BIRTH PREVALENCE OF ANO-RECTAL MALFORMATIONS FOR THE WESTERN CAPE PROVINCE, SOUTH AFRICA

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THRAND009

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree

Masters of Medicine in Paediatric Surgery

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Date: 30 March 2016

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DECLARATION

I, **André Pieter Theron (THRAND009)**, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: 30 March 2016…….

ACKNOWLEDGEMENTS

With sincere gratitude to:

- Prof A Numanoglu, head of Department of Paediatric Surgery at Red Cross War Memorial Children's Hospital and supervisor for this dissertation.
- My colleagues at Red Cross Hospital. For allowing me the extended time to concentrate on this dissertation
- Prof R Brown and his personnel for making me feel welcome and for permitting me to have access to his patients' medical folders.
- Duane Davids, the ward clerk for ward D2 at Red Cross Hospital. He was always willing to acquire the needed patient records.
- To the medical records personnel at Tygerberg Hospital. Your help is much appreciated.
- Henri Carrara who helped in providing advice and getting me to understand even the most basic stats for this dissertation.
- To the best wife a husband could ask for. Joji, your enthusiasm for research is contagious. The support and encouragement for this dissertation is extremely appreciated.

TABLE OF CONTENTS

ABBREVIATIONS

ARM	Anorectal Malformation
DHIS	District Health Information System
EUROCAT	European Concerted Action on Congenital Anomalies and Twins
RCWMCH	Red Cross War Memorial Children's Hospital
RSA	Republic of South Africa
TCH	Tygerberg Children's Hospital
UCT	University of Cape Town
WCP	Western Cape Province

ABSTRACT

Title: Birth Prevalence of Anorectal Malformations for the Western Cape Province, South Africa

Keywords: Anorectal malformation, prevalence, delayed diagnosis, South Africa, Western Cape,

Background: Anorectal malformations (ARMs) are a major birth anomaly worldwide. South Africa has ethnically and geologically diverse populations. A recent publication indicated an increased birth prevalence of ARMs in the Witwatersrand referral area between 2005 and 2010. The purpose of this study was to determine the birth prevalence of ARM and its various sub-types in the Western Cape referral district over an 8 year period

Methods: For an eight year period from 01 January 2005 to 31 December 2012; retrospective data was collected from the Paediatric Surgical Departments of Red Cross War Memorial Children's Hospital, Tygerberg Children's Hospital as well as the private sector health registries. The number of live births per year for a specific municipal district was obtained from the National Department of Health. The Chi square for trend test was used to determine statistical significance.

Results: The birth prevalence for ARM in the Western Cape Province in 2012 was shown to be 1:5572 live births (1.79/10 000 live births). The West Coast Municipality district had the highest average birth prevalence rate of 1:3063 (3.26/10 000) live births for years studied. There was a male predominance (1.6:1), the most common ARM was the vestibular fistula (19.2%) and in 26% of the patients there was an initial delay in the diagnosis.

Conclusion: This study has provided some recent data for ARMs for the Western Cape Province. There was no statistical significant change in the prevalence of ARMs over the eight year period for the Western Cape Province as well as in any of the individual six municipal health districts. ($\chi 2$ *for trend* p=0.52). The number of delayed diagnosis of ARM is of concern.

PART A: THE PROTOCOL

Birth Prevalence of Ano-rectal malformations for the Western Cape. South Africa

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Defining the research problem

Anorectal malformations (ARM) are a one of the more common major congenital anomalies in the newborn. They usually require a multitude of surgical procedures at a very early age and have a large impact on the lives of patients and their parents. As there is no accurate current literature for Western Cape Province, South Africa; it would be beneficial to identify the current birth prevalence and any geographical predilection to the occurrence of ARM in newborns. Gender, race, age of mother, gestational age, birth weight, classification of the ARMs, and associated medical conditions will also be reviewed in order to investigate a common trend which may be linked to certain areas from which the patients are referred from.

Literature overview and motivation

Anorectal malformations are a common major congenital anomaly in the newborn. There is significant geographical variation with the birth prevalence varying from 1 in 1500 to 1 in 5000 [1-2]. In addition to geographical variations, inter-registry variation has also been reported between different countries in Europe as well as fluctuations between the individual years studied [2-3].

Louw et al in the 1960's reported an overall birth prevalence for ARM of 5.5/10 000 live births in South Africa [4-5]. In a more recent study published in 2008, Moore et al reviewed the number and type of ARM presenting in various South African tertiary referral hospitals [6]. This study only reported on the occurrence of ARM and the different types of ARM and made no reference to the birth prevalence. It also suggested the need for more objective data to assess the geographical differences. As such, no recent local studies have been done to look at accurate birth prevalence in a given area.

In Alberta, Canada ARM appears to on an upward trend, even though the study did not show a statistically significant difference [7].

The aetiology of ARM is still largely unknown and it is assumed to be multifactorial [8]. Environmental and genetic risk factors may play a role, but to what extend it is not known.

Studies have found that there is a difference between the ethnic populations with regards to the type of anorectal malformation [6].

Information gleaned from this study will identify possible geographical and presenting trends of ARM in the Western Cape area. This will be the platform from which future studies may identify likely causative or predictive factors which may lead to earlier prenatal detection or even prevention of the condition

Aim and objectives

Aim: To determine the birth prevalence of ARM in neonates for the Western Cape area over an eight year period from 01 January 2005 to 31 December 2012.

Objectives: 1) To determine the current birth prevalence of ARM in neonates for the Western Cape Province for 2012.

2) To determine geographical predominance of the referral patients

3) To determine any clusters in gender, maternal age, gestational age, race, birth weight, classification of ARM and any associated medical conditions in patients referred from the various areas.

4) To determine the incidence of a delay in making the diagnosis of ARM.

Methods

Study design: Retrospective folder review

Review the patient's records for an eight year period from 01 January 2005 to 31 December 2012.

Patient information will be obtained by reviewing the admission registry, patient's medical records and theatre notes from record archives from Red Cross War Memorial Children's Hospital (RCWMCH) and Tygerberg Children's Hospital (TCH).

Paediatric surgeons working in the private sector will be approached to obtain their patient's medical records for the same time period.

The Ethics committee for University of Stellenbosch will be approached to obtain ethics approval for the Tygerberg Children's Hospital.

Department of Health will be approached to obtain the figures for the number of live births in a given health district for a specific year

Exclusion criteria:

1) Any treated neonates that were referred from hospitals falling outside the usual stipulated Provincial Health guidelines and criteria for the referral to the RCWMCH and TCH. That is any hospital that does not usually refer to RCWMCH and TCH.
2) Any neonate that was treated in the private sector whose parent's residential address in not within the Western Cape Province.

Measurements:

Demographics to be collected:

1) Number of babies born with ARM in the referral area to RCWMCH, TCH and the private sector
2) Referral hospitals
3) District municipal area the parents of the newborn reside in
4) The number of live births per year in referral area/health district for the Western Cape
5) Maternal age
6) Gestational age

7) Race – black, white, Asian, Indian, other

As this is a retrospective study; the race will be determined by what is recorded in the patient's file.

8) Gender – male, female, ambiguous

9) Birth weight of neonate

10) Type/Classification of ARM according to the Krickenbeck Classification (See appendage 1)

11) Any congenital deformities present

12) Any congenital abnormalities in siblings

13) If there was a delay in making the diagnosis

a) A "delayed" diagnosis is defined as neonates who have been examined by a medical personal member and were subsequently allowed to feed, irrespective of post-partum timing.

Data analysis

Birth prevalence will be calculated from available data. The *Chi squared test for trend* will be used for statistical analysis.

Correlation and regression analysis will be done to look for any associations in the demographic data.

Ethical Considerations

No direct patient contact will be needed. There will be no risk to the patient as this is a retrospective folder review. No personal content or confidential information contained within the patient's file will be linked to the patient's name. Any paper/computer records will only be accessible to the author.

This study complies with the Helsinki Declaration of 2008

Budget (including Funding obtained)

No funding will be needed

Time lines

Date of start of proposed study: Pending ethics approval

Date of completion of proposed study: July 2014

Reporting

Submissions for publication will be made to medical journals

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Appendages: Attached at end of dissertation

1) Krickenbeck Classification

2) The data collection form

PART B: LITERATURE REVIEW AND MOTIVATION

ARM, even though being a rare congenital disease, is one of the most common major gastrointestinal anomalies in the newborn. The neonates require a multitude of surgical procedures with a multi-disciplinary approach at a very early age resulting in having a large impact on the lives of the neonates and their parents.

This study has two components. The main component and primary aim is to determine the current birth prevalence in 2012 of ARM in neonates for the WCP. The secondary aim is to determine if there is any statistically significant change in the prevalence of ARM over an eight year period for the six municipal districts of the WCP beginning 2005 to end of 2012. Any geographical predominance for the different municipal districts in the WCP of the referred patients will be sought. Clusters in gender, maternal age, gestational age, race, birth weight, classification of ARM and any associated medical conditions will be determined.

The second component of the study will evaluate a concern regarding the delay in making the diagnosis of ARM in the WCP It will provide the overall incidence of the patients that had their diagnosis delayed over the studied eight period for WCP

This main objective of this literature review is to analyse the different studies concerning birth prevalence of ARM. . It will briefly mention the studies and their results and highlight if there were a difference in the trends in the prevalence of ARM. It will also discuss the some aetiological factors affecting ARM. There is an important connection between prevalence and aetiology of ARM and this concept will be explored.

The literature review will also provide data for the incidence in the delay in making the diagnosis of ARM. The potential reasons for the delay and the average time from birth till the diagnosis are looked at.

Searching the database PUBMED found on the University of Cape Town Library website (http://www.lib.uct.ac.za/) the terms ano rectal malformation, imperate anus, prevalence, incidence, epidemiology, delay diagnosis were used. No specific exclusion criteria were used.

The current worldwide prevalence for ARM is usually quoted as 1:5000 live births in most textbooks and review articles. There is however a significant geographical variation ranging from 1 in 1500 to 1 in 10 000 live births. (1-5) In addition there is also inter-register variation between different countries in Europe as well as fluctuations between the individual years studied. (1, 2, 6) There is a marked difference in prevalence and distribution of anal anomalies among the EUROCAT registries and The International Clearing House Study (1, 2). In

Alberta, Canada one study that looked at the prevalence of ARM from 1990 to 2004 showed that over a 15-year period the prevalence rates do fluctuate with an upward trend in the prevalence, but this was not a statistically significant difference.(6) Epidemiological studies in developing countries are fewer and less accurate than in developed countries as there is often a scarcity of reliable data collection. Vital statistics are most effectively generated by comprehensive civil registration which is often lacking in developing countries. (7)

South Africa has very few accurate studies looking at the prevalence of ARM. Louw et al in the late 1950's and 1960's reported an overall birth prevalence of 5.5/10 000 in South Africa(8, 9). In a more recent study published in 2008, Moore et al reviewed the number and type of ARM presenting in various South African tertiary referral hospitals. This study only reported on the occurrence of ARM and the different types of ARM and made no reference to the birth prevalence. It made reference to the difference in ethnic groups showing for example that female rectovestibular fistulas were more common in the black population. It also suggested the need for more objective data to assess the geographical differences. (10) Theron, Loveland in 2015 published an article looking into geographical variations of the prevalence of ARM's for the referral area of the University of Witwatersrand Paediatric Surgical Unit, Gauteng, RSA (11). In this article it was found that the current prevalence for ARM in 2010 was 1: 3989 live births for the referral area of the University of Witwatersrand Paediatric Surgical unit. There was a statistically significant increase in the prevalence of ARM between 2005 and 2010 in two of the seven municipal districts found in the two provinces looked atIt recommended that more epidemiological studies be done in South Africa to identify any epidemiological trends which may be utilized in the screening, detection and prevention of ARM.

The aetiology of ARM is still largely unknown and it is assumed to be multi-factorial with both environmental and genetic risk factors. (12-16).

Environmental risk factors including the use of multivitamins, paternal smoking, occupational exposure to industrial cleaning agents may play a role. (12) . Other studies could however not replicate those results, so to what extend those environmental factors play a role is not known (13) It has even been suggested that daily intake of folic acid reduces the risk of ARM (17). Wijers et al in 2014 did a literature review by summarising and critically appraising all available literature on the genetic and non-genetic aetiology of non-syndromic ARM. Only a few non-genetic factors of were consistently associated with ARM. These were: assisted reproduction, multiple pregnancy, preterm delivery, low birth weight, maternal overweight or obesity, and pre-existing diabetes. (18) Ongoing research is thus needed.

With regards to genetic risk factors only a few identified genes have been implicated in syndromes where ARM can also be present. . There is for example a fifteen percent increased incidence of ARM in patients with Trisomy 21 (Down's syndrome) (19-21). It has also been noted that 95% of patients with Trisomy21 and ARM have a certain type of ARM namely imperforate anus without fistula, compared with only 5% of all other patients with ARM... This significant predominance of Downs syndrome in ARM without a fistula may provide some insights into the pathogenesis of ARM in the field of molecular genetics (21)

Cuschieri and the EUROCAT Working Group suggested that anal anomalies are defects of blastogenesis attributable to disorders in expression of pattern determining genes. (22)

Landau et al suggested that there was an autosomal dominant inheritance component when he reported on a three-generation family with four members affected with ARM. (23) However Murken and Albert thought that the mode of inheritance was autosomal recessive when they reported on 169 patients with ARM with the genetic risk of isolated ARM to be estimated to below one percent. (24) Falcone et al found a positive family history in 1.4% which they said is supportive of a strong genetic component to ARM. The risk of having an affected family member is significantly increased in the presence of a vestibular or perineal fistula (15). A more recent literature review by Wijers et al in 2014 showed that research into identification of genes involved in the aetiology of non-syndromic ARM was limited. In the review article it noted that several genes were involved in signalling pathways for embryogenesis were investigated, but none revealed any strong correlation with the occurrence of ARM. (18)

The classification of ARM has undergone multiple changes with the last being in 2005 from the Wingspread to the Krickenbeck (International) ClassificationThis change in classification was deemed necessary as the Wingspread Classification was deemed not useful for therapeutic and prognostic evaluations . (25) This change in classification has made comparison of certain ARM data especially the different types of ARM prior to 2005 difficult to compare to the more recent data collection. One such article written by Ratan et al published in 2004 commented on this when he compared the incidences of various associated anomalies with high and low ARM. Here he suggested the need for a more uniformity in the classification of the anomalies. (26)

The numerous epidemiological studies that have looked at associated malformations with ARM vary widely. Stoll et al concluded that close to one in every two infants with ARM had an associated malformation. These were chromosomal, cardiac, urinary, genital, musculoskeletal, digestive system, cardiovascular, abdominal wall, central nervous and respiratory system (4) Spinal and renal anomalies where the most common associated

malformations found with ARM. (26, 27) It has been noted that there is a higher incidence of associated anomalies among patients with a more severe ARM. Girls with a more severe ARM were observed to have significantly more urologic anomalies compared with the boys with the same type of ARM. (26) The male to female ratio varies on the type of ARM (4), but there does seem to be a male predominance. (2, 3, 6, 26).

Ideally, the full-term newborn should be examined at least two to three times between birth and discharge. In the delivery room immediately after birth; in the nursery within 12hours, and at discharge from the hospital. Therefore, standardised guidelines recommend a routine physical examination of all newborns at least within the first 48hours of life. Particular attention should be given to a thorough examination of the perineum. The patency of the anus must be ensured in the newborn even if meconium has been passed. (28). The number of ARM which had delayed diagnosis is surprisingly not uncommon. Between 21% to 53% of ARM present with a delayed diagnosis (29-34). This was despite routine physical examinations postpartum. The definition for delayed diagnosis of ARM differed between studies. Turowski et al defined delayed diagnosis as diagnosis made after 48hours of life(30). Eltayeb used 48hours after birth and after three months of age with low lesions in females. Wilson et al used 24hours and 48hours for his different cohort of patients. Haider, Fisher used 24hours. (31)

Tareen el al found no difference in the incidence of delayed diagnosis of ARM between 1999 to2012 for the two regional referral units for neonatal paediatric surgery for the Republic of Ireland. (34)

The most common lesion missed was the perineal lesion with the male perineal ARM being more frequent than the vestibular ARM or female perineal fistula. (30) However Wilson et al and Haider et al found no difference (29, 31). These studies however had a small cohort of patients.

The causes of delayed presentation include delayed detection, wrong advice to parents, inadequate treatment offered and social reasons. (33)

Part of the contributing factors that lead towards the delayed diagnosis in developing countries is the lack of proper guidelines for screening and newborn physical examination. Socio-demographic factors include age younger than 30 and a lower educational level (32). Interesting it was noted that it was thought the potential to miss an ARM has increased since the discontinuation of routine rectal temperature readings.(29, 34)

The delay in diagnosing ARM can result in significant morbidity and mortality, prolongs inpatient care and impedes optimal surgical management. (29)Morbidity includes additional often unnecessary surgical procedures including the formation of a colostomy, chronic

constipation, mega rectum, failure to thrive and recurrent urinary tract infections. Mortality secondary to intestinal perforation and sepsis can occur. (31, 33) With the general trend to repair the ARM in the neonatal period in the select case the need to have a prompt diagnosis of ARM becomes even more important, (35, 36)

Research into ARM is ongoing. The epidemiology and aetiology is still poorly understood as there are genetic and environmental components that have varying contributions to the development of ARM. It can be argued that with the environment being an important component in the development of ARM the data obtained from epidemiological studies gives an indication of the health of the countries environment. There is a current lack of data regarding the prevalence of ARM in South Africa highlighting the need for further studies to determine the overall prevalence of ARM in South Africa and thus giving a small glimpse into the health of the South African environment. As more information becomes available the prevention of ARM could become a reality. The need and importance of a complete and proper newborn examination cannot be over emphasised. Current guidelines appear to be insufficient to ensure prompt diagnosis of ARM. Proper guidelines that are implemented would prevent any potential morbidity resulting from a delayed diagnosis of ARM providing the neonate with the best prospect of having a good quality of life.

'With the evidence of delayed diagnosis of ARM, more systems should be put in place to ensure that the newborns are examined at least two times before discharge and that particular attention is paid to the perineum as it is oftern overlooked.

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PART C: PUBLICATION READY MANUSCRIPT

BIRTH PREVALENCE OF ANORECTAL MALFORMATIONS FOR THE WESTERN CAPE PROVINCE, SOUTH AFRICA. 2005 TO 2012

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Keywords:

Anorectal malformation

Prevalence

Delayed diagnosis

South Africa

Western Cape Province

Introduction

Anorectal malformations (ARMs) remain one of the most common gastrointestinal abnormalities of neonates. The infant requires a multitude of surgical procedures within a multi-disciplinary team approach at a very early age, which has a large impact on the lives of these patients and their parents.

The current worldwide prevalence for ARM is quoted as 1:5000 live births in most textbooks (1, 2). There is however significant geographical variation ranging from 1 in 1500 to 1 in 10 000 live births (1-5). In addition there are also inter-register variations between different countries, as well as fluctuations between the specific years studied (3-5).

The Republic of South Africa (RSA) is a diverse country encompassing a wide variety of genealogies, cultures, languages and religions. RSA has nine provinces which are further divided into municipal districts. The Western Cape Province (WCP) has six municipal

districts which include the City of Cape Town, West Coast, Cape Winelands, Overberg, Eden and Central Karoo Municipal District (figure 1).

Figure 1: The municipal districts of the Western Cape Province, South Africa. (Modified from Wikimedia Commons (24)

These six municipal districts form the basis of the referral platform to the two academic tertiary medical centres that manage paediatric surgical conditions as stipulated by the Provisional Health guidelines. The two state tertiary medical centres, namely the Red Cross War Memorial Children's Hospital (RCWMCH) and Tygerberg Children's Hospital (TCH) are affiliated to the University of Cape Town and the University of Stellenbosch respectively. The RSA healthcare system also has insurance-based private health care facilities which treat paediatric surgical patients. Currently an estimated 29% of South Africans are treated in private health care facilities (6).

Theron & Loveland conducted a retrospective study in 2014 in which the birth prevalence of ARM for the referral area of the Witwatersrand University was elucidated (7). This study reported an increased trend in the birth prevalence of ARMs from January 2005 till December 2010 for two municipal districts in this region. Additionally, this paper reported the current birth prevalence rate for ARM to be 1 in 3989 live births for this referral area. Due to the geographical and ethnical diversity within the various populations of RSA, the authors suggested the need for further studies within the other provinces so that collectively any regional or national changes in the birth prevalence of ARM could assist in identifying possible epidemiological trends (7).The current study comprises of a retrospective analysis of

the prevalence and type of ARM within the Western Cape Province of RSA over an 8 year period from 2005 to 2012.

Methods

This research project was approved by the Human Research Committee (Medical) at the University of Cape Town and the University of Stellenbosch (clearance certificate: HREC REF: 500/2013 and X14/01/001).

Retrospective data was obtained by analyzing patient's records over an eight year period from 01 January 2005 up to and including 31 December 2012 of all patients diagnosed with ARM. The patient records for the public sector were obtained from the Paediatric Surgical Department database systems within the RCWMCH and TCH. The predominant private paediatric surgery practice in Cape Town was approached to access their data capturing systems in order to collect the pertinent retrospective data, representing the private health sector component of ARM management. The main points of data collected included the year the patient were born in, the municipal district from which they were referred, the hospital at which they were managed, birth weight, gender, gestational age, any family history of ARM, type of ARM, any other congenital abnormality, and delayed diagnosis of ARM. Any patient that was referred from outside the WCP was excluded from the study. Inaccurate, inconsistent and unreliable classification by the booking clerks unfortunately forced exclusion of data on ethnical background and population race classification.

The number of live births for a specific municipal district was obtained from the National Department of Health and was calculated using the "District Health Information System". These are based on midyear population estimates which are issued annually by Statistics South Africa. Statistics South Africa is a governmental organization responsible for the collection, production and dissemination of official population statistics, as well as conducting of the official national census of the population (8). If the neonate was allowed to feed after examination by medical personnel, the infant was classified as having a delayed diagnosis of ARM. The *$\chi 2$ test for trend* was used for statistical analysis.

Results

A total of 209 patients were treated for ARM in the WCP over an eight year period from 2005 to 2012. RCWMCH treated 113 (52.8%) of these patients. TCH and the private sector treated 80 (38.2%) and 16 (7.5%) patients respectively. There were two patients that were treated both in the public and private health sector. These two patients were only included in the RCWMCH numbers. The total number of births increased from 97 832 to 105 874 per year

for the WCP. The City of Cape Town Municipality had the most infants born with ARMs over this 8-year period, with a total of 145 patients managed for this condition. The Central Karoo Municipality documented one baby born with an ARM (in 2007), but also had the least number births over the 8 year period studied (reported at 9447).

Table 1: Number of anorectal malformations per year in each municipal district of the Western Cape, South Africa.

Municipal	2005	2006	2007	2008	2009	2010	2011	2012	Total
Cape Wine	3	3	1	4	2	4	6	2	25
Central Karoo	0	0	1	0	0	0	0	0	1
CPT	22	22	16	14	17	21	21	12	145
Eden	4	1	3	1	0	4	2	2	17
Overberg	1	0	0	0	3	1	0	1	6
West Coast	2	2	2	0	1	1	5	2	15
Total	32	28	23	19	23	31	34	19	**209**

The live birth prevalence of ARM for the WCP in 2012 was calculated to be 1:5572 live births (1.79/10 000 live births). There was no statistically significant change in the prevalence of ARM within neither for the different municipal districts nor for the WCP as a whole over the eight year period (*χ2 for trend* p=0.52). The West Coast Municipality district had the highest average birth prevalence rate for ARM at 1:3063 live births (3.26/10 000 live births).

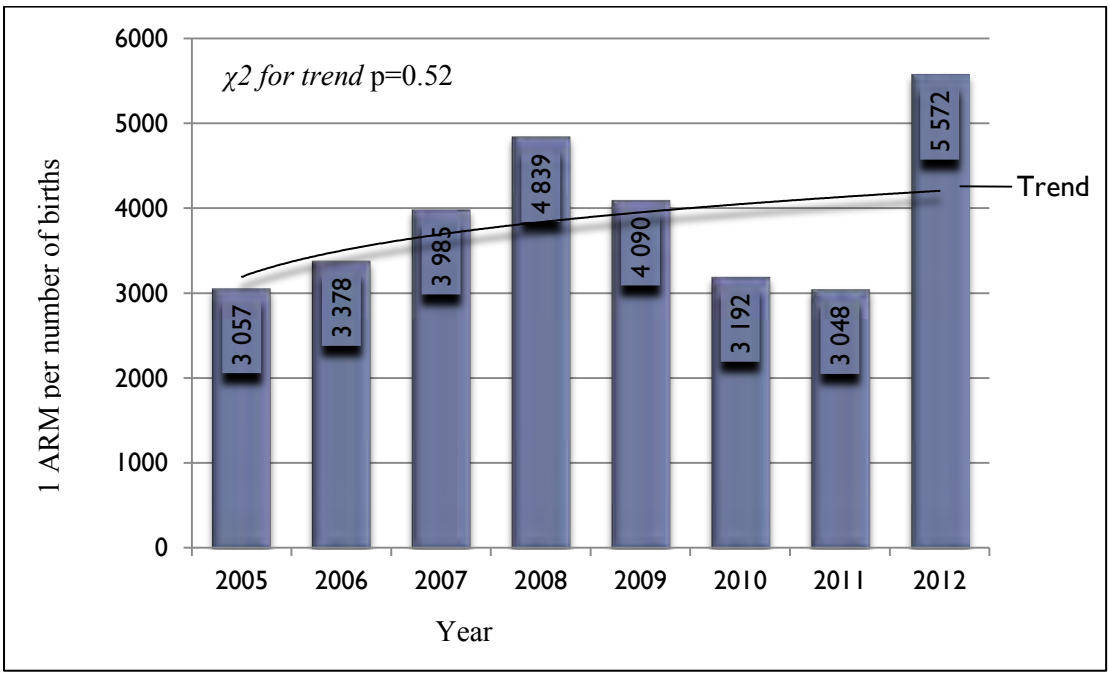

Figure 2: Birth prevalence trend of anorectal malformations for the Western Cape Province in South Africa over an 8 year period from 2005.

There was a male predominance of 1.6:1 in the presentation of ARMs. Three of the babies had ambiguous genitalia. The mean gestational age was 37 weeks. The lowest birth weight was 900g, the highest birth weight 4 530g with the mean birth weight of 2 722g. No siblings or any other family members were found to have any ARMs is this cohort of patients.

The most common ARM in the male patient population was the perineal fistula (15.4 %) followed by the bulbar fistula (14.5%). In female patients, the most common ARM was the vestibular anus (19.2%). There was however a high percentage of malformations which were not accurately classified in the patient records (20%).

One third (31.6%) of the patients had no other associated congenital malformations, while 21.7 % had multiple congenital abnormalities, with cardiac and renal abnormalities being the most common. Fifteen percent of the cases had ambiguous records for inclusion/exclusion of coexisting congenital abnormalities, and thus could not be included. Two patients presented with concurrent oesophageal atresia. (Table 2)

Table 2: Percentage of associated congenital abnormalities

	Percent
Nil	31.3
Vertrebral	4.7
Cardiac	11.2
Oesophageal Atresia	0.9
Renal	11.7
Limb abnormalities	0.9
Mutiple	21.5
unknown	15.4
Other	1.4
Total	100%

There was an initial diagnosis delay in 26 % of patients born with ARM. The two most frequent malformations which were initially missed were the male perineal fistula (an initial delayed diagnosis in 15 out of 18 cases or 83%) and the female vestibular fistula (a delay in diagnosis in 15 out of 26 cases or 57%). Patients presenting with isolated ARMs in the absence of other congenital abnormalities had a higher incidence of a delayed diagnosis (31%). The longest delay in diagnosis was in a male infant with a perineal fistula at 1year of age. (Table 3)

Table 3: Comparative table for sub-types of anorectal malformations diagnosed in the Western Cape Province of South Africa over an 8 year period from 2005 to 2012

	Type of ARM		Congenital Abnormality	Delayed diagnosis
Type of ARM	**Frequency**	**Percent**	**Frequency**	**Frequency**
unknown	44	20.6	39	7
Male Perineal fistula	33	15.4	13	15
Male Bulbar fistula	31	14.5	20	7
Male Prostatic	20	9.3	15	6
Male Rect bladder	4	1.9	3	0
Male Imperforate anus	13	6.1	9	3
Male Complex	1	.5	1	0
Female Perineal fistula	12	5.6	6	3
Female Vestibular fistula	41	19.2	26	15
Female Short Common channel cloaca	7	3.3	6	1
Female Long Common Channel Cloaca	3	1.4	3	0
Female Imperforate anus	2	.9	1	0
Female Complex defects	2	.9	2	0
Rectal Vaginal	1	.5	1	
Total	214	100%	145	57

Table 4: Comparative table showing the prevalence of ARM for each municipal district for 2005 till 2012

ARM 1/how many births (Number ARM *10 000/Births)									
Municipality	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**Average**
Cape Wine	4219 (2.37)	3870 (2.58)	10965 (0.91)	2772 (3.61)	5932 (1.69)	3247 (3.08)	2350 (4.26)	7414 (1.35)	4004 (2.50)
Central Karoo	Nil ARM	Nil ARM	1018 (9.98)	Nil ARM	Nil ARM	Nil ARM	Nil ARM	Nil ARM	9447 (1.06)
CPT	2821 (3.54)	2741 (3.65)	3675 (2.72)	4223 (2.37)	3597 (2.78)	3056 (3.27)	3213 (3.11)	5754 (1.74)	3463 (2.89)
Eden	2745 (3.64)	10923 (0.92)	3601 (2.78)	10686 (0.94)	Nil ARM	2622 (3.81)	5240 (1.91)	5168 (1.94)	5016 (1.99)
Overberg	4612 (2.17)	Nil ARM	Nil ARM	Nil ARM	1455 (6.87)	4377 (2.28)	Nil ARM	4383 (2.28)	5938 (1.68)
West Coast	3100 (3.23)	3013 (3.32)	2788 (3.59)	Nil ARM	5055 (1.98)	5711 (1.75)	1165 (8.85)	2956 (3.38)	3063 (3.26)
TOTAL	3057 (3.27)	3378 (2.96)	3985 (2.51)	4839 (2.07)	4090 (2.44)	3192 (3.13)	3048 (3.28)	5572 (1.79)	

Discussion

The prevalence of ARM for the referral area for the Paediatric Surgical Department of the University of Witwatersrand (South Africa) has been reported at 1:3 989 live births (2.5/10 000 live births) at the end of 2010 (7). Additionally, the authors reported an increased overall birth prevalence of ARM in this area between January 2005 and December 2010. ARMs are one of the most common gastrointestinal malformations of the intestinal tract worldwide, with extensive socio-economic ramifications to the patient, family and health-care systems particularly in third-world settings. An increased prevalence and the large regional differences in ARMs is thus significant in warranting epidemiological studies to elucidate predisposing and preventable factors, as well as in governance policies for strategies to manage these skill-intensive patients.

The populous of the inland Witwatersrand referral area contrasts sharply with that of the coastal Western Cape Province of South Africa. The differences are not merely geographical, but encompass different genetic and ethnical predominance which accompany distinct

cultural, religious and dietary practices. This population has heritage from Europe, Asia and Africa with differences between the admixtures of the various ancestries within subpopulations (9). The Cape Coloured population, for instance, is derived from minimally 5 parental origins, including Bantu, European, Indian, and Southeast Asian links, with very strong Khoisan contribution as determined by mitochondrial DNA (10).

As mentioned the WCP has six municipal districts namely 1) City of Cape Town Metropolitan 2) Cape Winelands 3) Central Karoo 4) Eden 5) Overberg and 6) West Coast Municipal District. The City of Cape Town Metropolitan District is situated in the southern peninsula of the Western Cape Province. It has a coastline of 294km. The City is South Africa's second-largest economic centre and second most populous city after Johannesburg. The Cape Winelands District has rural and small-town sub regions, but with a relatively high and diverse level of development. The mountain ranges provide ideal microclimates. The Central Karoo District is a semi-desert natural region with most of the population being Coloured living in the rural towns with large surrounding farms; where keeping livestock, especially sheep, is the main agricultural activity. The Eden District has a diverse natural resource base. The Overberg District has the second smallest population with the majority, as with the other municipal districts, being Coloured. The West Coast District lies along the Atlantic coast, extending approximately 350 kilometres from north to south, bordered by the Cederberg Mountains in the east. (11)

The current study aimed to determine the ARM prevalence and sub-type occurrence within the Western Cape Province. The referral centres comprised of two academic tertiary hospitals, namely RCWMCH and TCH which are affiliated to two different academic universities. Statistics from the private medical sector of the referral area were also included. Patients referred from different regions were excluded from data analysis. Results revealed that the prevalence of ARM in the Western Cape Provence was 1:5572 live births (1.79/10 000 live births) at the end of 2012. There was a male predominance of 1.6:1 of ARM, with the most common presentations identified as perineal fistulas in males and vestibular fistulas in females. There was no statistically significant increase in ARM prevalence over the 8-year study period. The large regional differences in the prevalence of ARM cannot yet be explained, but with ongoing epidemiological studies hopefully that data can be inferred for the WCP. The most common associated congenital abnormalities as expected involved the renal and cardiac systems.

Although data from this study is in keeping with various other studies on ARM prevalence globally (3, 4, 12) it differs from statistics published for the Witwatersrand district (7). The Witwatersrand referral district reported much higher birth prevalence rates of 1:3989(2.5 per 10 000 live births) for ARMs, with a noteworthy increase in birth prevalence of ARMs over a five year period (7). Extensive extrapolation from these data was limited mainly due to a poor hospital record keeping systems. These caveats were partially circumvented in the current study, as the RCWMCH and private sector hospitals have a modernised central computerised data base. The TCH's record keeping system is in process of becoming computerised, and thus for this study period admission and theatre registries were used. Despite the more advanced record keeping system, medical notes were not sufficiently comprehensive allowing 20% of the ARM type to remain unidentified. Additionally, ethnicity categories were not reliably completed with any comprehensive histories documented. This could have attributed to the absence of familial ARM and skewing the results, and an inability to identify ethnical predisposition. Other reasons for skewed results have been discuss in the Witwatersrand study and can also be inferred for this WCP study (7)

With 1530 persons/km^2 the City of Cape Town Municipality has 64% of the province's population and thus the highest population density (13). Therefore it is in keeping that the majority of the ARM cases were diagnosed in the City of Cape Town, with 145 cases presenting over the eight year period. The provincial average tends to mirror that of this municipality. The Western Cape metropolis has fairly good access to primary and secondary health care facilities, and has reliable and effective patient referral and transport infrastructure.

Ideally, the full-term newborn should be examined at least two to three times between birth and discharge. That being immediately after birth in the delivery room, in the nursery within 12 hours and at discharge from the hospital. Particular attention should be given to a thorough examination of the perineum. The patency of the anus must be ensured in every neonate even if meconium has been passed (14). The definition for delayed ARM diagnosis differs between studies, ranging from 24 hours to 48 hours of life (15). Eltayeb (2010) even suggested using three months of age as a delayed ARM diagnosis for females within the old classification of low lesions (15). In this study, a "delayed" diagnosis was defined as neonates who had been examined by a medical personal member and were subsequently allowed to feed, irrespective of post-partum timing. This study reported an incidence of 26% delayed ARM diagnosis,

which was in keeping with the 21% to 53% published in various internationally published studies (15-20).

As was reported by Turowski *et al.* the most commonly delayed diagnosed ARM lesion was the male perineal fistula and the vestibular fistula in females (17). We also found that patients with no other congenital abnormalities were more likely to have their diagnosis delayed (31% of patients with ARM).The contributing factors for delayed presentation include initial missed diagnosis by a medical practitioner, incorrect advice given to parents, inadequate treatment offered for symptoms, together with socio-demographic factors including maternal age younger than 30 and a lower educational level (15, 19).It was interesting to note the possible correlation of increased missed ARMs with the discontinuation of routine rectal temperature readings (16, 20).

The time frame for this study's defined delayed diagnosis may be considered very short but, with most delays in diagnosing ARM resulting in significant morbidity and mortality it is imperative that the diagnosis is made as early as possible. Having a delayed diagnosis results in prolonged inpatient care, impedes optimal surgical management with unnecessary surgical procedures such as the formation of a colostomy. Chronic constipation, mega rectum, failure to thrive and recurrent urinary tract infections have all been attributed to subsequent morbidities of a delayed ARM diagnosis (15). Mortality secondary to intestinal perforation and sepsis may be a more sinister consequence of a missed diagnosis (15, 16, 18). With the recent trend to repair certain ARMs within the neonatal period the need to make a prompt diagnosis becomes even more important. (21,22). Furthermore, evidence indicates that long-term functional results are better if the repair is performed as early as possible (23).

Conclusion

Research into ARMs is ongoing worldwide. There is still a current lack of data regarding the birth prevalence of ARM in South Africa. The current study reported a decreased prevalence of ARMs diagnosed in the Western Cape Province when compared to that in the Witwatersrand referral areas as reported in a previous publication. As these communities differ substantially in both heritance and lifestyle signatures, these data highlights the need for further studies to determine any epidemiological trends which may be utilized in the screening, detection, or the prevention of this condition, as well as health ministry resource distribution planning. Additionally, evidenced of a high number of late ARM diagnoses

emphasise the need and importance of a complete and proper newborn examination. Current neonatal screening and examination guidelines and/or enforcement appear to be insufficient to ensure prompt diagnosis of ARM.

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APPENDAGES

Appendage 1: Standards for diagnosis international classification (Krickenback Clasification)

Major clinical groups	Rare/regional variants
Perineal (cutaneous fistula)	Pouch colon
Rectourethral fistula	Rectal atresia/stenosis
Prostatic	
Bulbar	
Rectovesical fistula	Rectovaginal fistula
Vestibular fistula	H fistula
Cloaca	Others
No fistula	
Anal stenosis	

Appendage 2: Data Collection Form

Title: Birth Prevalence of Ano-rectal Malformations for the Western Cape, South Africa

Principle Investigator: Dr Andre Theron

1) Case number: …….…….
2) Initials of baby: ……
3) Hospital Number: ……
4) Date of birth (dd/mm/yyyy): …….
5) Birth weight (kg): …….
6) Hospital where referred from: ……...
7) Hospital where treated
    - **a.** Red Cross War Memorial Children's Hospital (1)
    - **b.** Tygerberg Children's Hospital (2)
    - **c.** Private (3)

8) Municipal district parents reside: ..……
    a. Cape Winelands District Municipality (1)
    b. Central Karoo District Municipality (2)
    c. City of Cape Town Metropolitan Municipality (3)
    d. Eden District Municipality (4)
    e. Overberg District Municipality (5)
    f. West Coast District Municipality (6)
9) Age of mother at birth of baby(years): ……..
10) Gestational age of mother (weeks): ……
11) Race as noted in file:
    a. Black: (1)
    b. White: (2)
    c. Asian: (3)
    d. Coloured: (4)
    e. Indian: (5)
    f. Other (6)
12) Gender of baby:
    a. Male: (1)
    b. Female: (2)

c. Ambiguous : (3)

13) Any congenital abnormalities of siblings:

a. Yes (1)

b. No (2)

14) Type of Anorectal malformation according to Krickenbeck Classification:

Major clinical groups	**Rare/regional variants**
Perineal (cutaneous fistula)	Pouch colon
Rectourethral fistula	Rectal atresia/stenosis
Prostatic	
Bulbar	
Rectovesical fistula	Rectovaginal fistula
Vestibular fistula	H fistula
Cloaca	Others
No fistula	
Anal stenosis	

15) Any other congenital malformations present:

a. Nil (0)

b. Vertebral (1)

c. Cardiac (2)

d. Oesophageal atresia (3)

e. Renal (4)

f. Limb deformities (5)

Appendage 3: University of Cape Town Ethics Approval Letter

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

12 September 2013

HREC REF: 500/2013

Dr A Theron
c/o Prof A Numanoglu
Paediatric Surgery
Red Cross War Memorial Children's Hospital

Dear Dr Theron

PROJECT TITLE: BIRTH PREVALENCE OF ANO-RECTAL MALFORMATIONS FOR THE WESTER CAPE SOUTH AFRICA

Thank you for your email to the Faculty of Health Sciences Human Research Ethics Committee dated 3rd September 2013.

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

Approval is granted for one year until the 30th September 2014

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

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

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

s.thomas

Appendage 4: University of Stellenbosch Ethics Approval Letter

UNIVERSITEIT·STELLENBOSCH·UNIVERSITY
jou kennisvennoot · your knowledge partner

Ethics Letter

11-Feb-2014

Ethics Reference #: X14/01/001
Clinical Trial Reference #:
Title: Birth Prevalence of Ano rectal malformations for the Western Cape, South Africa

Dear Dr Andre Theron,

We acknowledge receipt of documents pertaining to the above study and the approval letter from the University of Cape Town Human Research Ethics Committee(FHS), as well as the permission letter from the facility concerned for this project.

The approval of the University of Cape Town Human Research Ethics Committee is recognised by us for this particular project. Resubmission of this project to the Stellenbosch University Ethics Committee is not required.

Please note that research that will be conducted at any tertiary academic institution also requires approval from the relevant hospital manager.

If you have any queries or need further assistance, please contact the HREC Office 0219389156.

Sincerely,

REC Coordinator
Franklin Weber
Health Research Ethics Committee 1