THE CONTEXT OF FETAL VENTRICULOMEGALY IN A DEVELOPING COUNTRY.

A RETROSPECTIVE REVIEW.

by CHZ Pretorius

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Supervisor: Dr JL van der Merwe

Co-supervisor: Prof LTM Geerts

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Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own original work, that I am the authorship owner thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Signature: Nelis Pretorius

Date: December 2019

Abstract

Aim

The goal of this study is to describe fetal ventriculomegaly (VM) in a developing country population with regards to clinical presentation, associated findings, natural history and outcome.

Materials and methods

This retrospective observational study was conducted at Tygerberg Academic Hospital, a secondary and tertiary referral centre in the Western Cape Province. Data was collected from all pregnancies with a prenatal diagnosis of ventriculomegaly from 2013 to 2015. The initial presentation and associated findings with the natural history of VM was studied and a selection of perinatal outcomes was measured.

Results

A final cohort of 252 cases was analysed: 168 mild, 42 moderate and 42 severe cases of VM. The median gestational age at diagnosis was 23w4d, with 48,8% diagnosed after 24w0d. Mild VM was more likely to be unilateral ($p<0,001$) and isolated ($p=0,006$) when compared to moderate and severe VM. Mild VM was associated with multiple soft markers in up to a third of the cases and over half of the cases normalized during pregnancy; severe VM was associated with multiple major anomalies in 31,0% of the cases. The majority of major anomalies in all 3 groups were CNS defects in 25,8% and cardiac anomalies in 10,3%. Termination of pregnancy was opted for in 12,5% of mild, 35,7% of moderate and 59,5% of severe VM cases.

Conclusion

VM is a common prenatal finding but, in this setting, was often diagnosed late, which limits options for investigation and management. Associated findings included cardiac and other CNS abnormalities and increased with increasing severity of VM. Aneuploidies were encountered within all groups. In this cohort, unilateral VM was more associated with mild VM and may have been due to the inclusion of borderline VM, which was shown not to be a benign finding. Uptake of invasive testing and of TOP was low in this community and the late diagnosis may have contributed to that.

Opsomming

Doelwit

Die doelwit van die studie was om fetale ventrikulomegalie (VM) te beskryf in ‘n ontwikkelende land, spesifiek die kliniese beeld, geassosieerde bevindinge asook uitkomste.

Metodes

Die retrospektiewe observasie studie was gedoen te Tygerberg Akademiese Hospitaal, ‘n sekondêre en tersiêre verwysingshospitaal in die Wes Kaap. Data is gekollekteer van alle swangerskappe met ‘n prenatale diagnose van fetale ventrikulomegalie vanaf 2013 tot 2015. Die aanvanklike kliniese beeld en geassosieerde bevindinge was bestudeer, asook sekere perinatale uitkomste.

Resultate

‘n Finale kohort van 252 gevalle was geanaliseer: 168 geringe, 42 matige en 42 erge gevalle van VM. Die mediane gestasie van diagnose was 23w4d, met 48,8% gediagnoseer na 24w0d. Geringe VM was meer waarskynlik unilateraal ($p<0.001$) asook geisoleerd ($p=0,006$) wanneer dit vergelyk word met matige en erge VM. Geringe VM was geassosieer met veelvuldige sagte merkers in ongeveer ‘n derde van die gevalle en meer as die helfte hiervan het genormaliseer tydens swangerskap. Erge VM was geassosieer met veelvuldige major abnormaliteite in 31,0% van die gevalle. Die meerderheid van die major abnormaliteite in al 3 groepe was sentrale senuweestelsel defekte in 25,8% en hart-anomaliteite in 10,3%. Terminasie van swangerskap is ondergaan in 12,5% van geringe, 35,7% van matige en 59,5% van erge VM gevalle.

Gevolgtrekking

VM is nie ‘n rare prenatale bevinding nie en in die studie was dit dikwels laat gediagnoseer, met gevolglik beperkte ondersoeke en behandelingsopsies. Geassosieerde bevindinge, veral hart en sentraal senuweestelse, was algemeen en meer gesien met die toenemend graad van VM. Aneuploidies was in al drie groepe waargeneem. In die kohort was unilaterale VM frekwent, maar was meer gesien in geringe VM. Dit was heel moontlik as gevolg van die insluiting van grensgeval VM, wat nie ‘n onskuldige bevinding was nie. Die opname van invasieve toetse, insluitend terminasie van swangerskap, was laag. Laat diagnose mag hiertoe bygedra het.

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Dedication

To my parents.

Thank you for all the opportunities you created for me.

I will be forever grateful.

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List of Abbreviations

ADHD:	Attention deficit hyperactivity disorder
AIDS:	Acquired immunodeficiency syndrome
ANC:	Antenatal care
AST:	Aspartate transaminase
AVSD:	Atrioventricular septal defect
CD:	Caesarean delivery
CDH:	Congenital diaphragmatic hernia
CMA:	Chromosomal microarray
CMV:	Cytomegalovirus
CNS:	Central nervous system
CPAP:	Constant positive airway pressure
CSP:	Cavum septum pellucidum
CTG:	Cardiotocograph
CVS:	Chorionic villus sampling
DM:	Diabetes Mellitus
DORV:	Double outlet right ventricle
FBC:	Full blood count
GA:	Gestational age
GDM:	Gestational Diabetes Mellitus
GIT:	Gastro intestinal tract
HAART:	Highly active antiretroviral therapy
HIV:	Human immunodeficiency virus
INR:	International normalized ratio
IOL:	Induction of labour
IUFD:	Intrauterine fetal demise
IUGR:	Intrauterine growth restriction
MRI:	Magnetic resonance imaging

MTCT:	Mother-to-child transmission
NICU:	Neonatal intensive care unit
NVD:	Normal vaginal delivery
PCR:	Polymerase chain reaction
PPROM:	Preterm prelabour rupture of membranes
RPR:	Rapid plasma reagin
SA:	South Africa
SES:	Socio-economic status
TAH:	Tygerberg Academic Hospital
TGA:	Transposition of the great arteries
TOP:	Termination of pregnancy
VBAC:	Vaginal birth after caesarean delivery
VM:	Ventriculomegaly
VSD:	Ventricular septal defect
VZV:	Varicella Zoster virus

Chapter 1: Introduction

1.1 Background

Fetal ventriculomegaly (VM), the enlargement of the lateral ventricles of the developing fetal brain, is defined as a measurement of 10mm or more on an axial plane across the atrium; this being 4 standard deviations above the mean for the relevant gestation[1]. VM can be classified into mild (≥10 to <12mm), moderate (≥12 to <15mm), and severe (≥15mm)[2]. Although there is a wide range of reported incidences of antenatally diagnosed VM by ultrasound ranging from 1,5 – 22 per 1000[3,4], VM is the most common brain anomaly with a prevalence of 1/1000 live births. This led to the recommendation that the fetal cerebral lateral ventricles should be measured as part of the fetal anatomical review routinely performed during the second trimester to screen for fetal anomalies[5].

VM can be isolated[6] but is frequently associated with other anomalies in 42-84% of cases[7]. Central nervous system (CNS) anomalies are the most prevalent associated finding as reported by Sparey et al[6]. Furthermore, VM is typically bilateral but there have been reports of unilateral cases[8-10]. A study by Mehlhorn et al[11] showed the prevalence of unilateral VM in 59,5% of mild VM cases. The outcomes, especially the neurological outcomes of fetuses with prenatal diagnosis of VM are understandably dependent on the severity and the underlying cause. In “apparently” isolated mild VM, the outcomes are predominantly positive but neurodevelopmental delay has been reported in up to 28,6% of cases[12]. In contrast, severe VM is associated with a high risk of neonatal mortality[13,14] (16,2%), even in the absence of other prenatally detected associated anomalies[15]. A study by Breeze et al showed that severe VM is associated with disabilities such as isolated hemiparesis, features of cerebral palsy, seizures, abnormal visual development and severe learning disabilities due to cerebral atrophy[13].

Once there is a suspicion of fetal VM, current management dictates a detailed ultrasound anatomical review, screening for possible causative infections (i.e. CMV and toxoplasmosis) and offering invasive testing for especially fetal chromosome evaluation. Careful follow up is obligatory in on-going pregnancies to assess for progression to more severe VM[16] and to review for additional anomalies that can be assessed only later in the pregnancy. Ultimately the best timing, mode and place of delivery need to be planned and in severe or complex cases, with anticipated poor outcomes a termination of pregnancy can be offered[7].

In a developing society, socioeconomic status as well as conditions such as HIV may play a major role in the development of VM and data regarding causes and outcomes may well differ from those reported from developed countries.

1.2 Problem Statement

Fetal VM is a relatively common finding during the routine mid-trimester structural anatomy ultrasound examination. In the majority of cases it can be a transient finding, almost a variant of normality, with a good clinical outcome. However, VM is frequently associated with other disorders and acute conditions and in these settings the outcomes are directly dependant on several factors.

Currently the majority of publications of known outcomes and associations of fetal VM are from developed countries. Conditions common to developing countries like HIV and poor socioeconomic status play a major role in the causes, presentation and outcomes of a vast number of diseases. Unquestionably these conditions may have an influence on the developing fetal brain and specifically fetal VM as well.

The aim of this study is to assess the clinical presentation and associated findings of fetal VM as well as the natural history and short-term outcomes, including rates of fetal loss, spontaneous miscarriage, termination of pregnancy and stillbirth rates.

Chapter 2: Literature Review

2.1. Ventriculomegaly detection/definition

Ventriculomegaly (VM) is defined as an enlargement of the lateral ventricles of the developing fetal brain. The incidence of fetal VM diagnosed antenatally by ultrasound varies from 1,48 per 1000 (8/5400)[3] to 22 per 1000 (11/500)[4] the latter study being in a low risk population. Measurement of the size of the fetal cerebral lateral ventricles is recommended as part of the fetal anatomical review routinely performed during the second trimester to screen for fetal anomalies[5].

The ventricle is measured at the level of the atria of the lateral ventricles filled by the echogenic choroid plexuses, visible in an axial plane of the fetal brain also showing the frontal horns of the lateral ventricles and the cavum septi pellucidi[5]. The measurement is obtained at the level of the glomus of the choroid plexus, perpendicular to the ventricular cavity, positioning the callipers inside the echoes generated by the lateral walls[5]. The upper limit of the normal range for the ventricular atrial measurement is 10mm, this being 4 standard deviations above the mean for the relevant gestation[1]. VM can be classified into mild (≥10 to <12mm), moderate (≥12 to <15mm), and severe (≥15mm)[2].

VM may be an isolated finding or may be associated with other anomalies[6]. VM is considered ‘isolated’ when the fetus does not present any other structural anomalies. The diagnosis of isolated VM should be made only after having carried out a complete ultrasound evaluation for associated intracerebral or extracerebral anomalies[17]. Yet, studies of isolated VM have reported that 10-13% of associated anomalies are only recognized after birth[12,18]. It is therefore more appropriate to use the term “apparently isolated VM” in prenatal case series.

In 42-84% of cases, VM is associated with other anomalies[7]. These may be CNS or non-CNS malformations, fetal infections and/or chromosomal anomalies. A study by Sparey et al in 1998 showed that CNS anomalies are the most prevalent associated anomalies with neural tube defects making up 42,4% of associated anomalies and other intracranial anomalies 16,5%. In the same study the associated anomalies in other systems were as follows; skeletal 25,3%, genitourinary 17,2%, facial 14,9%, gastrointestinal 17,2%, cardiovascular 12,5%, anterior abdominal wall defects 5,7%[7].

VM is typically bilateral, but there have been reports of unilateral cases[8-10]. Most authors agree that unilateral VM is rare, resulting in research series that are small[19] Kinzler et al[20]

described 15 fetuses with unilateral VM, with an incidence of 1 per 1411 pregnancies. Durfee et al[21] described 14 fetuses with asymmetrical VM, 13 of whom had unilateral VM with a normal contralateral ventricle. More than half of their fetuses (58%) had abnormal outcomes, which included several syndromes, developmental delays and intracranial haemorrhages. Both groups agree that fetuses with asymmetrical unilateral VM have a better prognosis than those with bilateral hydrocephalus but, similar to bilateral VM, the degree of unilateral VM and the presence of other associated anomalies, have a major impact on prognosis[19].

2.2. Ventriculomegaly: current understanding of outcomes

There is wide variation in outcome of fetuses and infants with prenatally diagnosed VM. Probably, the first and most important question for the expectant parents is whether their child would be normal or otherwise stated: what is the anticipated long-term outcome?

The neurological outcome of fetuses with prenatal diagnosis of VM predominantly depends on the severity of the dilatation and the underlying cause[17]. Neurological, motor and cognitive impairment are more likely when associated anomalies are present, with early onset, with persistence or progression of VM and with more severe VM[13,22,23]. In utero progression of VM plays an important role. A retrospective observational study[24] concluded that the progression of VM increased with the degree of severity, when mild, moderate and severe VM were compared.

2.2.1. Mild VM

Mild VM, especially when apparently isolated, is the most common brain abnormality found on prenatal ultrasound[25]. Overall the outcomes of isolated mild VM vary in different studies with the prevalence of neurodevelopmental delay ranging from 0% to 28,6%. Pagani et al[16] reported neurodevelopmental delay in 7,9%. Melchiorre et al[12] and Devanseelan et al[26] found the prevalence to be higher: 10,9% and 12% respectively. Relatively little is known about long-term outcome of children following prenatal detection of mild VM. Studies that have evaluated neurodevelopmental outcome in these children have found that about one third have some degree of neurodevelopmental abnormalities (mostly attention deficit hyperactivity disorder, learning disability, motor and language delays) that are generally mild. In one small series of nine children who had had mild, prenatal VM, 33% had nonverbal learning disabilities at ages 6 to 9 years[27].

More specifically the outcomes are mainly determined by the associated findings, the underlying cause and the presentation of the VM itself. A detailed anatomic ultrasound

evaluation must include examination for aneuploidy markers, the corpus callosum, other CNS abnormalities and a fetal echocardiogram. Additionally, on subsequent follow-up visits the fetal anatomy must be reviewed since in up to 8,6% of cases additional associated findings can be discovered[28]. In these cases with associated findings the outcomes are mainly determined by these findings and the management thereof depends on this. The absence of an associated anomaly also plays a role in the prognosis of ventricular brain enlargement[29-32].

Asymmetry of VM seems to be another marker as noted in a review of 366 cases where 97% of the children had a normal development in the event of unilateral VM versus 89,6% in the event of bilateral enlargement[25]. In line with this remark, ventricular asymmetry when there is a difference of more than 2 mm between the two atrial widths[21] seems to be another poor prognostic marker.

Lastly, the progression of mild VM over the course of the pregnancy seems to play a role. Understandably, the best outcomes seem to be in cases where the VM resolves but also in non-progressive non-resolving isolated mild VM cases more than 80% of infants will have a normal development[4,25,33,34].

2.2.2. Moderate VM

The classification of VM is not always consensual as in some studies mild VM includes all cases of atrial measurements between 10 and 15mm[12]. In these studies, moderate VM was not seen as a separate entity. Nevertheless, as in the case of mild VM, moderate VM can be an isolated finding, but is more often associated with other anomalies. Gaglioti et al[22] subdivided borderline VM into mild (<12 mm) and moderate (≥ 12mm) and found a significant difference in the incidence of associated malformations of 41,0% vs 75,0% respectively. CNS anomalies were found in 51,2% (21/41) of cases of moderate VM, compared to 18,7% (14/75) and 41,7% (25/60) of mild and severe cases respectively[22]. Sethna et al[35] found similar results in that CNS associated anomalies were more common in moderate VM compared to mild VM.

The study by Gaglioti et al[22] found that in moderate VM, TOP was performed in 29,3% (12/41) and neonatal and infant death occurred in 7,3% (3/41) and 4,9% (2/41) respectively. Gaglioti only considered long-term outcome data for isolated cases since the outcomes were dependant on the structural and/or chromosomal anomalies. Herein, 80,0% (8/10) of those with moderate VM were alive at 2 years of age and the neurodevelopmental outcome at that age was normal in 75,0% (6/8) of cases while 97,7%

(43/44) of mild VM cases were alive at 2 years of age, with neurodevelopmental outcome being normal in 93,0% (40/43).

2.2.3. Severe VM

Malformations are more often found in cases of severe VM[18] with up to 50% of all cases associated with a chromosomal and/or structural abnormality[15]. Gaglioti et al[22] confirmed this finding and noted that the most commonly anomalies were of the nervous system particularly spina bifida in 16,7% (10/60) and agenesis of corpus callosum in 18,3% (11/60) whereas non-CNS abnormalities were found in 16,7% (10/60) of cases.

Outcomes in cases of severe VM are complicated by this high incidence of additional structural anomalies and terminations of pregnancy[13]. Prenatally detected severe VM is known to have a poor prognosis both in terms of survival and neurodevelopmental outcome[36]. This remains true even in the absence of prenatally detected associated anomalies[15]. Specifically, Hannon et al[15] reported a 64,3% TOP rate with a 7,0% neonatal death rate.

When reflecting on 'apparently' isolated severe VM neurodevelopmental outcomes, Kennelly et al[37] reported a major morbidity in 50,0% (5/10) and a mild morbidity in 40,0% (4/10) of cases, with a normal outcome in only one case. Severe neurodevelopmental outcomes included severe developmental delay, blindness and cerebral palsy while mild handicap included gross motor delay, speech delay, nystagmus and squint.

The paediatric outcomes of antenatally diagnosed cases of severe VM also appear guarded. Graham et al[14] found major neurological morbidity at paediatric follow up (from birth to 4 years of age) in 33,3% (3/9) of survivors with isolated severe VM. Major neurological morbidity included cerebral palsy, epilepsy, bradyacusia with prosthesis, mono/bilateral blindness and mental retardation.

2.3. Ventriculomegaly: current management

Once the diagnosis of VM is made, it is essential that a detailed ultrasound anatomical review be done, to search for other anomalies (especially CNS and cardiac). It is commonly accepted that dedicated transvaginal fetal neurosonography has a much greater diagnostic potential

than that of the standard transabdominal examination and is particularly helpful in the evaluation of complex malformations[5]. This examination however requires a degree of expertise that is not yet universally available[5].

The basis of the neurosonographic examination of the fetal brain is the multiplanar approach that is obtained by aligning the transducer with the sutures and fontanelles of the fetal head[5]. Refinements in 2D fetal neurosonography have paved the way for improved visualization of normal CNS development and hence appreciation of abnormality[37]. A 2D ultrasound of the midsagittal plane of the brain has proven to be a powerful source of information and D'Addario et al reported a 93,1% detection rate for the cause of the ventricular dilatation by using the midsagittal view[38].

Follow-up ultrasound examinations help in assessment for regression or progression of VM and provides an opportunity to re-evaluate for anomalies, as follow up ultrasound examinations have detected fetal abnormalities not detected on the initial scan in 13% of cases[12]. There is no agreement regarding the timing and frequency of follow-up in fetuses with VM, and this will depend on the gestational age at diagnosis. Most authors have suggested that the minimal time interval before performing a follow-up study should be 2 weeks after detailed initial assessment[39]. Baffero et al[40] suggests that a follow up scan is indicated between 28 and 34 weeks of gestation in all cases of prenatally ultrasound diagnosis of VM. Sparey et al[7] states that the intervals between scans will be determined by the initial atrial width and subsequent progression. They reassess atrial size two weeks after the initial examination. If there has been a significant increase, regular follow up (every 2-4 weeks) may be appropriate. If the ventricular dilatation appears to be stable or resolving, less frequent follow up is appropriate.

Additional imaging by fetal magnetic resonance imaging (MRI) can be used to identify underlying CNS abnormalities not detected by sonography[41]. The indication for fetal MRI remains a subject of debate, partly because of questions concerning its diagnostic accuracy compared to ultrasound, partly because of practical factors such as accessibility, high costs and available expertise[42]. Many studies have evaluated the role of fetal MRI in the discovery of associated anomalies in fetuses with apparently isolated VM[43]. Quahba et al[17] assessed 123 of 167 cases of isolated mild fetal VM (diagnosed by ultrasound) by fetal MRI between 24 and 39 weeks of gestation. The MRI showed major cerebral anomalies in 15 cases, 4 of them being also revealed by ultrasound monitoring. In one of the most important studies, Griffiths et al[6] showed additional brain abnormalities detected in 17,0% of fetuses thought to

have isolated VM on ultrasound only. 147 fetuses with isolated VM diagnosed by ultrasound were included in the study and after performing fetal MRI in all the cases, 25 fetuses had associated anomalies. The most common associated anomaly was agenesis of corpus callosum (11 cases). Simon et al[44] found that 46,0% of 52 cases of VM needed a different management plan after performing fetal MRI[43].

Most studies reported in the literature advocate the added value of MRI in cases of moderate and severe VM, not only to confirm the severity, but also to further detect and characterize additional anomalies[42]. Fetuses with severe VM had a probability ten times higher than fetuses with mild VM of having other abnormalities. Therefore, it could be suggested that in cases of moderate and severe VM, MRI of the fetus can be considered, where the expertise is available.

Infection acquired in utero is a significant cause of fetal and neonatal mortality and morbidity. The fetal phenotype depends on the gestation at which the infection occurs. In general, infections in the first trimester are more likely to cause major structural malformations compared with infections later in pregnancy[45]. Therefore, in cases of suggestive structural abnormalities, screening for underlying congenital infections should be considered. The most common congenital infections associated with VM are toxoplasmosis and cytomegalovirus (CMV) infection. The prevalence of primary congenital CMV infection in newborn infants in the developed world is 0,25 to 2%, but the rates vary considerably among different populations[46]. Cerebral VM is present in 18% of the fetuses with proven intrauterine CMV infection[47]. The prevalence of congenital toxoplasmosis varies between 1:1000 and 1:10000 live births. The CNS is frequently affected, with cerebral calcification, VM and cerebrospinal fluid abnormalities[43]. Screening for toxoplasmosis and CMV infection with maternal serology during pregnancy is simple, low-cost, and safe but interpretation can be challenging if a blood sample is only drawn a long time after infection has occurred[43].

The finding of a fetal structural anomaly increases the possibility of a chromosome abnormality or genetic molecular defect and should prompt further evaluation into genetic aetiologies[48]. Gaglioti et al[22] demonstrated that chromosomal anomalies were found in 10,7% (8/75) of mild VM, 2,4% (1/41) of moderate VM and in 3,3% (2/60) of severe VM, the most prevalent being Trisomy 21. They concluded that the degree of VM is not predictive of the risk of aneuploidies. This is in contrast to Nicolaides et al[49] who reported that the incidence of an abnormal karyotype is lower when VM is severe than when it is borderline (mild to moderate). Kennelly et al[36] showed that in fetuses with apparently isolated severe VM, the incidence of

chromosomal defects was 8,3%. Their conclusion was that karyotyping in cases of severe VM, whether isolated or associated with other abnormalities, should strongly be considered.

Prenatal diagnosis of chromosomal abnormalities is accomplished by invasive techniques, such as amniocentesis and chorionic villus sampling (CVS). CVS is performed in the first trimester from 10 to 13 weeks, whereas amniocentesis can be performed starting at 15 weeks' gestation[50]. Amniocentesis should be offered to determine the fetal karyotype, as VM is often associated with an abnormal karyotype. Chromosomal microarray (CMA) should be offered to patients with isolated mild VM and recommended when additional abnormalities are detected. CMA has been recommended in the evaluation of fetal anomalies, including VM, and can be used as an alternative to fetal karyotype, or as a reflex test following a normal karyotype[51]. The yield of CMA is likely higher when VM is associated with other abnormalities.

Once the antenatal care pathway has been established and the pregnancy is ongoing then the delivery and immediate post-natal care of these infants presents another challenge with regards to management. It is therefore important that these pregnancies are delivered in a tertiary referral centre if immediate paediatric and/or neurosurgical intervention is anticipated.

Most infants with VM have a normal head circumference; therefore, there is no increased risk of cephalopelvic disproportion and poor progress in labour[51]. Yet, VM is at times accompanied by macrocephaly, which will require a Caesarean delivery. The cut-off for determining when a caesarean delivery is indicated will vary with gestational age at delivery, the absolute and relative head circumference and the size of the maternal pelvis. When the head circumference exceeds 40cm, abdominal delivery should be considered[51]. Senior obstetricians should be involved in these cases and the most appropriate route of delivery needs to be determined. With the availability of paediatricians as well as neurosurgeons at these centres, early intervention if needed and if appropriate, is possible to optimize immediate and long-term outcome.

In many cases, especially when severe or complex, a very poor prognosis is anticipated and the role of TOP needs to be discussed. In the study by Sparey et al[7] overall survival of cases of severe VM was 47,9%. The outcome of pregnancies with severe VM is very poor. In these cases, as well as in complex cases involving mild and moderate VM, TOP can be offered.

2.4 Ventriculomegaly in a developing country setting

2.4.1 General

Very little is known about fetal VM in a developing country setting. The majority of studies regarding VM are being done in developed countries, where early diagnosis leads to early investigation and timely interventions when possible. A major problem in developing countries is ‘late booking’, lack of routine ultrasound screening and lack of sufficient expertise leading to missed diagnoses or limited/superficial review of these cases. This leads to late diagnosis (often after the immediate postnatal period) or staggered and haphazard referrals biased towards more severely affected fetuses. In severe or complex cases, this may result in late (rather than early) TOP, which can have a major psychological impact on the expecting mother.

2.4.2 Socio-economics

Congenital anomalies are major causes of neonatal and infant mortality[39]. Socioeconomic inequalities in congenital anomalies have been shown to exist in the rates of stillbirth and perinatal, neonatal and infant mortality[39]. Socio economic status (SES) have a major influence on access to, and timing of, antenatal detection services through the provision of information, the interpretation of risk and the consequent decision regarding continuation or termination of pregnancy[39].

Low-income pregnant women who experience other negative life events (poor housing conditions, substance use, lack of social support, child care and transportation) are least likely to seek prenatal care[52]. This will then lead to ‘late booking’ or no booking with delay or no diagnosis of potential fetal anomalies.

Low income may be an indirect determinant of congenital anomalies, with a higher frequency among resource-constrained families and countries. It is estimated that worldwide about 94% of severe congenital anomalies occur in low- and middle-income countries. An indirect determinant, this higher risk relates to a possible lack of access to sufficient, nutritious foods by pregnant women, an increased exposure to agents or factors such as infection and alcohol, or poorer access to healthcare and screening. Factors often associated with lower income may induce or increase the incidence of abnormal prenatal development[53].

2.4.3 Communicable and infectious diseases

Several different bodies of evidence support a link between infection and altered brain development. Several viral, bacterial and parasitic illnesses are associated with alterations in fetal brain structural anomalies including brain calcifications and hydrocephalus[54].

The development and maturation of the human brain occur throughout the fetal period and is modulated by a set of complex interactions among various signalling receptors, genetic/epigenetic factors and environmental influences. The location and timing of insults have an important role in cerebral development and, ultimately, function[48]. Maternal HIV infection has been consistently and conclusively associated with poor neurodevelopmental outcomes, specifically cognitive and neurodevelopmental delays. [54]

Some congenital viral illnesses produce distinct clinical pathology in fetal brain structure and anatomy of varying severity. VZV and CMV are associated with hydrocephalus and calcifications[54]. Certain bacterial and parasitic illnesses, similar to viral illnesses, are also associated with alterations in brain development. For example, syphilis is associated with hydrocephalus, whereas toxoplasmosis is associated with diffuse calcifications in the basal ganglia, periventricular calcifications and progressive hydrocephalus[54].

Infectious diseases have been a major human enemy in the course of history. The situation is worse in the developing countries that are already suffering from poverty, hunger, and lack of resources, infrastructure, political stability and will. One may witness several such infectious diseases in these parts of the world that hardly exists in today's industrialized countries. In recent decades, trend of greatest burden of infectious diseases is observed in remote regions of developing countries[55].

2.4.4 Role of invasive testing

In developing countries and in South Africa particular, the high prevalence of HIV infection puts a huge burden on the health care system. More than half of the estimated 33 million people in South Africa living with HIV/AIDS are women, and most are of childbearing age[56]. The SA Department of Health study estimated that in 2011, 29,5% of pregnant women were HIV-positive[57].

The use of highly active antiretroviral therapy (HAART) has led to a significant reduction in morbidity and mortality from HIV infection and a decline in mother-to-child transmission (MTCT)[58]. Before HAART, invasive procedures such as amniocentesis were avoided owing to the increased risk of MTCT. Recent literature suggests that it is safe to perform amniocentesis in women on HAART with suppressed, preferably undetected, viral loads and when transplacental passage of the needle is avoided[59].

Unfortunately, in SA many women initiate antenatal care late in pregnancy. All women will ideally be offered a fetal abnormality scan between 18 and 22 weeks if resources are available. If a fetal abnormality is detected and amniocentesis is offered, there is often insufficient time to attain an undetectable viral load within the pre-viability period. [58]

As clinicians, we have a responsibility to the mother to offer care that is standardized and does not discriminate in the presence of HIV infection. However, we also have a responsibility to the fetus and should not be exposing that fetus to an unnecessary risk of HIV transmission[58]. The risk of possible HIV transmission in women undergoing amniocentesis needs to be weighed against the benefits of a prenatal diagnosis. This should then be communicated clearly to the patient. Adequate counselling should take place, in order for an informed decision to be made[58].

2.5 Conclusion

Developing countries face many health challenges. Pregnancy related diseases might present in a similar way as compared to developed countries. This is true for congenital abnormalities as well, but the associations and eventual outcome might differ significantly. Especially low socio-economic status, HIV infection, limited resources and late initiation of antenatal care are some of the factors that play a significant role in the presentation, associations and eventual outcome VM. Very little is known about VM in developing countries and these factors mentioned above are not always as big a challenge in developed countries and therefore not always included in studies done. In our study we take these factors into account when evaluating the primary and secondary outcomes, in order to determine if they play a significant role in the presentation, associations and eventual outcome of VM.

Chapter 3: Methods

3.1 Research Design

3.1.1. Type of study

This was a retrospective observational study.

3.1.2. Study setting

Tygerberg Academic Hospital (TAH) is a secondary and tertiary referral centre in the Western Cape Province responsible for the Metro East region of Cape Town and designated rural areas, located in Parow, Cape Town. The hospital is the largest hospital in the Western Cape and acts as a teaching hospital in conjunction with the University of Stellenbosch's Faculty of Medicine and Health Sciences. It has a catchment population of over 2.6 million people.

3.1.3. Study subjects

Data was collected from all pregnancies with a prenatal diagnosis of VM noted on the Astraia database and the congenital anomaly database from the TAH O&G ultrasound unit (SUNCAD) in 2013 to 2015.

For the purpose of this study, all cases at the O&G ultrasound unit of TAH, with a ventricular atrium width of 9.5mm and above were included. This included patients referred from the peripheral units, for a fetal anatomical review at TAH. It is possible that the measurements of 10mm obtained with old equipment actually included values between 9,5 and 10,5mm. No exclusion criteria were used.

3.2 Data collection

The principal investigator (PI) extracted all relevant data from the medical records and Astraia database file and completed a coded data sheet, reflecting no patient identifiable information. This data was then loaded onto a MS Excel database in strictly anonymous fashion.

3.3 Outcome measures

3.3.1. Primary outcomes included:

3.3.1.1. The clinical presentation, associated findings and identified causes of ventriculomegaly.

3.3.1.2. Natural history and short-term outcomes of fetal VM, including rates of fetal loss, spontaneous miscarriage, termination of pregnancy and stillbirth, live birth rate, survival to discharge, (very) low birth weight.

3.3.2. Secondary outcomes included:

3.3.2.1. Natural history and short term outcomes of “apparently” *isolated* fetal VM, including rates of fetal loss, spontaneous miscarriage, termination of pregnancy and stillbirth, live birth rate, survival to discharge, (very) low birth weight.

3.3.2.2. Maternal morbidity outcomes including preterm labour (onset of labour before 37 completed gestational weeks), preterm rupture of membranes (rupture of membranes before 37 completed gestational weeks) and mode of delivery.

3.4 Ethics

The protocol was submitted for local ethical review and was approved by the Health Research Ethics Committee of Stellenbosch University (S16/01/016). Individual consent was waived in view of this being an anonymous audit.

3.5 Data analysis and statistical methods

Statistical analysis was performed with SPSS® Statistics software v24.0. (IBM®, Company). A p-value of <0,05 was considered significant. Continuous variables were tested for normal distribution by Kolmogorov-Smirnov test and expressed as means with standard deviation (SD) or medians with interquartile range. Binomial and ordinal variables were expressed as percentage and score, respectively.

One-way ANOVA with Bonferroni adjusted post-hoc analysis was used to compare normally distributed continuous variables and Kruskal-Wallis test for non-normally distributed continuous variables. Chi-square test was used for binomial and ordinal variables. Multiple logistic regression analysis was used to assess factors associated with “normalization” of atrial width. A backward stepwise model was used based on likelihood ratios with an entry and exit probability set at 0,05 and 0,1 respectively.

Chapter 4: Results

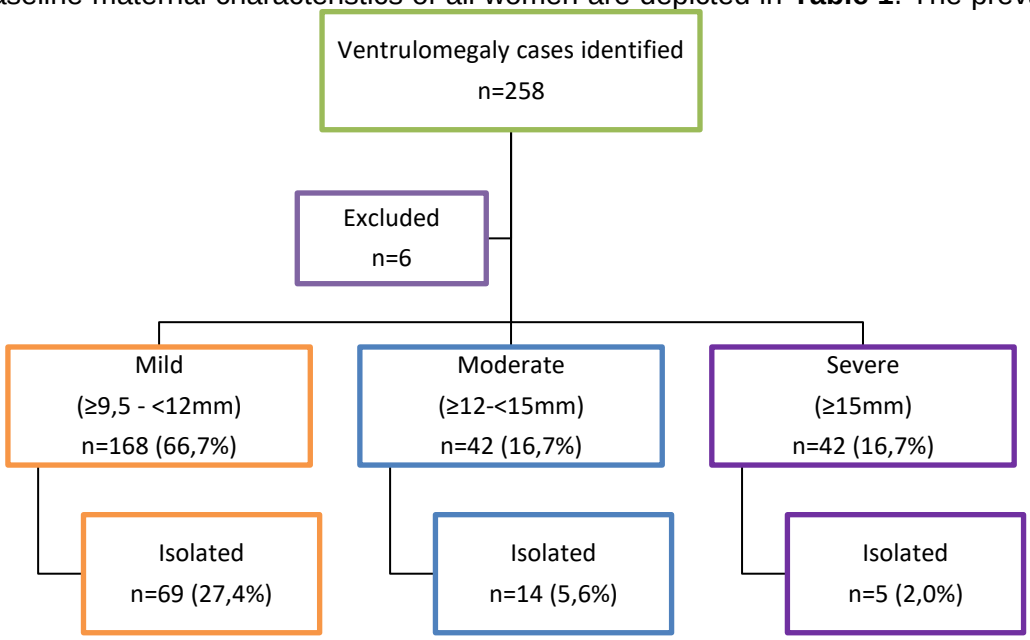
4.1. Baseline maternal characteristics

Initially, 258 cases of fetal VM were identified for the time period 1 January 2013 to 31 December 2015. Upon review of the reports, 6 of these cases were excluded, as it was clear that there were data entry mistakes and the fetus did not have VM.

A final cohort of 252 cases was analysed. The patients were either referred with the presumptive diagnosis of VM that was then confirmed, or it was a new finding during an assessment for another reason or a finding during a routine assessment in a high-risk patient. Complete data could not be obtained in 27,0% (68/252) of cases with 31,0% (52/168) in the mild, 19,0% (8/42) in the moderate and 19,0% (8/42) in the severe group, mainly due to missing delivery details in 51,9% (27/52), 87,5% (7/8) and 75,0% (6/8) of the mild, moderate and severe groups respectively. Other missing data related to details of previous obstetric history, medical history as well as booking blood results. Patients were still included in this study as long as part of the primary outcome data was available.

The study flow diagram is depicted in **Figure 1**.

Figure 1. Study flow diagram



The baseline maternal characteristics of all women are depicted in **Table 1**. The prevalence of HIV in this cohort was 18,3% with the highest prevalence of 26,2% (11/42) seen in the severe VM group. This was not a significant finding. (p= 0,5).

Syphilis was noted in 2,8% of the women through routine RPR screening while smoking (16,7%) and alcohol use (12,7%) were common in this cohort with 5,2% of women disclosing that they used both during the perinatal period. The prevalence of any of these exposures did not differ according to VM severity. No women disclosed to using any other recreational drugs such as methamphetamine.

Table 1. Maternal characteristics, displayed as median (IQR) or n (% of VM cases), according to severity of prenatal VM

	All cases n=252	VM Mild n=168	VM Moderate n=42	VM Severe n=42	p*
Age (years)	27,5 (23,7 – 33,6)	27,4 (23,6 - 33,6)	28,4 (24,5 – 33,8)	27,3 (22,9 – 32,2)	0,8
HIV positive	46 (18,3%)	27 (16,1%)	8 (19,0%)	11 (26,2%)	0,5
RPR[#] positive	7 (2,8%)	6 (3,6%)	1 (2,4%)	-	0,2
Smoking	42 (16,7%)	30 (17,9%)	9 (21,4%)	3 (7,1%)	0,2
Alcohol	32 (12,7%)	18 (10,7%)	8 (19,0%)	6 (14,3%)	0,3

*Kruskal-Wallis (for continuous) or Pearson Chi-Square (for frequencies) test

[#]RPR: Rapid plasma reagin

4.2. Obstetric and medical risk profile/history

The previous obstetrical history is depicted in **Table 2** and did not differ with VM severity. Most women had at least one previous live birth at term and nobody had a previous fetal abnormality. Only 3 (1,2%) women had a previous fetal loss after 24 weeks gestational age, but early miscarriage was common (15,1% and equally distributed amongst the groups).

Table 2. Previous obstetrical history, displayed as median (IQR) or n (% of VM cases).

	All cases n=252	VM Mild n=168	VM Moderate n=42	VM Severe n=42	p*
Gravidity	2 (1-4)	3 (1-3)	2 (2-4)	2 (2-4)	0,9
Parity (≥24w)	1 (0-2)	1 (0-2)	1 (0-2)	1 (1-2)	1,0
Previous Miscarriage (<24w)	38 (15,1%)	22 (13,1%)	10 (23,8%)	6 (14,3%)	0,8
Previous fetal abnormality	-	-	-	-	-
Previous fetal loss (≥ 24w)	3 (1,2%)	2 (1,2%)	-	1 (2,4%)	0,6

*Kruskal-Wallis (for continuous) or Pearson Chi-Square (for frequencies) test

From the maternal records, nearly 1 in 15 women (6,3%) were noted to have a medical disorder other than HIV. The most prevalent condition was Diabetes Mellitus (DM) with 3,2% of all women taking glycaemia reducing medication. Maternal medication use is depicted in **Table 3**.

Table 3. Maternal medication use, displayed as n (% of VM cases).

	All cases n=252	VM Mild n=168	VM Moderate n=42	VM Severe n=42	p
Diabetic medication	8 (3,2%)	4 (2,4%)	2 (4,8%)	2 (4,8%)	0,6
Epileptic medication	4 (1,6%)	2 (1,2%)	-	2 (4,8%)	0,3
Warfarin	2 (0,8%)	2 (1,2%)	-	-	NA
Anti-psychotic medication	2 (0,8%)	2 (1,2%)	-	-	NA
HAART[#]	45 (17,9%)	26 (15,5%)	8 (19,0%)	11 (26,2%)	0,3

*Pearson Chi-Square (for frequencies) test

[#]HAART: Highly active antiretroviral therapy

4.3. Initial antenatal assessment

The initial antenatal assessment of the 252 cases with confirmed VM is depicted in **Table 4**. The median gestational age of diagnosis was 165 days (23 weeks 4 days), with 1,6% (4/252) diagnosed before 18w0d, 49,6% (125/252) between 18w0d and 23w6d and a "late" diagnosis after 24w0d in 48,8% (123/252) of the cases. The gestational age at diagnosis was not significantly different between the groups (p=0,08).

In a total number of 9 cases (6 mild, 1 moderate, 2 severe) it was unclear whether VM was a unilateral or bilateral finding, as this was not specified in the Astraia database. Of the remaining 243 cases, unilateral VM occurred in 50,2 % and was more frequent in the mild VM group (65,4%) while most of the cases of severe VM (92,5%) were bilateral. Mild VM, when compared to moderate/severe VM together, was significantly more likely to be unilateral (p<0,01) and isolated (p<0,01).

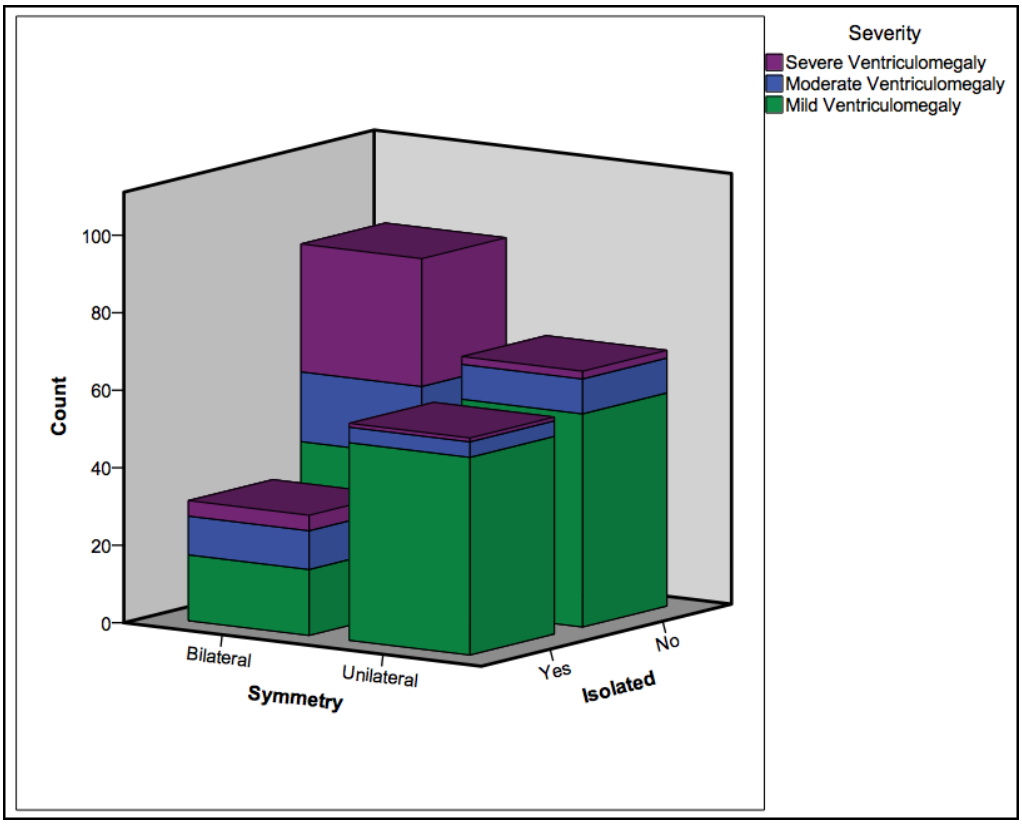
Table 4. Initial antenatal assessment, displayed as median (IQR) or n (% of VM cases).

	All cases n=252	VM Mild n=168	VM Moderate n=42	VM Severe n=42	P*
GA at diagnosis (days)	165 (151-191)	163 (150-187)	171 (152-188)	172 (155-221)	0,08
Largest of the two atrial widths (mm)	11,0 (10,3-12,7)	10,5 (10,0-11,0)	12,7 (12,2-13,6)	20,1 (16,9-25,9)	<0,01
Unilateral VM [#]	122/243 (50,2%)	106/162 (65,4%)	13/41 (31,7%)	3/40 (7,5%)	<0,01
Bilateral VM [#]	121/243 (49,8%)	56/162 (34,6%)	28/41 (68,3%)	37/40 (92,5%)	<0,01
Isolated finding	88 (34,9%)	69 (41,1%)	14 (33,3%)	5 (11,9%)	<0,01

*Kruskal-Wallis (for continuous) or Pearson Chi-Square (for frequencies) tests across the three severity groups. [#] cases with known data only.

Figure 2 better illustrates the interactions between the symmetry and complexity of VM at presentation.

Figure 2. Symmetry and complexity of ventriculomegaly at diagnosis



4.4. Ventriculomegaly – associated anomalies

Additional soft markers were noted in 32,7% (55/168), 31,0% (13/42) and 19,0% (8/42) of cases of mild, moderate and severe VM respectively (p 0,2).

A single major anomaly was detected in 20,8% (35/168), 28,6% (12/42) and 38,1% (16/42) of cases of mild, moderate and severe VM (p 0,06 for all three, p 0,03 for severe VM compared to others) respectively while multiple major anomalies were detected in 4,8% (8/168), 7,1% (3/42) and 31,0% (13/42) of cases of mild, moderate and severe VM respectively (p <0,01). The structural anomalies diagnosed during the initial ultrasound assessment are depicted in **Table 5**. The majority of major anomalies in all 3 groups were CNS defects in 25,8% (65/252) and cardiac anomalies in 10,3% (26/252). The most common CNS defects seen were open spina bifida in 9,1% (23/252), cerebellar and vermis dysgenesis in 6,7% (17/252) and corpus callosum dysgenesis in 4,4% (11/252).

Table 5. Concurrent structural abnormality findings detected during the initial ultrasound assessment, displayed as n (% of VM cases)**.**

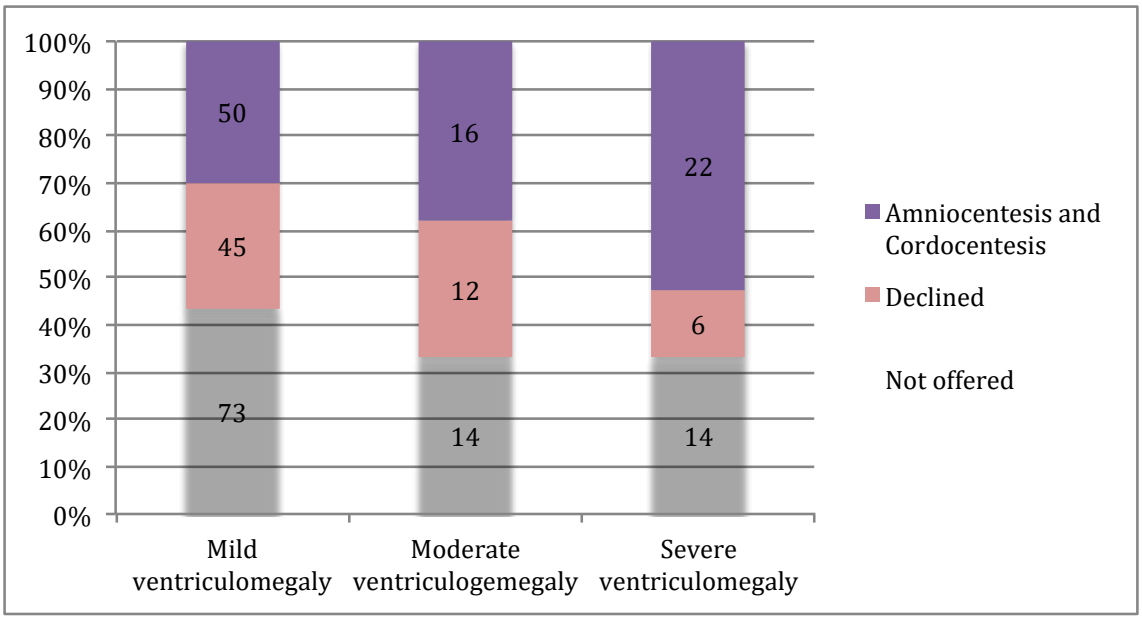
	All cases n=252	VM Mild n=168	VM Moderate n=42	VM Severe n=42
Cardiac:	**26 (10,3%)**	**14 (8,3%)**	**4 (9,5%)**	**8 (19,0%)**
– AVSD	8 (3,2%)	5 (3,0%)	-	3 (7,1%)
– DORV	1 (0,4%)	1 (0,6%)	-	-
– Interrupted aortic arch	1 (0,4%)	-	1 (2,4%)	-
– TGA	1 (0,4%)	-	-	1 (2,4%)
– VSD	7 (2,8%)	5 (3,0%)	1 (2,4%)	1 (2,4%)
– Cardiomegaly	8 (3,2%)	3 (1,8%)	2 (4,8%)	3 (7,1%)
CNS:	**65 (25,8%)**	**28 (16,7%)**	**10 (23,8%)**	**27 (64,3%)**
– Corpus Callosum dysgenesis / hypoplasia	11 (4,4%)	5 (3,0%)	2 (4,8%)	4 (9,5%)
– CSP abnormalities	3 (1,2%)	2 (1,2%)	-	1 (2,4%)
– Cerebellar and vermis dysgenesis	17 (6,7%)	6 (3,6%)	-	11 (26,2%)
– Dandy Walker malformation	2 (0,8%)	1 (0,6%)	-	1 (2,4%)
– Encephalocele	2 (0,8%)	2 (1,2%)		-
– Holoprosencephaly	2 (0,8%)	-	-	2 (4,8%)
– Open Spina Bifida	23 (9,1%)	9 (5,4%)	6 (14,3%)	8 (19,0%)
– Schizencephaly	3 (1,2%)	3 (1,8%)	-	-
– Microcephaly	1 (0,4%)	-	1 (2,4%)	-
– Colpocephaly	1 (0,4%)	-	1 (2,4%)	-
Renal:	**3 (1,2%)**	**1 (0,6%)**	**1 (2,4%)**	**1 (2,4%)**
– Renal agenesis	3 (1,2%)	1 (0,6%)	1 (2,4%)	1 (2,4%)
GIT:	**3 (1,2%)**	**3 (1,8%)**	**-**	**-**
– CDH	2 (0,8%)	2 (1,2%)	-	-
– Esophageal atresia	1 (0,4%)	1 (0,6%)	-	-
Skeletal:	**2 (0,8%)**	**-**	**1 (2,4%)**	**1 (2,4%)**
– Hemivertebrae	1 (0,4%)	-	-	1 (2,4%)
– Skeletal dysplasia	1 (0,4%)	-	1 (2,4%)	-
Facial:	**5 (2,0%)**	**2 (1,2%)**	**-**	**3 (7,1%)**
– Cleft lip/palate	4 (1,6%)	1 (0,6%)	-	3 (7,1%)
– Microphthalmia	1 (0,4%)	1 (0,6%)	-	-
Intracranial haemorrhage / haematoma	**4 (1,6%)**	**2 (1,2%)**	**2 (4,8%)**	-
Generalized fetal hydrops	**2 (0,8%)**	**1 (0,6%)**	**1 (2,4%)**	-

4.5. Invasive procedures for genetic and infective markers

Antenatal diagnostic procedures were offered in 59,9% (151/252) of cases; 56,5% (95/168), 66,7% (28/42) and 66,7% (28/42) of patients with mild, moderate and severe VM respectively (p 0,3). Ultimately, 58,3% (88/151) of the patients agreed to undergo invasive testing once offered, while 47,4% (45/95), 42,9% (12/28) and 21,4% (6/28) of patients with mild, moderate and severe VM respectively declined any further invasive testing (p 0,02 for severe VM compared to others). Herein, 40 patients had an amniocentesis, 34 patients a cordocentesis and 14 patients had both. This is depicted in **Figure 3**.

In 40,1% (101/252) of the women invasive testing was not offered. In the mild VM group, 83,6% (61/73) of women not offered invasive testing were too advanced in gestation with no associated lethal anomalies. The other 16,4% (12/73) were offered TOP without preceding invasive testing as they were associated with lethal anomalies or a very poor prognosis. These proportions were similar in the moderate VM group, where 78,6% (11/14) of cases were too far advanced without any lethal anomalies and 21,4% (3/14) were offered TOP. However, all cases (14/14) in the severe VM group who weren't offered invasive testing already had an indication for TOP without requiring confirmatory invasive testing.

Figure 3. Invasive testing offered and procedures performed



Of the 88 women who underwent invasive testing, karyotype was requested in 84,1% (74/88) while in 15,9% (14/88) invasive testing was only done for infection screening.

4.6. Genetic test results

An abnormal prenatal karyotype was detected in 12 cases (4,8% of all cases or 13,6% of procedures); 3,6% (6/168) of mild, 2,4% (1/42) of moderate and 11,9% (5/42) of severe VM cases (p 0,02 for severe VM compared to others) (**Table 6**). In those with an abnormal karyotype, associated major anomalies were seen in 50,0% (3/6) of mild, none of moderate and 83,3% (5/6) of severe VM cases and soft markers in 50,0% (3/6) of mild, 100% (1/1) of moderate and 20,0% (1/5) of severe VM cases. As expected, the three most common aneuploidies accounted for 66,7% (8/12) of all the abnormal karyotypes.

Table 6. Chromosomal abnormalities from prenatal testing, data displayed as n (% of genetic results).

	All cases n=74	VM Mild n=42	VM Moderate n=14	VM Severe n=18
Common Trisomies:	**8 (10,8%)**	**5 (11,9%)**	**1 (7,1%)**	**2 (11,1%)**
– **T21**	3 (4,1%)	1 (2,4%)	1 (7,1%)	1 (5,6%)
– **T18**	3 (4,1%)	2 (4,8%)	-	1 (5,6%)
– **T13**	2 (2,7%)	2 (4,8%)	-	-
Other:				
– **22q11.2**	1 (1,4%)	1 (2,4%)	-	-
– **46,XX inv dup 7**	1 (1,4%)	-	-	1 (5,6%)
– **45,XX der 13,18**	1 (1,4%)	-	-	1 (5,6%)
– **47,XX + 9**	1 (1,4%)	-	-	1 (5,6%)

4.7. Infective workup

An infective workup was performed in 142 patients (56,3% of all cases). Maternal serology for Cytomegalovirus was done in 45,2% (114/252) of cases; 53,6% (90/168), 45,2% (19/42) and

11,9% (5/42) of the mild, moderate and severe cases respectively ($p < 0,01$ for severe VM compared to others). No recent infection or perinatal seroconversions were confirmed on these results alone.

Maternal serology for Toxoplasmosis was tested in 52,8% (133/252) of women; 62,5% (105/168), 45,2% (19/42) and 21,4% (9/42) of the mild, moderate and severe VM cases respectively ($p < 0,01$ for mild VM compared to others) and also did not reveal any recent infection or perinatal seroconversions.

Invasive testing for infection was performed in 51 cases (38 mild, 7 moderate and 6 severe VM) either as part of a meningitis screen PCR on amniotic fluid (including Cytomegalovirus, Human Herpes Virus-6, Epstein Barr Virus, Herpes Simplex Virus 1 & 2 and Varicella Zoster Virus) or for a CMV PCR on fetal blood. Congenital CMV was confirmed in 5,9% (3/51) of these samples (3/252 cases: 1,2%).

- The first case had mild VM at 30w1d with bilateral periventricular 'flaring', irregular choroid plexus, septae in posterior horns of lateral ventricles, abnormal cerebellum with 'flat' hemispheres and calcifications in the cerebellar lobes, a pericardial effusion and mildly echogenic bowel with dilated loops of small bowel. Prenatal invasive testing (amniocentesis and cordocentesis) revealed a positive fetal CMV PCR, a normal karyotype (46,XY), fetal IgM below threshold, platelet count of $107x10^9$/L and AST of 66U/L. Maternal serum CMV serology only noted CMV IgG positive and IgM negative. The possibility of TOP was discussed and offered on the subsequent visit but declined. The baby had an uneventful delivery at 37w5d with a 5-minute Apgar score of 9 and birth weight of 2140gm (birth weight < p3, in spite of normal umbilical artery Dopplers throughout the pregnancy). Details regarding the neonatal period could not be retrieved and no confirmatory blood work was done but on a brain ultrasound on day 3 of life, no clear pathology was noted. The baby was however seen at 1 year of age with developmental delay and profound sensory-neural hearing loss for which hearing aids were provided. No further follow up notes could be found.
- The second case was a dichorionic diamniotic (DCDA) twin pregnancy where the affected fetus screened high risk (1:6) for T21 due to "apparently isolated" mild VM at 20 weeks. Amniocentesis and cordocentesis noted a positive fetal CMV PCR, fetal IgM below threshold, platelet count of $311x10^9$/L, AST of 64U/L and a normal karyotype (46,XX). TOP was offered but the patient chose to continue with the pregnancy. Follow up ultrasounds revealed discordant growth, but review of the

anatomy became completely impossible. An emergency caesarean delivery was done at 32w0d due to a pathological CTG, related to pre-eclampsia. The affected twin had a birth weight of 1850gm and 5-minute Apgar score of 5 and received CPAP for one day and nasal prongs oxygen for another four days. CMV retinitis was excluded. By day 15, the baby was discharged in good condition but no further follow up notes could be traced.

- The third fetus had severe VM at 32w0d with additional findings of small fused cerebellar hemispheres, thromboencephalosynapsis, abnormal cortical development of the medial surface of the occipital and parietal lobes with increased subarachnoid space in this area, abnormal cavum septum pellucidi and a short corpus callosum with a thin posterior part on neurosonography. Amniocentesis was performed and revealed congenital CMV infection. In this case the mother opted for TOP with fetocide. On cordocentesis a normal karyotype (46,XY) was noted and no post mortem was done.

4.8. Haemorrhage

Signs of intracranial haemorrhage were observed in 1,2% (2/168) of mild and 4,8% (2/42) of moderate VM.

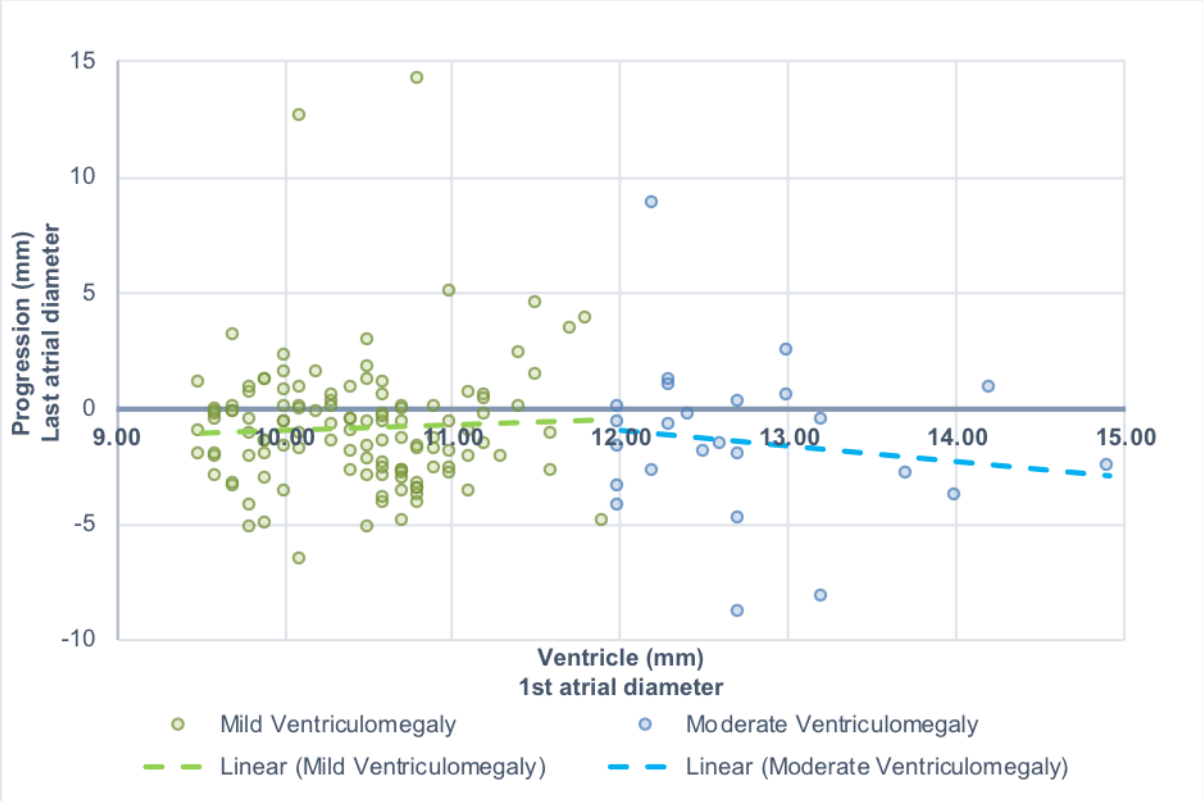
- The first case of mild VM was a patient without any medical co-morbidities but 3 previous caesarean sections. Ultrasound at 23w4d revealed supra and infra tentorial haemorrhage. The patient declined invasive testing and fetocide but opted for TOP with hysterotomy. Placental histology revealed desidual vasculopathy and edematous villi. Fetal autopsy revealed extensive intraparenchymal and intraventricular haemorrhage with the epicentre in the fourth ventricle with extensive infarction involving the pons, medulla and cerebellum with no clear cause.
- The second case of haemorrhage with mild VM occurred in a patient on warfarin treatment for mixed post-rheumatic mitral valve disease. At the time of diagnosis, her INR was therapeutic, ranging between 3,0 - 3,5. A subarachnoid haemorrhage of 12mm was seen on the left side, lateral to the right sided anterior horn. The patient opted for a medical TOP at 23w4d and no autopsy was performed.
- Both cases of intracranial haemorrhage with moderate VM opted for TOP with fetocide. In the first case, ultrasound revealed a large subdural haematoma, compressing and displacing the fetal brain. The patient underwent fetocide at 25w3d. Blood results showed a normal karyotype but the full blood count and anti-platelet antibodies, to exclude rare haematological conditions, failed. No postnatal investigations were done.

- The second case was a dichorionic diamniotic twin pregnancy without any anomalies noted on the initial ultrasound at 20w4d gestation. At 24w5d however, twin B had evidence of a major intracranial haemorrhage, moderate bilateral VM, with echogenic material in and around the lateral, 3rd and 4th ventricles. The option of selective fetocide was discussed but the patient opted to continue with close observation. At 29w5d gestation a fetal MRI demonstrated intracranial periventricular haemorrhage with extracellular methaemoglobin, prominent subdural spaces and Sylvian fissures; normal grey-white matter differentiation and sulcation in keeping with the gestational age. Based on these findings the patient opted for selective TOP with fetocide of the affected twin by cordocentesis at 32w5d weeks. Blood results showed a white cell count of 1,73x10^{9}/L, platelet count of 33x10^{9}/L, smear result of reduced platelets, leukopenia and toxic granulation, total IgM <0,25. The patient presented with spontaneous preterm labour at 34 weeks, resulting in an emergency caesarean section for breech presentation. The surviving co-twin had a birth weight of 2110gm with a 5-minute Apgar score of 9 and had an uneventful neonatal course.

4.9. Ventricle dimensions – antenatal trends

Of the initial 252 patients, 45 underwent TOP after the first assessment (17,9%) and 49 never returned (19,4%), leaving 158 women (62,7%) with follow up antenatal scans, including 72,0% (121/168) of the mild, 59,5% (25/42) of the moderate and 28,6% (12/42) of the severe group ($p < 0.01$). Of these 121 mild VM cases, 39,3% (66/168) “normalised” to a measurement of less than 10mm while 6 progressed to moderate (5,0% of mild VM follow ups, 3,6% of all mild VM cases) and 5 to severe (4,1% of mild VM follow ups; 3,0% of all mild VM cases) and the remaining 44 cases remained mild. A similar trend of “regression” was seen in the moderate VM cases that followed up, with 56,0% (14/25) having subsequently smaller atrial width than at the initial diagnosis and 24,0% (6/25) of them “normalised” to below the cut-off of 10mm; 12,0% (3/25) progressed to severe VM. In only three severe VM cases were the subsequent measurements smaller than the initial assessment but none were below 15mm. **Figure 4** depicts the progression of the mild and moderate VM groups with follow up data.

Figure 4. Progression in the mild and moderate VM group, displaying the difference between the last and initial atrial width measurement.



Exceptional cases: As can be seen from **Figure 4**, 3 cases had substantial progression, i.e. more than 5mm increase in subsequent measurements.

- The first case was a poorly controlled epileptic who was using Carbamazepine, Sodium Valproate and Lamotrigine. The ultrasound examination at 20w6d showed mild unilateral VM with an abnormal cavum septum pellucidum (CSP) and agenesis of the corpus callosum. The patient declined any invasive testing and on subsequent assessment the VM progressed to bilateral severe VM with a largest diameter of 22,7mm. The patient had a caesarean section for failed induction of labour at 41 weeks. The birth weight was 3680gm with a 5-minute Apgar of 10. A postnatal cranial ultrasound confirmed an absent corpus callosum and the VM. The baby was discharged in good condition on day 6 but did not follow up for the planned genetic and neurology review.

- The second case involved a dichorionic diamniotic twin pregnancy in an epileptic patient, using Carbamazepine and Phenytoin. At 18 weeks, open spina bifida, myelomeningocele and Arnold Chiari malformation were noted but with normal ventricles. She declined TOP and no invasive testing was offered as the anti-epileptic medication was presumed to be the likely cause for the neural tube defect.. The VM progressed to bilateral severe VM with a final largest diameter of 25mm. The patient went into spontaneous preterm labour at 36 weeks and the birth weight of the affected twin was 2160gm, with a 5 minute Apgar of 9. The myelomeningocele was repaired on day 2 of life and a VP shunt was placed at 6 weeks of age. The baby had an uneventful course until discharge, but no further follow up could be traced.
- The third case was a 37-year-old woman who had a diagnostic cordocentesis for isolated mild bilateral hydronephrosis at 20w0d, resulting in an adjusted risk for Down syndrome of 1:199. The karyotype was normal (46,XY) but at 22 weeks, on review of the hydronephrosis, bilateral moderate VM was noted. The patient declined TOP and the VM worsened with advancing gestation, the largest diameter being 21mm. A fetal MRI at 26 weeks showed delayed cortical development, eventually resulting in the parents opting for late TOP with fetocide at 29 weeks' gestation. No postnatal investigations were done.

When reflecting exclusively on evolution in the 88 cases of "apparently isolated VM" a higher resolution trend was noted in the mild VM group (62,3%) with none of the cases in this subgroup progressing to severe VM, while none of the severe VM cases showed resolution.

Lastly, 35 patients presented with initial "borderline" measurements between 9,5 – 9,9mm and subsequent measurements were recorded in 31 cases: 67,7% (21/31) normalized to below 9,5mm, 12,9% (4/31) remained stable, 16,1% (5/31) progressed to more than 10mm and 3,2% (1/31) progressed to moderate VM. Of the 17 borderline cases without associated anomalies, sixteen had follow up scans and 68,8% (11/16) resolved, 12,5% (2/16) remained stable and 18,8% (3/16) progressed to more than 10 mm.

4.10. Pregnancy outcomes

4.10.1. General outcomes (n=252)

The delivery outcomes of this cohort are depicted in **Table 7**. The spontaneous PTB rate, before 37 weeks, was 6,3% (16/252); being 7,1% (12/168), 2,4% (1/42) and 7,1% (3/42)

for the mild, moderate and severe VM groups respectively. However, the overall PTB rate, excluding the TOP cases, was 21,4% (54/252).

Table 7. Delivery outcomes, displayed as median (IQR) or n (% of total VM cases in group)

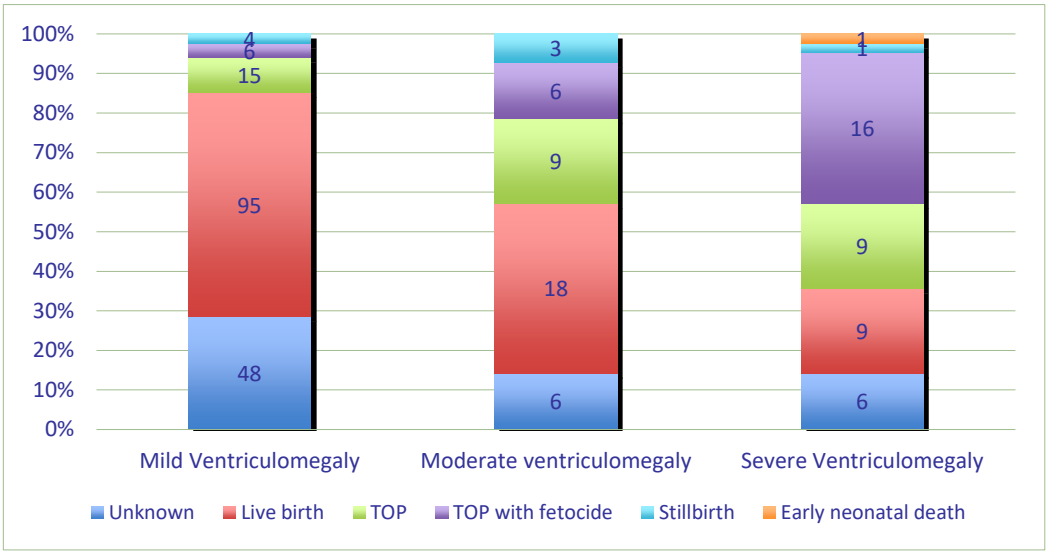
	All cases n=252	VM Mild n=168	VM Moderate n=42	VM Severe n=42	p*
GA at delivery (days)	246 (193-269)	256 (219-271)	219 (173-267)	216 (165-257)	0,005*
TOP	61	21	15	25	
Spt IUFD	8	4	3	1	
Delivery mode					
– **Spontaneous NVD**	49 (19,4%)	38 (22,6%)	8 (19,0%)	3 (7,1%)	0,08
– **Induced NVD**	74 (29,4%)	32 (19,0%)	17 (40,5%)	25 (59,5%)	<0,001
– **Elective CD**	18 (7,1%)	15 (8,9%)	2 (4,8%)	1 (2,4%)	0,1
– **Emergency CD**	50 (19,8%)	35 (20,8%)	8 (19,0%)	7 (16,7%)	0,8
– **Unknown**	61 (24,2%)	48 (28,6%)	7 (16,7%)	6 (14,3%)	0,07
Live borns	122	95	18	9	
– **Birth weight (g)**	2620 (840-4500)	2650 (840-4120)	2785 (1050-4500)	2300 (1340-4010)	0,42
– **Apgars**	9 (1-10)	9 (1-10)	9 (4-10)	9 (7-10)	0,92

*Kruskal-Wallis (for continuous) or Pearson Chi-Square (for frequencies) test

Perinatal outcomes were known in 76,2% of cases (192/252): 71,4% (120/168) of mild, 85,7% (36/42) of moderate and 85,7% (36/42) of severe VM (**Figure 5**).

There were no cases reported of spontaneous miscarriage and only one early neonatal death. This particular patient had a fetus with a low open spina bifida and severe VM. She presented in spontaneous preterm labour at 35w6d, with a breech presentation and delivered by caesarean section. The baby weighed 2690gm, had grade 3 meconium stained liquor and a 5-minute Apgar score of 1. The baby did not qualify for NICU care and received only palliative care in view of the antenatal findings, resulting in demise.

Figure 5: Perinatal outcomes



*TOP – termination of pregnancy

4.10.2. Termination of pregnancy (n=61)

TOP was offered to 102 women (43 mild, 19 moderate and 40 severe VM cases). Sixty-one women opted for TOP (24,2%) including 12,5% (21/168) of mild, 35,7% (15/42) of moderate and 59,5% (25/42) of the severe VM cases (p <0,001). Fetocide was performed in 28,6% (6/21), 40,0% (6/15) and 64,0% (16/25) of TOPs for mild, moderate and severe VM respectively. The initial presentation and associations of the cases resulting in TOP are depicted in **Table 8**.

Table 8. Prenatal associations in TOP cases

Prenatal VM Associations	All TOP	TOP without Fetocide n = 33	TOP with Fetocide n = 28
None i.e. Isolated	Mild: 0/21 Mod: 3/15 Severe: 2/25	Mild VM: 0/15 Mod VM 3/9 Severe VM: 0/9	Mild VM: 0/6 Mod VM: 0/6 Severe VM: 2/16
Additional soft markers only	Mild: 4/21 Mod: 2/15 (*1) Sev: 4/25 (*2)	Mild VM: 2/15 Mod VM: 1/9 Severe VM: 2/9	Mild VM: 2/6 Mod VM: 1/6 Severe VM: 2/16
Major structural anomalies	Mild:17/21 (*1) Mod:10/15 Sev: 19/25 (*3)	Mild VM 13/15 Mod VM 5/9 Severe VM 7/9	Mild VM 4/6 Mod VM 5/6 Severe VM 12/16

Abnormal karyotype	Mild: 1/21 Mod:1/15 Sev: 5/25	Mild VM 0/15 Mod VM 1/9 Severe VM 2/9	Mild VM 1/6 Mod VM 0/6 Severe VM 3/16

(N*) N with abnormal karyotype

Amongst the 21 TOPs for mild VM, 81,0% (17/21) of cases had associated major anomalies. The anomalies included mostly CNS (n=11) and cardiac (n=4) anomalies and one Trisomy 13 out of 6 karyotypes. All major anomalies were regarded to have a poor prognosis. In 4 cases, only multiple soft markers were noted and invasive testing was accepted in 3 noting normal karyotypes and negative infective work up. All four cases screened high for aneuploidy. The first case was diagnosed at 17 weeks. The corpus callosum could not be identified due to position of fetal head. The second case was diagnosed at 21w4d. Follow up ultrasound two weeks later revealed cerebellar hypoplasia. The third case was diagnosed at 23 weeks gestation. The mother was of advanced maternal age. The fourth case was diagnosed at 23 weeks gestation. Follow up ultrasound two weeks later revealed very abnormal Dopplers (AEDF) with subsequent hypertension, and thus the diagnosis of pre-eclampsia was made.

Overall, karyotyping was performed in 42,9% (9/21) of the mild VM cases who accepted TOP and a single case of Trisomy 13 was diagnosed.

Amongst the 15 TOPs for moderate VM, 66,7% (10/15) of cases had associated major anomalies that comprised almost exclusively of the CNS (n=8). The three isolated cases of moderate VM will be discussed in the next section. Karyotyping was performed in 53,3% (8/15) of moderate VM cases who accepted TOP and only one case of Trisomy 21 was diagnosed.

Amongst the 25 TOPs for severe VM, 76,0% (19/25) had associated major anomalies and half of these comprised of multiple structural anomalies (n=10/19). In 4 of the remaining 6 cases only multiple soft markers were noted, one of which was associated with Trisomy 21. In the remaining 2 cases, there were no clear antenatal associations found. Karyotyping was performed in 64,0% (16/25) of severe VM cases accepting TOP and an abnormal karyotype was found in 5 cases (**Table 6 & 8**).

4.10.3. Borderline cases (n=35)

Of the borderline VM cases, 12 (34,3%) were associated with multiple soft markers, 6 (17,1%) with major anomalies and 17 (48,6%) had no associated anomalies. Genetic testing was done in 10 cases (28,6%) and abnormal in 2 cases (5,7%; one Trisomy 21, one Di George syndrome). The Trisomy 21 case had soft markers only and the Di George syndrome had a large VSD. Only one case in this subgroup had a confirmed CMV infection (the DCDA twin pregnancy discussed in section 4.7). In 25,7% (9/35) the outcome was not known and the remainder were live born, apart from two cases resulting in TOP. The first case was for severe intracranial haemorrhage secondary to warfarin treatment for mixed mitral valve disease. The second case was for non-immune hydrops fetalis, with multiple soft markers at 22 weeks' gestation, negative infective work up and normal karyotype but with a guarded prognosis. Of the 17 borderline cases without associated anomalies, none had infection or an abnormal genetic result.

4.10.4. "Apparently isolated" cases (n=88)

When reflecting exclusively on the overall outcome of 88 cases of apparently isolated VM (**Table 9**) none were associated with an abnormal karyotype or confirmed congenital infection and 17,0% (15/88) could be discharged back to their referring institution after resolution/normalisation.

Yet, in 5,7% (5/88) the pregnancy ended in a TOP (3 moderate VM, 2 severe VM cases).

- The first TOP was for a patient with chronic hypertension, moderate VM and severe IUGR at 20 weeks' gestation.
- The second TOP was in a patient with well controlled DM, epilepsy and chronic hypertension, but moderate VM at 22 weeks' gestation.
- The third TOP was in a healthy woman, who gave history of a rash two weeks prior to ultrasound. Moderate VM at 21 weeks was diagnosed and TOP was accepted.
- The fourth TOP was for a morbidly obese patient who booked late and had severe VM at 33 weeks
- The fifth TOP was in a healthy woman with severe fetal VM diagnosed at 27 weeks' gestation and persisting on follow up scans. After consulting with the paediatric neurologist the woman opted for TOP with fetocide at 30 weeks' gestation.

Table 9. Outcomes of apparently isolated VM cases displayed as median (IQR) or n (% of cases in the group).

	All cases n=88	VM Mild n=69	VM Moderate n=14	VM Severe n=5	p*
GA at diagnosis (days)	168 (151-194)	164 (150-194)	163 (149-193)	236 (204-251)	0,06
Bilateral	30 (34,1%)	17 (24,6%)	10 (71,4%)	3 (60,0%)	0,003
Ventricle diameter (mm)					
– **At diagnosis**	10,7 (10,1-11,6)	10,5 (10,0-10,8)	12,7 (12,3-13,0)	24,1 (20,4-37,6)	<0,01
– **At last visit**	9,9 (8,2-11,0)	9,3 (8,0-10,4)	12,4 (10,6-13,3)	23,4 (19,5-37,3)	<0,01
Natural history					
– **Resolved (<10mm)**	46 (52,3%)	43 (62,3%)	3 (21,4%)	0	<0,01
– **Persisted (in same category)**	41 (46,6%)	26 (37,7%)	10 (71,4%)	5 (100,0%)	0,06
– **Progressed to severe VM**	1 (1,1%)	0	1 (7,1%)	NA	0,200
Outcome					
– **Unknown**	32 (36,4%)	29 (42,0%)	2 (14,3%)	1 (20,0%)	0,2
– **TOP (± feticide)**	5 (5,7%)	-	3 (21,4%)	2 (40,0%)	0,6
– **Stillbirth**	-	-	-	-	
– **Live born**	51 (58,0%)	40 (58,0%)	9 (64,3%)	2 (40,0%)	0,6
– **Early neonatal death**	-	-	-	-	

*Kruskal-Wallis (for continuous) or Pearson Chi-Square (for frequencies) test

Chapter 5: Conclusion

5.1. Summary of main findings

The median gestational age at diagnosis was 23w4d, with 48,8% diagnosed after 24w0d. There were no maternal predictors identified; the maternal characteristics as well as the obstetric and medical risk profile did not differ with VM severity. Mild VM was more likely to be unilateral ($p<0,01$) and isolated ($p<0,01$) when compared to moderate and severe VM. Mild VM was associated with multiple soft markers in up to a third of the cases and over half of the cases normalized during pregnancy; severe VM was associated with multiple major anomalies in 31,0% of the cases. The majority of major anomalies in all 3 groups were CNS defects in 25,8% and cardiac anomalies in 10,3%. Termination of pregnancy was opted for in 12,5% of mild, 35,7% of moderate and 59,5% of severe VM cases.

5.2. General discussion

In almost half of the patients, the diagnosis was made after 24w0d when offering of TOP becomes more restrictive and TOP requires fetocide. Although not specifically investigated in this study, this can at least partly be attributed to late initiation of antenatal care. The WHO recommends initiation of ANC during the first trimester but far later first ANC presentation remains widespread in sub-Saharan Africa. Lack of education, attitudes, knowledge regarding pregnancy, cultural beliefs, availability, affordability and accessibility of health care services all contribute to delay in ANC initiation. A recent cross-sectional study done by Ebonwu et al[60] in South Africa showed that unplanned pregnancies, teenage pregnancies and being married all contributed to late initiation of ANC.

Mild VM, when compared to moderate/severe VM, was more likely to be unilateral ($p<0,01$) and in our study, almost half of all the cases of VM, 48,4% (122/252) were unilateral VM. This differs from international literature where most researchers agree that unilateral VM is rare, resulting in research series that are small[19]. A possible explanation for our findings is that older studies assumed bilateral VM whenever VM was diagnosed, as it was not the custom to routinely measure the most proximal hemisphere that is obscured by acoustic shadowing. In our unit, we make an effort to change the transducer or fetal position to allow visualization of both hemispheres. An alternative explanation is

the inclusion of borderline cases in our series, which may not have formed part of other studies.

The majority of studies reporting the perinatal and long-term outcomes in fetuses with an antenatal diagnosis of fetal VM have assessed the bilateral condition[61]. Kinzler et al and Durfee et al both agree that fetuses with asymmetrical unilateral VM have a better prognosis than those with bilateral VM[20,21].

5.3. Associations and population risk profile

Mild VM, when compared to moderate/severe VM, was more likely to be isolated (p<0,01). Once the diagnosis of VM is made, a rigorous search for associated anomalies should be done, because VM is frequently associated with other anomalies. Follow up assessment is extremely important, as anomalies may manifest only later on during the pregnancy. The most common major structural anomalies in all 3 groups of this study were CNS defects in 25,8% and cardiac anomalies in 10,3% in line with Sethna et al [35] who reported 31,8% (113/355) CNS anomalies and 3,9% (14/355) cardiac anomalies in 355 cases of mild and moderate VM respectively. The most common CNS defects seen in the current study were open spina bifida and cerebellar and vermis dysgenesis, in line with Sethna (spina bifida and absence of the corpus callosum). A striking difference between this study and studies from developed countries is the limited use of MRI to search for more anomalies not seen on ultrasound. Limited access and cost prevent use of MRI in most cases and therefore it is only used in selected cases.

Aneuploidy was associated with VM (4,8%; 12/252) but mainly limited to cases with associated ultrasound findings (in 9/12). Our incidence was lower than reported by Gaglioti et al (>15% when severe or borderline VM is associated with structural malformations)[18] or Sethna[35] (11,0% on prenatal karyotype, increasing to 14,1% when post-natal karyotypes were included). It is likely that the low incidence of abnormal karyotype in our study is due to the fact that only 74 cases (i.e. less than a third) had prenatal genetic testing (but it was offered to almost 60% of patients) and post-natal karyotype results were not reviewed. Of the ones that were tested, the abnormal yield of 16,2% (12/74) was more in line with the other studies.

The three most common aneuploidies accounted for 66,7% of all abnormal karyotypes. Trisomy 21 & 18 were the commonest aneuploidies overall. Consistent with data from

Lam[24] and Gaglioti[18] the severity of VM is not predictive of the risk of aneuploidy. In our study more cases of aneuploidy were seen in the mild VM group as compared to moderate and severe VM.

5.4. Evolution of VM

The importance of follow up assessment is clearly demonstrated in this study. It is well known from the literature that VM can remain stable, show progression or regression. As can be seen in **Figure 4**, the trend of progression or regression in the mild and moderate groups is demonstrated. 54,5% (66/121) of mild VM cases that had follow up scans, showed regression and in the moderate group 24% of cases that had follow up scans, 'normalized' to below the cut off of 10mm. In the severe group, only 3 cases had smaller measurements, but none were below 15mm. This is consistent with findings by Lam et al[24] who found the rate of regression in mild and moderate VM to be 46% and 26% respectively. They confirmed that when ventricles exceed 15mm, they do not tend to normalize. It is clear from this study that the rate of progression of VM increases with severity and that resolution in severe VM is unlikely to occur.

5.5. Acceptance rates

5.5.1. Acceptance rates of invasive testing

The main reason for declining invasive testing was the fear of a possible miscarriage associated with the procedure. This is quoted as less than 1%. Lack of education and poor understanding contribute to this. Another reason for declining invasive testing is religion. Patients will not consider TOP under any circumstances and will accept a child irrespective of the diagnosis or prognosis, based on their religious beliefs.

5.5.2. Acceptance rates of TOP

TOP was accepted in 24,2% (61/252). The study demonstrated that rates of termination increased with severity of VM, as can be seen in **Figure 5**. This is consistent with data from Lam et al. [24] They found that TOP was done in 25%, 53% and 72% of mild, moderate and severe VM respectively. One explanation for acceptance of TOP in the current study is that patients from a developing country and low SES don't have the financial capacity to care for infants with special needs and poor neurological outcome if they do survive.

Provision of and access to rehabilitation services are limited and the financial implications play a major role.

The diagnosis of fetal anomaly triggers intense distress and discomfort in the expecting mother regardless of severity[62]. Counselling plays an important role regarding the decision of the mother to undergo a TOP. At our unit, counselling focuses on the five key aspects that are the basis for understanding fetal prognosis[63]. This includes but are not limited to diagnosis and certainty thereof, likelihood of survival beyond neonatal period, likely duration of survival if life-sustaining treatment is provided, range of possible physical and cognitive impairments if the new-born survives and the burden of treatment required to keep the baby alive. Non-directive counselling is provided so that patients can have a clear understanding of VM as well as the poor outcome associated with increasing severity, but patient autonomy is always respected.

5.6 “Apparently isolated” cases

88 cases of ‘apparently isolated’ VM were identified, the majority being in the mild VM group. 62,3% of the mild cases resolved. The diagnosis of isolated VM should only be made after having carried out a complete and rigorous ultrasound search for associated intracerebral and extracerebral anomalies[17]. The use of MRI, if available, can play an important role in diagnosing associated anomalies not seen on ultrasound. In developing countries, this should be on a case-to-case basis only, as cost limits its use. In our study, the isolated cases were considered truly isolated, as follow up ultrasound assessment were available in all these cases.

Isolated mild VM represents a considerable diagnostic dilemma as it can be seen as a variation of normality, but still is associated with chromosomal abnormalities, congenital infections, cerebral vascular accidents or haemorrhage and other fetal cerebral and extracerebral abnormalities in some cases. It may also have implications regarding long-term neurodevelopmental outcome. [12] It is thus imperative to follow up these ‘apparently isolated’ cases after the diagnosis is made, as associated anomalies may appear later on with advancing gestation and the truly isolated cases are not ‘innocent’ or less important compared to those cases with associated findings. As seen in **Table 9**, in 58,0% (40/69) of mild isolated VM the outcome was a live born infant. 42,0% (29/69) of mild cases were lost to follow up; the reason therefore can be twofold, namely they were truly lost to follow up or the VM normalized and the patients were discharged from TBH.

Progression/Non-progression in isolated cases

None of the mild isolated cases progressed to moderate or severe VM. Only one case of moderate VM progressed to severe VM. This is in contrast to the study done by Quahba et al[17] follow up scans in 167 fetuses with mild isolated VM showed progression in 11% of cases, but they made use of MRI as a complementary investigation to ultrasound. Infants with progression were at higher risk of subsequent neurodevelopmental delay that those with no progression. In our study we didn't consider neurodevelopmental outcome, but it is well known from the literature that in non-progressive isolated VM the prognosis seems better and the rate of normal post-natal development is still higher if VM resolves antenatally[17].

Chromosomal abnormalities in isolated VM

A literature review done by Kelly et al[25] showed that the incidence of chromosomal abnormalities varied from 3% to 12,6% in fetuses with mild VM. In our study, none of the isolated cases (mild, moderate and severe isolated VM) that were tested had an abnormal karyotype. We acknowledge that only 21,6% (19/88) of the isolated cases had karyotyping done, that could have contributed to the result. Invasive testing is offered to patients who screens high risk for aneuploidy based on their background risk as well as ultrasound findings. Currently we don't offer serum screening during the first or second trimester. This can probably influence the uptake of invasive testing that will lead to more cases of aneuploidy being diagnosed.

Isolated VM and TOP

Quahba et al[17] reported a TOP rate for isolated mild VM of 3,5% when truly isolated mild VM were considered. In our study, the overall TOP rate was 5,7% (5/88); none of the known outcomes of mild VM ended in TOP whereas 21,4% (3/14) of moderate VM and 40,0% (2/5) of severe VM underwent TOP. The decision for TOP for isolated moderate and severe VM is easier as it is known that increasing severity of VM is associated with poor neurodevelopmental outcome. For mild isolated VM it remains a difficult decision. Vigorous search for associated anomalies that may appear only later on, progression of VM, invasive testing for aneuploidy and testing for fetal infections can all contribute and aid in the decision-making regarding TOP in mild cases.

5.7 Borderline measurements

The majority of the literature and studies on VM are limited to measurements ≥10mm. As mentioned earlier, VM with a measurement of 10mm can actually be measurements ranging between 9,5-10,5mm due to older equipment being used. We identified a subgroup of 35 patients with mild VM, with initial measurements of 9,5-9,9mm. More than half of these cases had associated anomalies. As seen from our study, this is not a 'benign' group of cases: 34,3% had soft markers and 17,1% had major anomalies. 12,9% remained stable and 19,4% progressed to a measurement of more than 10mm. It can be associated with poor outcomes, even if they normalize or remain stable. It is thus important that this subgroup of patients is followed up closely to look for progression, regression and associated anomalies that are only apparent at a later gestational age, as this can have a major impact on the initial and long-term outcome.

5.8 Limitations of the study

The study has several limitations. As with retrospective studies based in a referral centre, the findings do not necessarily represent the population. Significant selection bias is likely, with more severe cases more likely being suspected and referred. Incomplete medical records as well as the high rate of loss to follow up could've had an impact on some of the results. Long-term neurological outcome was not assessed so no comparison is possible with data from developed countries to assess similarities as well as significant differences.

5.9 Strengths of the study

This is the first detailed report of VM from a developing country. According to the investigators' knowledge, it is the first study from a South African perspective. It gives a detailed account of pregnancies referred for VM in a defined geographical area of South Africa with a fairly well established obstetric ultrasound service and access to special investigations. Another strength of our study is that we were able to stratify according to the degree of VM in three separate categories with distinct clinical differences. The number of "apparently isolated" cases was sufficient to enable comments on a number of key outcomes and the subgroup analysis on borderline cases (9,5-9,9mm) provided clinically useful additional information.

5.10 Conclusion and future directions

Conclusion

VM is not an uncommon prenatal finding but, in this setting, was often diagnosed late, which limits options for investigation and management. Associated findings, esp. cardiac and CNS, were common and increased with increasing severity of VM but aneuploidy occurred with any severity. In this cohort, unilateral VM was associated with mild VM and may have been due to the inclusion of borderline VM, which was shown not to be a benign finding. Uptake of invasive testing and of TOP was low in this community, and late diagnosis may have contributed to that.

Future directions

Future research can include long-term postnatal neurodevelopment, specifically in relation to VM severity and progression as well as apparently isolated VM. This will aid in counselling of expectant parents regarding this challenging diagnosis, prognosis and its management options.

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