal age; gestational age (GA) at diagnosis; potential management of the diagnosed CA; and frequency of termination of pregnancy (TOP) after diagnosis.

Methods

This was a retrospective study conducted over a 14 month period on pregnant women with a diagnosed CA. Data were obtained from the fetal medicine unit's record books and electronic database. SPSS software was used for data analysis.

Setting

The study was done at Chris Hani Baragwanath Academic Hospital, a tertiary level hospital in Johannesburg, South Africa. It is the third-largest hospital in the world. Participants were attendees at the hospital's Fetal Medicine Unit (FMU), led by a team of three fetal medicine specialists.

Results

Four hundred and fifty-one records were extracted, with 404 participants enrolled into the study. The mean GA at diagnosis of a CA was 27 weeks and 4 days; 21/404 (5.1%) were confirmed chromosomal abnormalities. Central nervous system (CNS) was the leading system in structural CAs, followed by musculoskeletal and soft tissue (MSS), renal and cardiac systems. Trisomies 21 and 18 had similar occurrences. After sonographic diagnosis of a CA, 94/404 women (23.3%) proceeded to invasive testing; 79 (19.6%) women opted for TOP after CA diagnosis, and 32.9% of these were fetocides. Teenage mothers had no diagnosis of a chromosomal CA during the study but had a 30.8% occurrence of gastrointestinal birth defects. A majority (52.4%) of chromosomal abnormalities were diagnosed in the advanced maternal age group; 71% of the chromosomal abnormalities had an MSS defect detected on ultrasound scanning.

Conclusion

This study has shown that we are diagnosing CAs in advanced pregnancies as a result of delayed referral and presentation, with likely consequent psychosocial and socioeconomic difficulties for the families involved. The overwhelmed system with an understaffed FMU is also of concern. Attempts should be made to reduce this delay, to prevent not only family distress, but also to decrease the rate of fetocide, which poses an ethical dilemma to the fetal medicine specialists. Our findings on CAs are similar to those in the developed world, and we must strive to have our patients managed with similar care. Fetal surgery capability is still limited in South Africa, and greater availability of such skills can improve outcomes in affected patients.

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LIST OF ABBREVIATIONS

AMA	Advanced maternal age
BDNT	Birth defect notification tool
CA	Congenital abnormalities
CHBAH	Chris Hani Baragwanath Academic Hospital
CNS	Central nervous system
CPAM	Congenital pulmonary airway malformation
CVS	Cardiovascular system
DNA	Deoxyribonucleic acid
FMU	Fetal maternal unit
GIT	Gastrointestinal tract
HIV	Human immunodeficiency virus
MSS	Musculoskeletal and soft tissue
NT	Nuchal translucency
TOP	Termination of pregnancy

CHAPTER 1

LITERATURE REVIEW

Information on trends and patterns of congenital abnormalities (CAs) in South Africa is still limited (1,2). Attempts have been made to develop a surveillance system nationally using the birth defect notification tool (BDNT) (3). A review of this system found that it was not an effective surveillance tool, with concerns regarding underreporting of cases nationally (1,3). Different definitions for CA have been used, and for the purpose of this paper we have defined CA as structural or functional abnormality that occurs intrauterine, with the diagnosis being made prenatally, at birth or later in life (4). To date, more than 7000 CAs are known to occur (5,6). Approximately half of all these abnormalities have no attributable causes, with the remainder being the result of genetic and environmental factors (6). It has been noted that causes of CA post-conception are primarily environmental, whereas those occurring preconception are mostly genetic and of multifactorial inheritance. Multifactorial inheritance contributes 20-30% of all birth defects (6,7). The commonest genetic causes of CA include single gene defects and chromosomal abnormalities (8). Chromosomal abnormalities are either numerical or structural abnormalities noted in autosomes and/or sex chromosomes, their prevalence increasing with advancing maternal age (6,9). Common examples of chromosomal abnormalities include autosomal trisomies 21, 13 and 18, with Turner and Klinefelter syndromes involving the sex chromosomes (6,7). Single-gene defects result from mutations in gene structure and can be inherited from one or both parents but can also be of sporadic *de novo* origin. Single-gene defects often show multiple CAs although they can also be associated with isolated anomalies such as cleft lip, cleft palate and congenital heart defects (8,10). Commonly recognized syndromes caused by single-gene defects include cystic fibrosis, fragile X syndrome, muscular dystrophy, sickle-cell disease and Huntington's disease.

Globally, 7.9 million children are reported to be born with a CA each year (2), which equates to 1 in 33 births. In 2005, these contributed to 2.68 million deaths during the neonatal period worldwide, with a higher prevalence in low-middle income countries (5). A review of neonatal mortality in South Africa reported that 12.3% of the deaths in neonates can be attributed to CAs (2).

Ultrasonography has proved to be an indispensable tool in antenatal screening for CAs (1,2,11). Some major anomalies are easily diagnosed in the first trimester of pregnancy by trained and experienced observers (2,11), but even in such capable hands some CAs will be missed as they may not be structural in nature, such as neurodevelopmental or metabolic disorders. Nuchal translucency (NT) scanning and detailed fetal anatomy scans have indeed improved the capability of prenatal screening, and this now allows for appropriate risk stratification of the pregnant patient and assists in determining the need for invasive testing thereafter (11-14). Prenatal screening not only involves ultrasound findings but also biochemical markers (11,12). In resource limited settings, accessibility to these biochemical tests is limited, but there is still great benefit in performing the ultrasound scans as they assist in identifying patients at increased risk of CA (11,13–15).

Genetic testing is available to confirm or exclude chromosomal defects, and procedures conducted to obtain genetic material are mostly invasive. These include amniocentesis, chorionic villous sampling and fetal blood sampling. A less invasive but still limited approach such as cell-free DNA testing may also be adopted (15,16). The choice of procedure is tailored to each woman, depending on the gestational age, as well as the risks and benefits that pertain in each individual maternal-fetal pair (15). A particular problem is HIV-infected patients who are virally unsuppressed, in whom it can be challenging to timeously and safely perform invasive procedures. The ideal is for knowledge of status, planned pregnancy, early booking and optimal antiretroviral management with viral suppression. Unfortunately, in our setting with a high prevalence of HIV in women of reproductive ages, we are still presented with large numbers of women who attend antenatal care only late in pregnancy, HIV-undiagnosed and therefore not on antiretroviral medication (14).

There are differences in the patterns of defects diagnosed in teenage pregnancies versus those of advanced maternal ages (AMA) (9,11), with a well-established higher incidence of chromosomal defects in the AMA group, as opposed to higher structural defect rates in teenage pregnancies. A study done by Chen et al looked into the most vulnerable systems involved in teenage pregnancies, and found that these were, in descending order, CNS, GIT and MSS (17).

Prenatal diagnosis of CAs provides essential information for decision-making by parents (18), whether for termination of pregnancy (TOP), conservative management, or available fetal or neonatal interventions (19). The Choice on Termination of Pregnancy Act of 1996 (20) allows for termination of a pregnancy if a severe abnormality is diagnosed. However, the exact definition of a severe abnormality is not stipulated in the Act. Also, the upper limit of gestational age at which a termination may be offered is also not stipulated. This lack of clarity in the law complicates management of pregnancies with a diagnosis of CA. Most institutions adopt individualized policies on TOP when CAs are diagnosed. The factors that influence decision making include gestational age at time of diagnosis, severity of the abnormality and presence of other or multiple abnormalities. Unquestionably, decision making by parents is not only influenced by medical findings, but also significantly by factors such as religion and cultural beliefs (21,22).

Fetocide is an important procedure in patients in whom TOP is being considered at advanced gestational age. This involves injection of a drug or drugs into the fetal circulation to induce fetal cardiac asystole. These agents include potassium chloride, digoxin, lignocaine and hyperosmolar urea. A non-pharmacological method, the injection of normal saline into the pericardial space to induce cardiac tamponade, has also been reported. Currently there is no specific legislation in South Africa regarding fetocide, but each fetal medicine unit across the country applies a multidisciplinary approach in managing such cases.

The option to terminate a pregnancy when a lethal abnormality is diagnosed is far less complicated. Chervenak et al considered difficulties and morality in TOP beyond the second trimester (22,23). Their criteria for late pregnancy termination involved conditions not compatible with life for more than a few weeks after birth, as well as those in which the fetuses had no potential for cognitive function. In either case, such conditions must be diagnosed antenatally by a reliable diagnostic procedure, and if the criteria are fully met, TOP can be reasonably justified. The most appropriate example of a fetus so affected is anencephaly.

Regrettably, there are still pregnancies with non-lethal CAs associated with severe later disabilities that are not normally considered for TOP at an advanced gestation. Some CNS defects such as ventriculomegaly and Dandy-Walker variants are associated with a high probability of reduced intellectual capacity in the child, but the literature is unclear on the exact risks and outcomes of such conditions and this complicates counselling of parents. Some CAs are correctable surgically and the correction can be done intrauterine and/or postnatally. There is a growing number of fetal surgical procedures being performed prenatally worldwide (19). Advanced expertise is required for intrauterine surgical procedures, and this is still limited in our setting.

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CHAPTER 2

SUBMISSIBLE PAPER

Introduction

Information on the prevalence and pattern of congenital abnormalities (CA) in South Africa (SA) is still limited (1,2) . More than 7000 CAs are known to occur (3,4), with approximately half having no attributable causes and the remainder being the result of genetic, environmental and multifactorial factors (4). Worldwide, in 2005, 7.9 million children were born with a CA (2–4). Low-middle income countries are especially affected by neonatal deaths related to birth defects. A review of neonatal mortality in South Africa reported that 12.3% of deaths in neonates weighing 1 kg or more at birth could be attributed to CAs (2). Timely antenatal diagnosis of CAs is of utmost importance and dependent on multiple factors including early antenatal care booking, availability of level one ultrasonography to detect obvious pathologies, and ability to refer to specialist services where indicated. A matter of concern in South Africa is a national shortage and maldistribution of fetal medicine specialists, who remain a precious and extremely limited resource.

Ultrasonography has proved to be an indispensable tool in antenatal screening and diagnosis of CAs (1,2,5), by first-trimester nuchal translucency (NT) scan and by second-trimester fetal anomaly scan. These two scanning approaches aid in early diagnosis, which can assist parents in decision making and so minimize dilemmas with termination of pregnancy (TOP) at advanced gestation (6–8), which is associated with increased maternal morbidity and psychological concerns.

The Chris Hani Baragwanath Academic Hospital (CHBAH) Fetal Assessment unit receives a large number of referrals from the surrounding areas and provinces, thus offering an instructive representation of CAs in a South African setting. As such, it seemed appropriate to conduct this study to gain a broad appreciation of the burden of CAs in and around Johannesburg. The primary objectives of the study were to list all CAs diagnosed in our unit, to describe the types of structural and confirmed chromosomal abnormalities, and to determine the proportion of surgically correctable CAs. Our secondary objectives included determining the mean gestational age at diagnosis, comparing abnormalities between advanced maternal age (AMA) and teenage pregnancies, tracking the outcomes after diagnosis of lethal abnormalities, and assessing how many patients opted for invasive testing and/or pregnancy termination thereafter.

Definition of Terms

- A fetal or congenital abnormality (CA) was defined as any abnormality detected in pregnancy by ultrasound scan or by an invasive procedure. Soft markers were not included
- A structural abnormality was defined as a defect relating to the structure of a body part
- Chromosomal abnormality result from mutations which changes the number or structure of the chromosome.
- Teenage pregnancy was defined as pregnancy at ages 13-19 years at antenatal booking
- AMA was defined as a pregnancy at 35 years of age and older at antenatal booking
- TOP involved induction of labour prior to 24 weeks of gestation or fetocide
- Fetocide was defined as an iatrogenic act to cause death of the fetus.
- Surgically correctable conditions referred to CAs with a structural birth defect amenable to surgical correction after birth

- Musculoskeletal and soft tissue (MSS) was defined as an abnormality involving bone, muscle and/or the integumentary systems

Methods

This was a retrospective record review of antenatally diagnosed CAs in the fetal medicine unit at CHBAH, from January 2016 to March 2018. CHBAH is a tertiary level hospital, being a referral centre for a number of local clinics, as well as for district and regional hospitals in Gauteng and other provinces (Northwest, Northern Cape and Limpopo). Data were retrieved from the unit's databases and records. Participants included patients referred from CHBAH's antenatal clinic as well as from the private sector and other hospitals. Variables of interest included the pregnant patient's age, diagnosis of the CA, gestational age at diagnosis, maternal conditions, use of invasive testing and if so, the method and results of the test. The patient's decision to terminate the pregnancy was also determined. This information was then entered onto a data collection sheet.

A separate record book in the fetal medicine unit documents all invasive tests performed and their results. These were cross referenced with patients who were diagnosed with CAs and opted for invasive testing, and then used to determine the number of confirmed chromosomal abnormalities.

Data captured on the data collection sheets was then transferred on to Microsoft Excel. SPSS software (IBM SPSS Statistics for Windows, version V25 [IBM Corp., Armonk, N.Y., USA]) was used for data analysis. Descriptive summary measures used were number with proportion (%), and mean.

Results

The records of 404 pregnant patients were included for the study time period. Twenty-six (6.4%) were teenage pregnancies and 113 (27.9%) were AMA. The mean gestational age at diagnosis was 27 weeks and 4 days. Twenty one of the 404 (5.1%) were confirmed chromosomal abnormalities on invasive testing. Defects of the central nervous system (CNS) were the leading CA under the structural abnormalities, followed by multiple congenital abnormalities and MSS (Figure 1). Of 21 chromosomal abnormalities, Trisomy 13 and Trisomy 18 had the same frequencies (n=6; 28.6%), with five cases of Trisomy 21 (23.8%). Ninety-four (23.3%) patients proceeded to invasive testing after a CA was diagnosed on ultrasonography. Of those patients, 63 (67.0%) had an amniocentesis done, and 28 (29.8%) underwent a cordocentesis. One patient (1.1%) had a fetal pericardiocentesis (Table 1).

Seventy nine (19.6%) patients opted to have a TOP after a CA was diagnosed and of those 26 (32.9%) required and underwent a fetocide. One hundred and eighty structural abnormalities (44.6%) were classified as correctable. Confirmed chromosomal abnormalities with diagnosed structural defects were not classified as correctable conditions.

Among teenage pregnancies, making up 26 (6.4%) of the study population, the leading CA was CNS defects (38.5%) followed by gastrointestinal tract (GIT) defects (19%). No chromosomal abnormalities were diagnosed in the teenage pregnancy group. CNS birth defects were the leading CAs in AMA pregnancies, followed by MSS defects, although multiple malformations predominated at 28% (32/113) of all birth defects in this age group. Just under half (47.6%) of the chromosomal abnormalities were diagnosed in the AMA group of patients. Seventy one percent of the chromosomal abnormalities had an MSS defect component detected on ultrasound. All 45 patients who had invasive testing with absent structural abnormalities on ultrasonography had normal karyotype results.

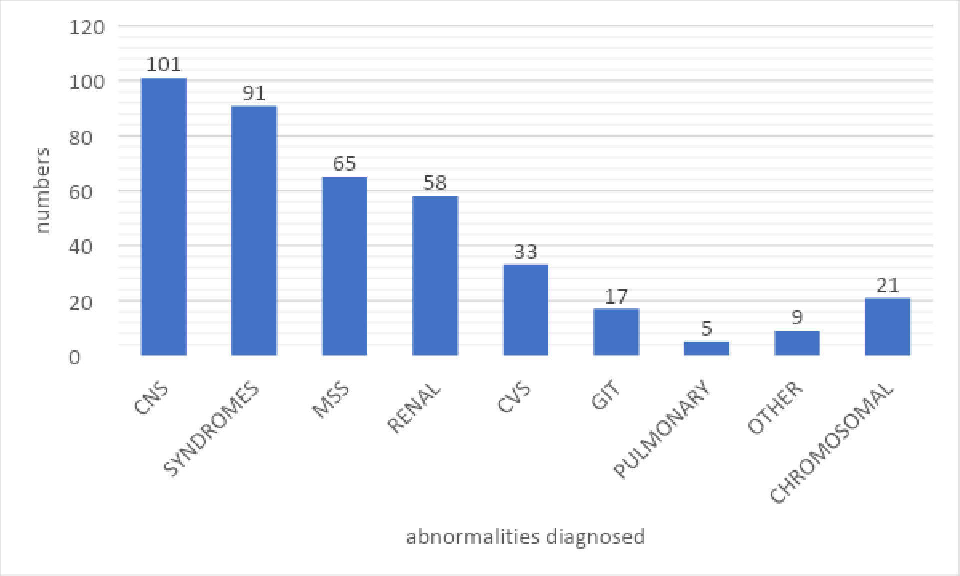

Figure 1. Diagnosed abnormalities during study period clustered into systems

Table 1: Successful procedures recorded during the study period.

Invasive procedure performed	Number performed	Results obtained	%
Amniocentesis	101	93	92.1
Cordocentesis	29	22	75.8
Fetocides	26	n/a	n/a
Pericardiocentesis	1	1	100

Fetal congenital abnormalities by systems (Table 2 and Figure 2)

CNS: the commonest CNS abnormalities diagnosed included, in descending order, ventriculomegaly (n=16), hydrocephalus (n=14), anencephaly (n=14), spina bifida (n=11) and hydranencephaly (n=9).

MSS: the commonest MSS abnormalities diagnosed were club foot (n=13), skeletal dysplasias (n=18), diaphragmatic hernia (n=7) and polydactyly (n=5).

Renal: the commonest renal abnormalities diagnosed were obstructive uropathies (n=22), multicystic dysplastic kidney disorders (n=17) and renal agenesis (n=7). Among the obstructive uropathies, pelvi-ureteric junction obstruction was the leading cause.

CVS (cardiovascular system): the commonest CVS abnormalities diagnosed were septal defects (n=9), cardiomegaly with associated pericardial effusion (n=8) and hypoplastic heart disease (6), right more common than the left.

GIT: disorders frequently diagnosed were gastroschisis (n=6), omphalocele (n=5) and bowel obstruction (n=5).

Pulmonary: Among five cases recorded, there were three with congenital pulmonary airway malformation (CPAM).

Other: some of the conditions not classified under the abovementioned systems included conjoined twins, ovarian cyst and a case of ambiguous genitalia

Chromosomal abnormalities: Trisomies 13 and 18 had the same frequency during the study with 6 cases each, followed by Trisomy 21 (n=5). There was one case of a balanced translocation.

Table 2. The abnormalities classified

CNS	MSS	RENAL	CVS	CHRMOSOMAL	GIT	PULMONARY
Ventriculomegaly (16) Hydrocephalus (14) Spina Bifida (11) Multiple CNS CA (4) Anencephaly (14) Arnold Chiari Malformations (1) Hydranencephaly (9) Absent cerebellar vermis (2) Choroid cyst (5) Holoprocencephaly (6) • Lobar (5) • Alobar (1) Dandy walker malformation (5) Encephalocele (4) ICH (5) Absent septum pellucidum (3)	club foot (13) skeletal dysplasia (18) • non lethal (12) • lethal (6) diaphragmatic hernia (7) Polydactyly (5) Microcephaly (4) Cleft lip/palate (4) Cystic hygroma (3) Facial teratoma (2) Scoliosis (1) warfarin embryopathy (2) Acrania (1) Sacral Agenesis (1) Amniotic band (1) Sacrococcygeal teratoma (3)	obstructive uropathies (22) • hydronephrosis (10) • PUJ obstruction (7) • vesicoureteric obstruction (6) • posterior valves (4) • urethral obstruction (1) multicystic dysplastic kidneys (17) Renal cyst (1) Renal agenesis (7) • bilateral (5) • unilateral (2) Keyhole bladder (1) Infantile polycystic kidney disease (2) Prune belly (1) Displaced kidney (1)	Septal defects (9) Hypoplastic heart disease (6) • Left (2) • Right (4) TAPVD (1) Dextrocardia (2) Valvular heart disease (2) Cardiomegaly +pleural effusion (8) TOF (1) Cardiac tumor (2) Congenital heart block (2) Ectopia cordis (1) Ebsteins anomaly (1)	trisomy 18 (6) trisomy 13 (6) trisomy 21 (5) Balanced translocation (1)	Gastroschisis (6) Ompha bowel obstruction (5) Gastro-oesophageal fistula (1)locele (5)	CPAM (3) Sequestration (1) pulmonary hypoplasia (1)

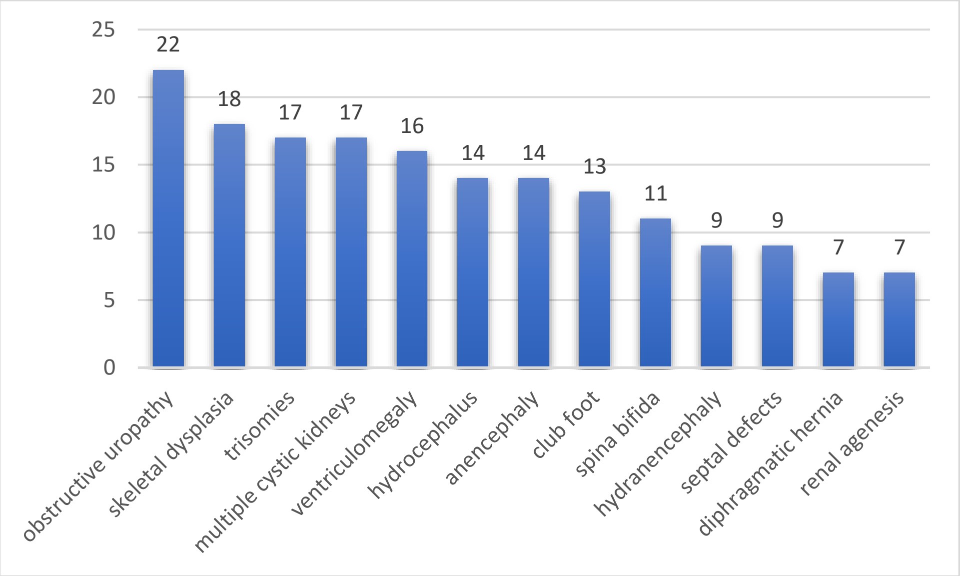

Figure 2. Leading isolated congenital abnormalities across all systems

Discussion

In the discipline of fetal medicine, there is increasing knowledge with improved techniques in detection and diagnosis of CAs, with conditions that historically were only detected at birth now diagnosed as early as the first trimester. As such, a prenatal diagnosis of an abnormality must be followed by a plan of action. This study looked at the types of CA diagnosed during the study period in a typical lower socio-economic urban community in South Africa at a resource-constrained tertiary hospital, and the choices of parents after the diagnoses were made.

The findings were mostly in keeping with prevalence seen in current literature from developed countries. The leading birth defects were CNS, multiple congenital abnormalities/syndromes, MSS, renal, cardiac and chromosomal abnormalities, in descending order. Pulmonary and genital tract systems were the least affected systems in all age groups and overall. Under each system, the anomalies diagnosed are listed. MSS defects in isolation were the third commonest, but they occurred frequently in conjunction with other defects; 71% of all chromosomal abnormalities had an MSS component diagnosed.

The GIT system overall was not commonly affected, although it was the second-most frequent system affected in teenage pregnancies. Why younger mothers are susceptible to these uncommon anomalies remains unclear from our study.

After diagnosis of a CA, 79 patients opted to have a TOP performed, of which 41% were in the AMA group. This not only highlights the increased burden of CA in this age group but the need for early screening, which is challenging in the resource-limited yet overburdened system in our setting. It is evident in the literature that there is an associated increase in CA with AMA (9), and this study showed a similar pattern. While there were no chromosomal abnormalities detected on invasive testing with a normal ultrasound exam, it is of note that this extended to even the patients with AMA, a well-established high-risk group for chromosomal abnormality. This highlights the importance of timely fetal anomaly scans done by trained and experienced personnel.

The choice to proceed with a TOP increased with increasing age. The younger the woman, the greater the likelihood of continuing a pregnancy with a diagnosed CA. This correlates with a study that was done by Govender et al, where the authors concluded that younger primigravidas were more likely to proceed with pregnancies affected by a CA, with the hope that the baby might be born normal (10). Factors that may contribute to this trend in our population might involve the social grants that affected mothers receive and which can support an entire household, the maturity level of the younger women, or the offered support from relatives that may reassure the young primigravida.

Secondary to the referral system in place, patients were referred back to their base hospitals for TOPs, except when fetocides were required, in which case the TOP process was completed at CHBAH. According to the local institutional protocol, fetocides are performed for terminations where the gestational age is above 24 weeks. With few follow-up reports from base hospitals, and with only fetocide terminations reliably completed locally, it was not possible to determine the outcomes of most patients.

Invasive testing has become standard practice in fetal medicine. During the study two methods were largely used, amniocentesis and cordocentesis. Chorionic villous samples were taken, but neither of the patients were included in the study as the fetal/embryonic findings did not meet the inclusion criteria (results were obtained for both and were normal). Of note is that all patients (n=45) who had an invasive test based on any factor other than abnormal ultrasound findings had normal karyotype results. These factors included AMA, maternal CA, previous offspring with a CA, certain maternal infections and conditions. One would argue the cost effectiveness of then conducting the test in those with normal ultrasound findings, but these factors can cause maternal distress, and prenatal testing does assist in assuring the couple. And testing in high risk cases is globally indicated. These women though were excluded from the study as they had no CA, structural or chromosomal.

In patients who opted for a TOP after sonographic diagnosis of a CA above 24 weeks, cordocentesis was performed at the time of fetocide as per hospital protocol. This is mainly how the cordocentesis numbers were obtained. As mentioned above, chorionic villous sampling was limited in our study and this can be attributed to a few factors. First, a study done in Cape Town revealed that 62% of women book for antenatal care after 20 weeks of gestation in the Western Cape province, and therefore cannot qualify for the procedure. Second, with the compounded factor that a large number of women are only diagnosed with HIV at their antenatal booking visit, it may prove difficult to conduct the first-trimester aneuploidy screening and performing certain invasive procedures such as CVS following the national guidelines (11), requiring viral suppression in order to perform the test, which then can explain the reason for the limited number of chorionic villous samples performed. Third is the delay in referral to the specialist unit from the peripheral clinics or hospitals, exacerbated by an overloaded fetal medicine service with the need to place referred patients on waiting lists. In our experience, there are also circumstances where women miss their appointments owing to financial issues affecting, for example, transport to the hospital, especially from remote localities in other provinces.

In comparison with amniocentesis, which yielded a result in 95% of procedures, only 75% of the cordocentesis yielded a result. Many of the specimens were rejected on the basis of no culture in the cordocentesis group. The fetal medicine unit raised concern with the cytogenetics laboratory regarding delays in receiving specimens from CHBAH, with dispatch delays up to 5 days and such specimens being of poor quality for assessment. The fetal medicine unit does not have direct access to the cytogenetics laboratory and relies on the National Health Laboratory Services for storage and transport to the cytogenetics laboratory. Also, it is documented in the literature fetal blood samples pose difficulties in cytogenetic analysis. A possible consideration is whether it would be more feasible to send amniotic fluid at fetocide rather than fetal blood, for better yield of results.

Defining surgically correctable conditions proved challenging during the study. The potential correction did not clearly define the prognosis and whether the condition was reversible or merely improved with surgery. Therefore, it was not possible to determine a conclusive number of correctable conditions. In a study done on neonatal surgical outcomes at one of the tertiary hospitals in Johannesburg, it was reported that one-third of neonatal intensive care admissions were secondary to surgical conditions, and that of these, 52% were associated with major birth defects (12). The authors noted mortality secondary to multiple factors, with infection accounting for approximately 30% of deaths. Surgical outcomes were not part of the scope of our study, but having information on the procedures performed on these surgically correctable conditions would have been valuable, as would have been assessing the success of such procedures in our hospital and the criteria used as to which cases qualify for surgery.

The leading teenage pregnancy CA trends were similar to those reported by Chen et al (13), being CNS, followed by GIT then MSS. It remains unclear as to why teenage pregnancies are disproportionately affected by GIT abnormalities, as noted earlier. A study done previously on gastroschisis and omphalocele found that younger mothers were indeed mostly affected, and associated documented risk factors included the use of tobacco, alcohol and ibuprofen (14). Our study did not look for usage of substances and therefore such information could not be reported.

There was a noted higher male predominance with the chromosomal abnormalities, including Down's syndrome, but the numbers examined do not have sufficient power to make a conclusion. A few studies have shown an increased prevalence of CAs among male pregnancies (15).

Conclusion

This series of CAs in our setting follows a similar pattern to those of developed countries, although in this study a large proportion of CAs were detected in advanced pregnancy, beyond the second trimester. Therefore, attempts should be made to reduce the phenomenon of late antenatal booking and delayed presentation and referral, as this is associated with increased fetocide rates and poses higher maternal morbidity, as well as psychological issues for affected families and ethical dilemmas for the fetomaternal specialists.

Awareness of the CAs diagnosed in our setting should encourage a search for these conditions at level one ultrasound scanning in district and regional hospitals, with timeous referrals leading to earlier diagnosis. Attempts at discerning possible causative factors where applicable, as in congenital infections, environmental and prescription drug exposures, should also be made. Improvements in following up antenatally diagnosed cases into the neonatal period would assist in assessing the accuracy of prenatal diagnosis in our setting in future. The field of fetal surgery can develop locally with improved skills and resources to lessen the burden on neonatal morbidity and mortality. As suggested in the study, a group of CAs may be amenable to surgery, be it curative or for alleviation of disease.

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Appendix A. Approved research protocol

Introduction/Literature Review

Congenital abnormalities (CAs) are defined as structural or functional anomalies that occur during intrauterine life and can be identified prenatally, at birth or later in life (1). There are other terms other than CA used to describe developmental disorders of the embryo or fetus (1, 2), and they include birth defects, congenital anomalies or congenital malformations. These attributed 2.68 million deaths during the neonatal period in 2015 worldwide (3), and higher prevalence in the low-middle income countries of which South Africa is one. The incidence of major congenital abnormalities is 2%, and although rare, it remains the responsibility of the physician to apply all possible means in order to make a diagnosis and hopefully improve pregnancy outcomes (4).

In 2006 the March of Dimes Foundation reported there were at least 7.9 million people born each year with a birth defect worldwide (5). Currently there are more than 7000 birth defects known to occur (6). Christianson reported that the five most common CAs in the year 2001 which were observed to account for an estimated 25% of genetic and multifactorial birth defects, were: (i) congenital heart defects, (ii) neural tube defects, (iii) the hemoglobin disorders: thalassemia and sickle cell disease, (iv) Down syndrome (trisomy 21) and (v) Glucose-6-phosphate dehydrogenase (G6PD) deficiency. The prevalence of CAs resulting in malformations of the CNS range from 2.73 per 1000 births to 14 per 1000 births. The prevalence for malformations due to MSS has a wider range in the literature; ranging from 1.36 to 42.7 per 1000 births (4, 7, 8).

The above estimates indicate that CAs are of global concern and there is a need for surveillance. A surveillance system, the birth defect notification tool, was established in SA the year 2001. It has unfortunately been less than informative in the birth defects being diagnosed countrywide, due to underreporting (9). Gauteng has the largest population in the country, yet the surveillance report during that 8 year period showed significantly lower numbers of CA reported, compared to other provinces.

In 2006, it was reported that amongst the chromosomal abnormalities seen in South Africa, Down’s Syndrome dominated whereas hand deformities (otherwise unclassified) dominated the structural abnormalities category (10). This is further substantiated by an earlier study done by Kromberg et al (11), who found that out of the commonest minor birth defects (structural) in SA Black population, polydactyly was the leading cause. A minor defect is defined as an unusual anatomic feature that is of no serious consequence to the patient, mostly cosmetic and not requiring intervention medically. Common major birth defects reported in the Kromberg study were hydrocephalus, spina bifida, anencephaly and facial clefts, in descending order. A major defect is defined as a defect having medical/social implications, often life-threatening and requiring surgical repair.

There are some documented causes and risk factors associated with CA, and these may be genetic or environmental. Approximately 50% of these cannot be linked to any specific cause (1). The established causes include single-gene defects, chromosomal disorders, multifactorial inheritance, environmental teratogens and micronutrient deficiencies (1, 2). Single-gene defects and chromosomal abnormalities can be grouped under hereditary causes, in this group conditions such as the trisomies (e.g. Down syndrome, Patau syndrome, Edwards syndrome) and X-linked abnormalities (e.g. Turner, Klinefelter) are found (4). Environmental causes house a large cluster of detrimental variables, including infections, drugs (prescription and recreational) and ionising radiation (1, 4). Maternal age is a well-recognized risk factor for CA, and Cambra et al (12) showed a correlation between chromosomal abnormalities with advanced maternal age (AMA), and non-chromosomal abnormalities with teenage pregnancy. There has been an increasing number of women postponing pregnancy for reasons including maternal education, later marriages and improved contraception (13), but unfortunately this also comes with increased risks such as chromosomal abnormalities, as well as increased risk of miscarriages and preterm births (14). There has been no proven extra risk in AMA with non-chromosomal abnormalities compared to the younger age groups. As for teenage pregnancy, an increased risk in abnormalities of the CNS, MSS and gastrointestinal systems has been noted (15)

Prenatal diagnosis of CAs provides essential information for decision-making by parents but also allows appropriate perinatal management for surgically correctable CAs which may improve outcomes (16). Surgically correctable conditions include abdominal wall defects, cleft lip and palate, congenital pulmonary anomalies and congenital cardiac conditions. A prenatal diagnosis allows for paediatric surgery and paediatric involvement to plan a controlled delivery in an institute with facilities for specialized care and repair of these conditions (17). This is of greatest importance for congenital cardiac defects as neonates may begin to decompensate as they switch from fetal to neonatal circulations and require intensive care in specialized cardiac intensive care units. Neonates with congenital pulmonary conditions also require specialized care in the immediate post delivery period. Ventilation is often required until pulmonary artery pressures decrease and surgical repair may be attempted (17). Surgically correctable CAs may also have favorable and unfavorable prognoses and a prenatal diagnosis allows for appropriate counselling of parents about anticipated outcomes. The presence of multiple abnormalities, a chromosomal defect and large defects are associated with unfavorable prognoses. Effects on surrounding adjacent structures such as pulmonary hypoplasia in the presence of congenital pulmonary anomalies are also considered in the counseling. The feasibility of repair with good outcomes are also considered. This is of most significance with severe cardiac defects such as hypoplastic left and right hearts with single ventricle and or atria anatomy (18). A multidisciplinary approach to prenatal care and counseling as well as post-natal care and counseling is always advised (17, 18).

Prenatal diagnosis also presents expectant parents with a choice of termination or continuing with a pregnancy if a severe or lethal abnormality is diagnosed. The Choice on Termination of Pregnancy (TOP) act of 1996 (19) allows for termination of a pregnancy if a severe abnormality is diagnosed but the exact definition of a severe abnormality is not stipulated by the act. The upper gestational age until when a termination may be offered is also not stipulated. This lack of clarity in the law complicates management of pregnancies with the diagnosis of CA. Most institutes adopt individualized policies on TOP when congenital abnormalities are diagnosed. The factors that influence decision making are gestational age at time of diagnosis, severity of the abnormality, presence of other or multiple abnormalities, presence of a chromosomal defect and parents’ wishes.

Ultrasound antenatal screening for abnormalities should be offered and available for all pregnant women. A retrospective study was done at CHBAH over a 2 year period that considered nuchal translucency (NT) as a screening tool to predict aneuploidy and structural abnormalities (20), and the authors concluded that this screening method “enabled prenatal karyotyping to become cost effective and allows concentration on pregnancies at highest risk for chromosomal abnormalities”. Advanced gestational age at diagnosis of a CA, lack of level three scanning expertise and poor access to ultrasound for many pregnant women in the community impact negatively on the diagnosis, investigation and management of pregnancies complicated by CA. A diagnosis of a severe abnormality at advanced gestational age presents the attending physician with the ethical dilemma of offering a termination of pregnancy or not. The situation may be further complicated by poor visualization of fetal anatomy on ultrasound owing to advanced gestational age to either confirm or exclude the presence of associated abnormalities. The option to terminate a pregnancy when a lethal abnormality is diagnosed is less complicated. Chervenak et al looked into difficulties and morality in TOP beyond the second trimester (21). They had criteria that involved conditions which are not compatible with life for more than a few weeks after birth, and fetuses with absent cognitive function. Both these conditions must be diagnosed by a reliable diagnostic procedure antenatally. The most appropriate example of such conditions is anencephaly. Based on the criteria fully met one could then justify the act of TOP. There is sadly still the group of pregnancies with non-lethal but crippling CA detected very late in their gestation and not considered for TOP, based on the advanced gestation. The diagnosis of some CNS defects such as ventriculomegaly and Dandy Walker variants may be associated with the risk of reduced intellectual capacity, but the literature is unclear on the exact risks and outcomes of such conditions and this complicates counseling of parents.

Diagnostic invasive procedures available prenatally include amniocentesis, chorionic villous sampling, and fetal blood sampling/cordocentesis (22). These are the gold standard diagnostic tests for pregnancies at high risk for CA. Once these samples are obtained they can be tested in the laboratory using methods such as full karyotype, rapid testing, molecular diagnosis of chromosomal imbalances and for diagnosis of monogenic disease (20).

The two most important factors that influence the choice of diagnostic invasive testing are gestational age and HIV positivity. The optimal gestational age to perform chorion villus sampling is 11 to 12 weeks (22). An amniocentesis may be performed from around 16 weeks of gestation because of the increased risk of limb defects if performed earlier. In the third trimester, the concern is that there may not be sufficient DNA in amniotic cells for culture and fetal blood may need to be sampled for karyotyping. The choice of testing in our setting is further complicated by the diagnosis of CA at advanced gestations. Amniocentesis is preferred over chorion villus sampling and cordocentesis in HIV positive patients even if they are virally suppressed. Even then, the decision to proceed with invasive testing should involve the weighing of benefits versus risks and the severity of the abnormality diagnosed on ultrasound.

Problem statement/Justification for the study

Information on the trend and pattern of CAs in South Africa is currently limited; hence, the only information in the literature is that acquired from estimates using modelled data.

The CHBAH fetal medicine unit is a referral unit for surrounding provinces, districts and regional hospitals and community health clinics. General practitioners and private gynaecologists also refer patients to the unit. Hence, an audit of the CAs diagnosed by the unit will provide valuable information about types and prevalence of CA in a typical South African setting. Parents' decisions regarding management may reflect cultural and social beliefs that may assist clinicians with counseling of patients.

Aim

We wish to describe the patterns and trends of congenital abnormalities, chromosomal and structural, diagnosed in the antenatal period in CHBAH fetal medicine unit.

Primary objectives

A. To describe all fetal abnormalities diagnosed at the fetal medicine department in CHBAH between January 2016 to March 2018
B. To describe the types of structural and confirmed chromosomal abnormalities diagnosed in the study time period
C. To determine the proportion of surgically correctable CA diagnosed during the study period

Secondary objectives

A. To evaluate the abnormalities, both structural and chromosomal, diagnosed in teenage pregnancies in comparison with advanced maternal age pregnancies
B. To evaluate pregnancy outcomes after diagnosis of a lethal or severe abnormality and to determine how many patients opt for TOP
C. To determine how many patients opt for invasive testing after sonographic diagnosis of a CA
D. To determine the mean gestational age at which CAs were diagnosed

Methodology

Study design

This will be a retrospective record review / clinical audit.

Setting

CHBAH Obstetrics and Gynaecology department, fetal assessment unit. It is a tertiary academic institute, government funded and is affiliated with the University of the Witwatersrand. The fetal medicine unit is part of the Obstetrics and Gynaecology department in CHBAH. It offers level 2 and 3 obstetrics sonography, equipped with two level 2 sonographers and two obstetricians offering level 3 sonography. Patients are seen via appointments made from within the obstetrics department as well as from outside the hospital, from both public and private sectors. Invasive procedures are performed by the fetal medicine specialist in the unit and carried out within the unit itself.

Study group

Patients who had a diagnosis of a fetal congenital abnormality made in the department from January 2016 until March 2018.

Inclusion criteria

- Pregnant women with a diagnosis of a fetal congenital abnormality made on ultrasonography and/ through an invasive procedure by the fetal medicine department at CHBAH
- Diagnosis made between January 2016 and March 2018

Data collection

Patients will be identified from a fetal abnormality record book in the fetal assessment Centre. A fetal abnormality will be defined as any abnormality detected in pregnancy by ultrasound or by an invasive procedure. These can be further classified as major and minor, where a major abnormality is defined as an unusual anatomic feature that is of serious medical or cosmetic consequences to the patient and the minor is of no serious consequence to the patient. A structural abnormality will be defined as a defect relating to the structure of a body part. A chromosomal abnormality will be defined as an abnormality secondary to a defect in a chromosome or in the genetic material arrangement of a chromosome

The patient's name, hospital number, diagnosis and date of diagnosis will be identified and entered onto a data collection sheet (attached). The fetal assessment centre database will then be searched for clinical ultrasound reports for the patients. Patients' demographics and detailed ultrasound findings will be entered onto the data collection sheet. A separate record book in the fetal medicine unit documents all invasive test results. This will be cross-referenced with patients who were diagnosed with CA and opted for invasive testing and used to determine the number of confirmed chromosomal abnormalities that were diagnosed. These data will be captured and entered on to data collection sheets. A teenage pregnancy will be defined as pregnancy between the ages 13-19 years at booking. Advanced maternal age will be defined as pregnancy at 35 years of age and older at booking

Clinical fetal medicine ultrasound reports will be used to determine the number of patients who opted for termination of pregnancy. Termination of pregnancy will include an induction of labour prior to 24 weeks of gestation or a fetocide before delivery. A fetocide will be defined as an iatrogenic act to cause death of the fetus. A lethal abnormality will be defined as an abnormality that is not compatible with life beyond the neonatal period. A surgically correctable condition will be described as a CA with a structural birth defect amenable to correction surgically postnatally. A severe abnormality will be defined as a condition that can cause significant suffering or long-term impairment.

The gestational age at which CA is diagnosed will also be determined and captured on the data collections sheets.

Study size

Anticipated number of records to be included in the study is 1000 files or more.

Data analysis

Means, frequencies and percentages will be estimated for each variable. Redcap will be utilised and the significance of the effects determined at a significance level of $\alpha = 0.05$; representing a confidence level of 95%. Comparisons will be made using appropriate Fisher's exact test.

Limitations

Incomplete reports

Inability to find clinical reports

Loss to follow up with patient's who did not return to the unit

Delivery/terminations outside CHBAH with no knowledge of outcomes

Patients who declined invasive testing can only be assumed to have a suspected chromosomal abnormality.

Ethical consideration

The study is retrospective and there will be no direct interaction with patients, therefore no patient consent is required. Approval from the WITS Health Research Ethics Committee has been requested. Application for consent to conduct the study at CHBAH from the Hospital CEO and the HOD in Obstetrics and Gynaecology has been submitted and is pending.

Funding

Administrative costs and statistician to be covered for by the researcher.

Timing

2018	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Protocol development		X	X									
Submission				X								
Correction					X							
Ethics					X							
Data collection						X	X	X	X			
Analysis										X	X	X
2019	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Analysis												
Write up	X	X	X									
Marking				X	X							
Corrections						X						

Appendix B. Data collection sheet

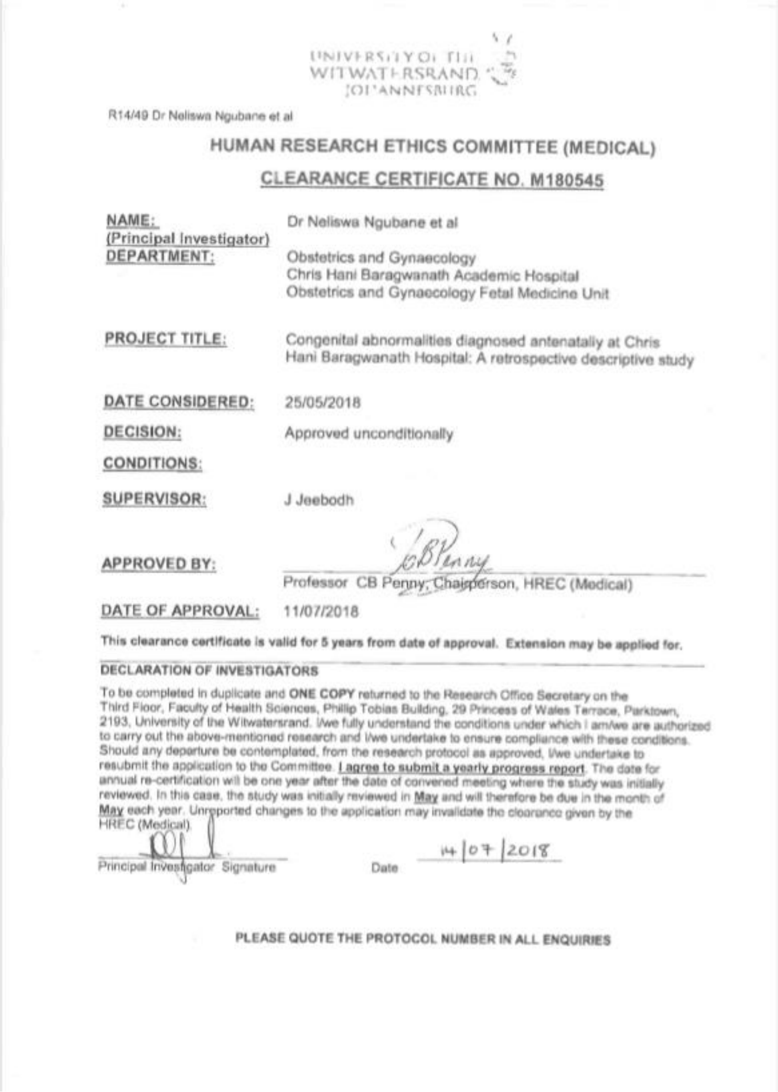
DATA COLLECTION SHEET

PATIENT STUDY NUMBER:…………...

RESEARCH VARIABLES	PATIENT INFORMATION
Name	
Hospital number	
Age	
Address (Town/City)	
Gravidity	
Parity	
Congenital abnormality diagnosed	
Structural	Chromosomal
☐ CNS……………………………………… ☐ Cardiac………………………………… ☐ MSS…………………………………….. ☐ Pulmonary ………………………… ☐ Renal ………………………………… ☐ GIT……………………………………….. ☐ Multiple systems, expand...................................... ☐ Other, specify………………………… Condition surgically correctable? ☐ Yes ☐ No	☐ Trisomy 13 ☐ Trisomy 18 ☐ Trisomy 21 ☐ X-linked ☐ Klinefelter ☐ Turner syndrome ☐ Other, specify……………………………….
Diagnosis made via: ☐ Ultrasonography ☐ Invasive procedure (if done) ☐ Both	Karyotype results:
Gestational age diagnosis	
Index pregnancy outcomes ☐ Liveborn ☐ Stillborn/IUFD	Relevant medical history ☐ Maternal congenital abnormality ☐ Family history of congenital abnormality

☐ Miscarriage ☐ TOP ☐ Lost to follow up ☐ Referred back to referral centre	☐ Diabetes Mellitus ☐ Infection: specify ☐ Other Treated Y/N ☐ Chronic medication Medication…………………………….. ➢ Condition…………………………….

Appendix C. Ethics clearance certificate



UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R14/49 Dr Neliswa Ngubane et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180545

NAME: **(Principal Investigator)**	Dr Neliswa Ngubane et al
DEPARTMENT:	Obstetrics and Gynaecology Chris Hani Baragwanath Academic Hospital Obstetrics and Gynaecology Fetal Medicine Unit
PROJECT TITLE:	Congenital abnormalities diagnosed antenatally at Chris Hani Baragwanath Hospital: A retrospective descriptive study
DATE CONSIDERED:	25/05/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	J Jeebodh
APPROVED BY:	CB Penny Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	11/07/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

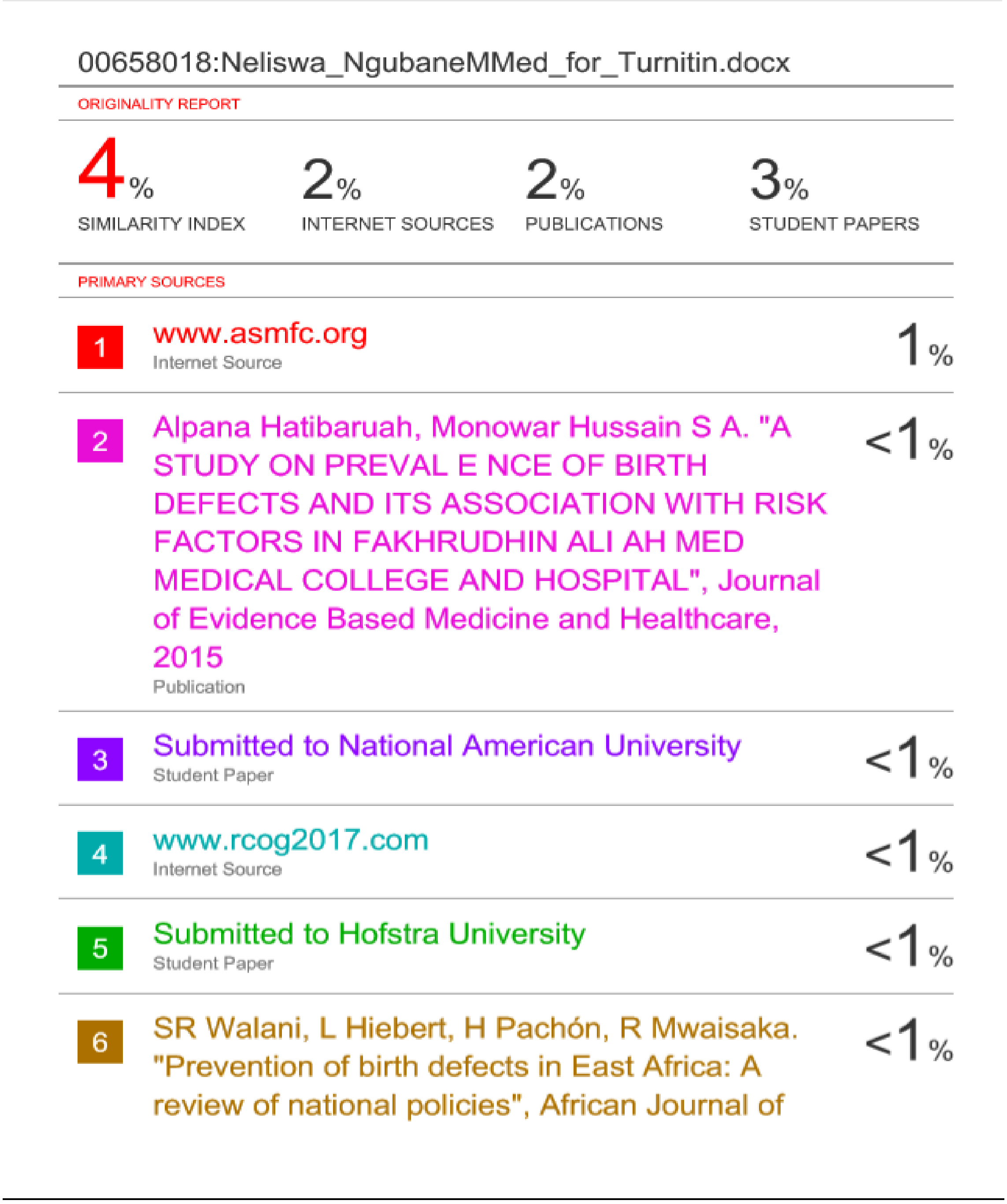
To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I agree to submit a yearly progress report. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in May and will therefore be due in the month of May each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 14/07/2018

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix D. Turnitin plagiarism report



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Appendix E. Plagiarism declaration

University of the Witwatersrand, Johannesburg

School of Medicine

SENATE PLAGIARISM POLICY

Declaration by Students

-

I, Neliswa Sibongile Ngubane (Student number: 308137) am a student registered for MMed in the year 2017-2021. I hereby declare the following:

- **I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.**
- **I confirm that ALL the work submitted for assessment for the above course is my own unaided work except where I have explicitly indicated otherwise.**
- **I have followed the required conventions in referencing the thoughts and ideas of others.**
- **I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this in not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.**

-

NGUBANE

19 May 2021