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Anorectal malformations and the impact of HIV on surgical outcome

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Anorectal malformations and the impact of HIV on surgical outcome

By

Dr. Tarryn Gabler



A research report for submissible paper submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Master of Medicine in Paediatric Surgery

November 2018

DECLARATION

I, Tarryn Gabler, student number 0200311G, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine within the Department of Paediatric Surgery of the University of the Witwatersrand, Johannesburg.



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Tarryn Gabler

November 2018

DEDICATION

I dedicate this work to Marilyn Delyse Gabler, my mother, whose example in life taught me dedication and perseverance and in death taught me grace and forgiveness, and to Andrew Egbers, my husband, who supports me unconditionally.

AKNOWLEDGEMENTS

I would like to acknowledge the following persons, without whom, this report would not have been possible:

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2. My head of department: Prof J Loveland
3. Petra Gaylard and Giulia Brisaghelli
4. All the nursing staff and doctors in the department of Paediatric Surgery who assisted and supported this study and the collection of data.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

- Gabler T, Loveland J, Theron A, Westgarth-Taylor C. Anorectal malformations and the impact of HIV on surgical outcome. 4th Annual Pediatric Colorectal, Motility and Pelvic Reconstruction Conference. Nationwide Children's Hospital, Columbus, Ohio, 15 – 18 November 2017.
- Gabler T, Loveland J, Theron A, Westgarth-Taylor C. Anorectal malformations and the impact of HIV on surgical outcome. SAMJ 2018: 108(11); 947-52.

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ABSTRACT

Background: Anorectal malformations (ARMs) represent a significant surgical load in South African pediatric surgical centers. Surgical treatment of ARMs may be associated with postoperative complications owing to the nature of surgical procedures necessary in the neonatal and infantile period. Human Immunodeficiency Virus (HIV), and its effect on the immune response compound postoperative surgical complications. The impact of HIV exposure and its effect on the child's immune status, independent of the child's HIV status, has yet to be studied in the surgical population.

Objectives: To assess the incidence of complications in our population of ARM patients and to explore whether these complications are increased in HIV exposed but serologically negative children compared to HIV not exposed children.

Methods: This was a prospective study of all patients presenting with ARMs to the paediatric surgery units attached to the University of the Witwatersrand. Specifically, exposure to an HIV positive mother, patient's HIV status, and presence of surgical complications were documented. This data was analysed for the period between August 2016 and September 2017.

Results: A total of 50 participants were included, and none excluded. Nineteen participants (38%) were HIV exposed and none were HIV positive. Twenty-eight (56%) were male and 22 (44%) were females. Seventy-six operative procedures were performed with 27 operative complications. In the HIV exposed group 68% of participants experienced operative complications compared to 45% in the not exposed group (P = 0.1). In participants who had stoma formation 50% of the HIV exposed participants complicated, compared to 20% in the non-exposed group (p = 0.08).

Conclusion: The incidence of postoperative infectious complications in HIV exposed patients is higher compared to HIV non-exposed patients. The

incidence of postoperative complications in HIV non-exposed patients parallels that in the international literature, except in the posterior sagittal anorectoplasty groups. It remains critical to follow stringent perioperative protocols for infection prevention and aggressively treat any infection that arises, particularly in patients born to HIV positive mothers regardless of the patient's HIV status.

INTRODUCTION

Anorectal malformations (ARMs) represent a large clinical and surgical load, especially in low and middle income countries (LMIC).[1] Human Immunodeficiency Virus (HIV) adds to this burden by increasing infectious surgical complications and medical morbidity.[2] ARM's are a spectrum of congenital anomalies leading to an imperforate anus with or without a fistula that opens into the male urinary tract, the female genital tract or onto the perineum. The aetiology is multifactorial. The incidence of ARM's in the referral area for the University of the Witwatersrand is 1:4000.[3] Typically, management of ARMs consists of three operations, these include an initial diverting colostomy, definitive repair by means of a posterior sagittal anorectoplasty (PSARP), and finally colostomy reversal. This traditional approach is especially applicable in LMICs where patients often present late, with established obstruction of the gastrointestinal tract, systemic sepsis and dehydration. [4-7] Some lesions are amenable to a primary PSARP without the formation of a colostomy, this if the anatomical defect is favorable, the child is clinically stable, has no associated life-threatening congenital anomalies, and there is absence of gross abdominal distension.[8] In the paediatric population, intra-abdominal surgery is associated with a 20% surgical site infection rate and an 11% anastomotic leak rate.[9] In terms of stoma formation and closure, this equates to a high morbidity and as Oda stated in 2013, 'creating a colostomy is a minor surgical procedure but with potentially significant morbidity'.[10]

The Republic of South Africa (RSA) is a country heavily burdened by HIV. In 2014, 6.8 million people were living with HIV, of which 3.9 million were females over the age of fifteen, and 340,000 were children.[11] Much of the burden of HIV infected children comes from mother-to-child transmission (MTCT) of the virus. The prevention of MTCT program improved rollout of antiretroviral (ARV) medicines to more than 90% of HIV infected pregnant females.[12] This effective use of ARVs in RSA has decreased MTCT of HIV to 2% in 2015.[12] However, in 2011, Venkatesh et al proved that infants born to HIV infected mothers had a two-fold greater risk of hospitalisation and a six-

fold greater risk of mortality independent of infant HIV status. This illustrated the impact of maternal immunodeficiency on childhood morbidity and mortality regardless of the child's HIV status.[13]

It is known that children undergoing major surgical procedures are at higher risk of surgical complications when compared to their adult counterparts.[9] It is also known that HIV infected children have a higher rate of post-surgical complications compared to HIV not exposed children[2]. The objectives of this study were to assess the incidence of complications in our own practice and to explore if these complications are increased in HIV exposed but serologically negative children compared to HIV not exposed children.

METHODS

After approval from The Human Research Ethics Committee, University of the Witwatersrand (M160.513), data were prospectively collected from patients presenting to either of the two paediatric surgery units linked to the University of the Witwatersrand, these being Charlotte Maxeke Johannesburg Academic (CMJAH) and Chris Hani Baragwanath Academic (CHBAH) Hospitals, in Johannesburg, South Africa. All patients under the age of six years, with ARM's requiring a surgical intervention were included. This was a prospective cross sectional descriptive study, and data collection occurred over thirteen months between 01 August 2016 and 30 September 2017. Data collected included mother's age and HIV test results, child's HIV test results (if HIV exposed), type of ARM, presence of associated anomalies, type of surgical intervention, peri-operative antibiotic use and presence and type of surgical complication if any.

The Chi-squared test was used to assess the relationships between categorical variables and HIV exposure group. Fisher's exact test was used where the requirements for the Chi-squared test could not be met. One-way Analysis of Variance (ANOVA) assessed the relationship between continuous variables and HIV exposure group. Where the data did not meet the assumptions of this test, a non-parametric Kruskal-Wallis test was used. Data

analysis was carried out using SAS (version 9.4 for Windows). A 5% significance level was used.

RESULTS

Entire cohort

Data was collected prospectively from 50 mother-child dyads. The majority (84%) of the children were referred in to our units from surrounding hospitals. Thirty-two of the children (64%) were operated on at CHBAH where there is a dedicated colorectal unit. None of the children in this cohort were antenatally diagnosed. (Fig. 1).

Mothers

The mean age of mothers in the cohort was 28 years old. Nineteen (38%) were HIV positive. All the mothers were diagnosed antenatally as HIV positive and were on antiretrovirals (ARVs) for an average of 30 months prior to delivery. As such, the median CD4 count was 537 cells/mm^3 (range: 363 – 730 cells/mm^3) and the median viral load (VL) was 147 IU/ml (range: 0 – 1075 IU/ml with a high of 14500 IU/ml).

Children

The median birth weight was 2970g (range: 2700g – 3300g). Median gestational age was 40 weeks (range: 37 – 40 weeks). Thirty-eight-percent of the children were HIV exposed, but notably there have been no seroconversions to date. All of the exposed children received post exposure prophylaxis for a minimum of six weeks after birth.

In total, 28 of the 50 child participants (56%) had at least one associated anomaly (Fig. 2). Ten participants (19.6%) had three or more systemic anomalies and, therefore, the VACTERL association (Vertebral anomaly, Anorectal malformation, Cardiac anomaly, Trachea-oesophageal fistula and oEsophageal atresia, Renal anomalies and Limb anomalies). One participant had a chromosomal anomaly (trisomy 21). The types of malformation encountered are represented in Fig. 3.

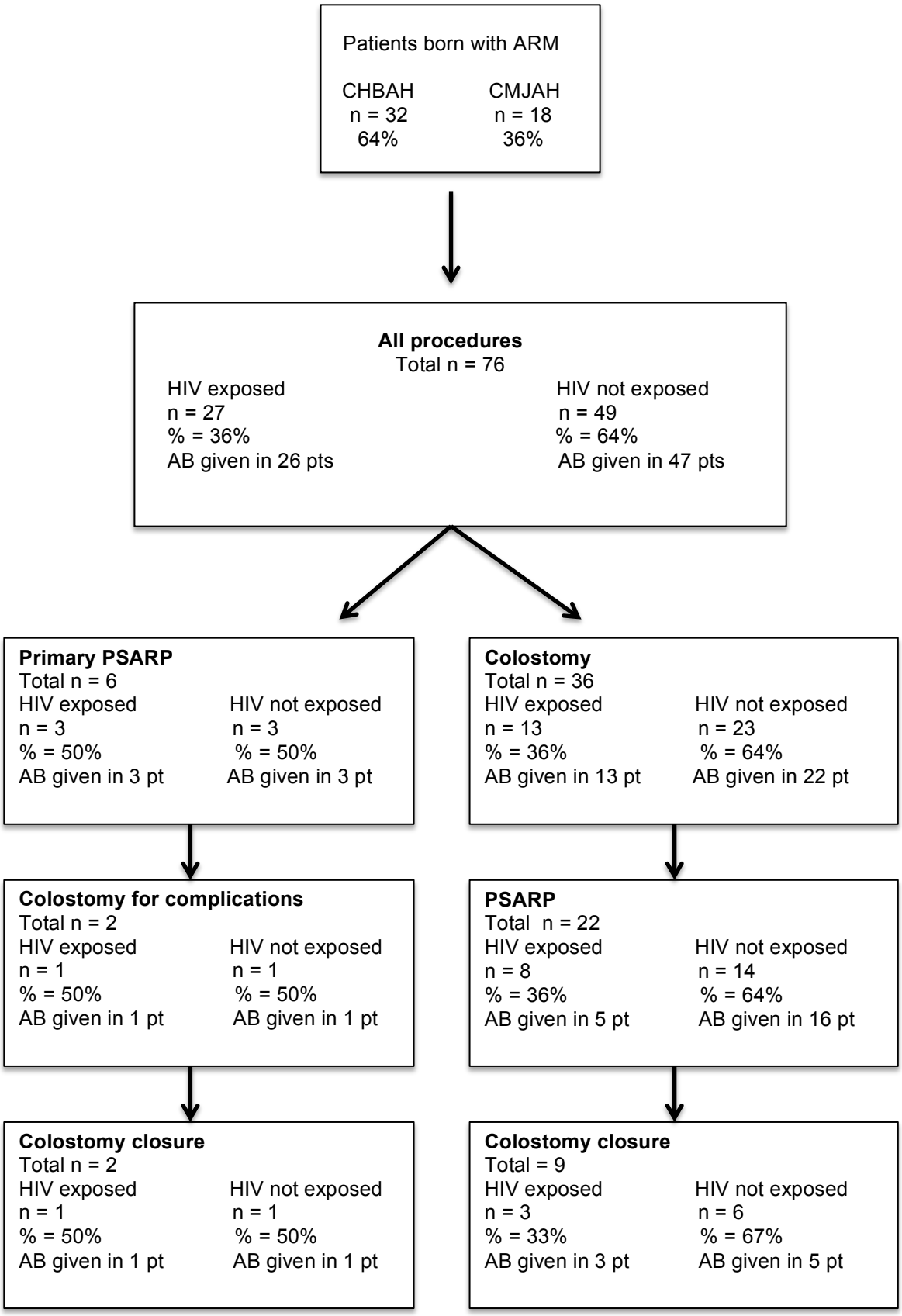


Figure 1. Flow diagram of results AB = antibiotics, pt = patients

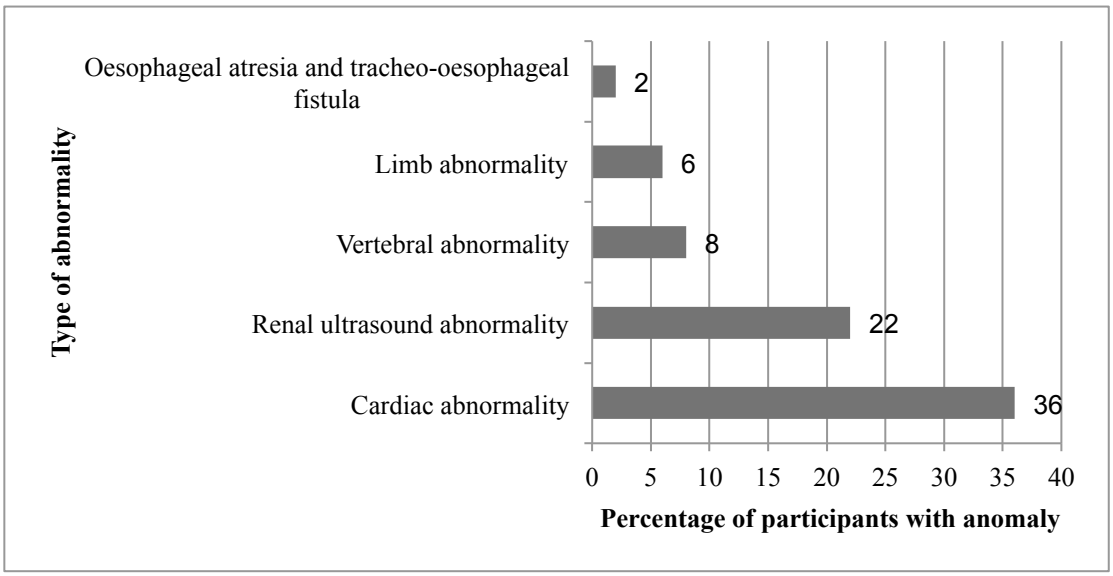


Figure 2. Types of associated abnormalities within the VACTERL association

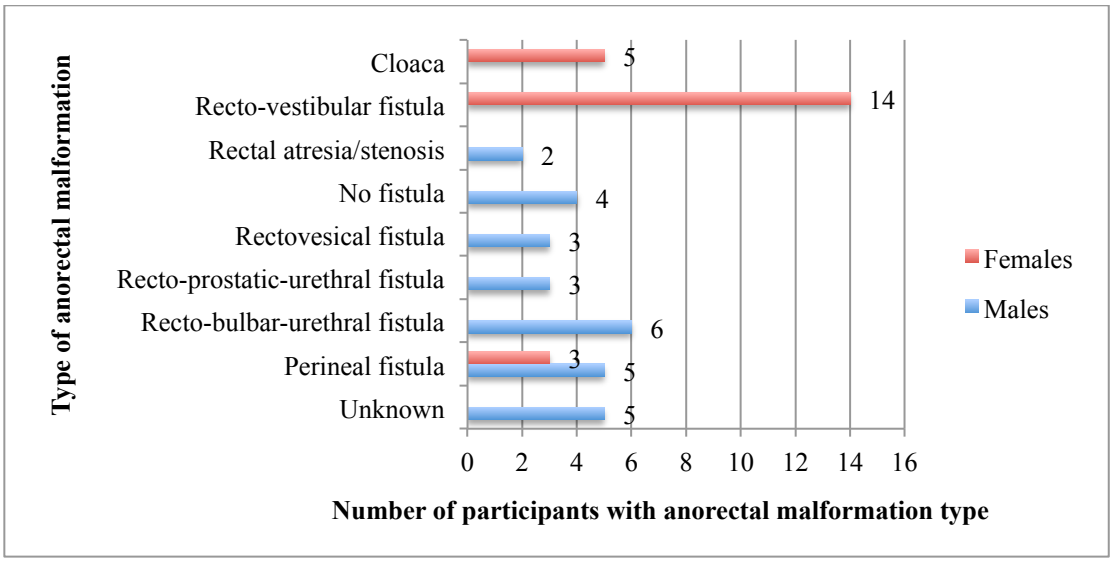


Figure 3. Distribution of anorectal malformation types

Management and complications

CHBAH performed 46 surgical procedures on 32 patients with 15 complications. CMJAH performed 31 surgical procedures on 18 patients with 15 complications.

Thirty-eight stomas were performed with twelve complications in twelve participants resulting in a 32% complication rate (Fig. 4). Seven of the

fourteen participants who were HIV exposed complicated (50%), whereas only five of the twenty-four participants who were HIV not exposed complicated (20%) (p = 0.081) (Fig. 5). Perioperative antibiotic use was erratic across all surgical interventions and was surgeon specific rather than protocol driven (Fig. 6)

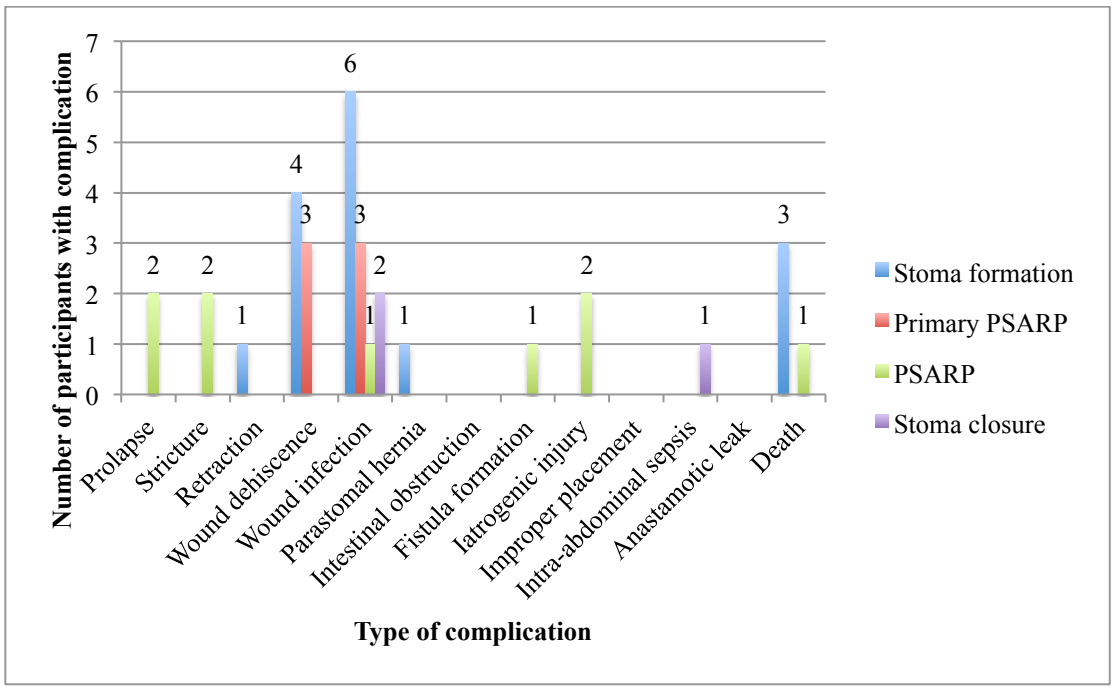


Figure 4. Distribution of complications across cohort

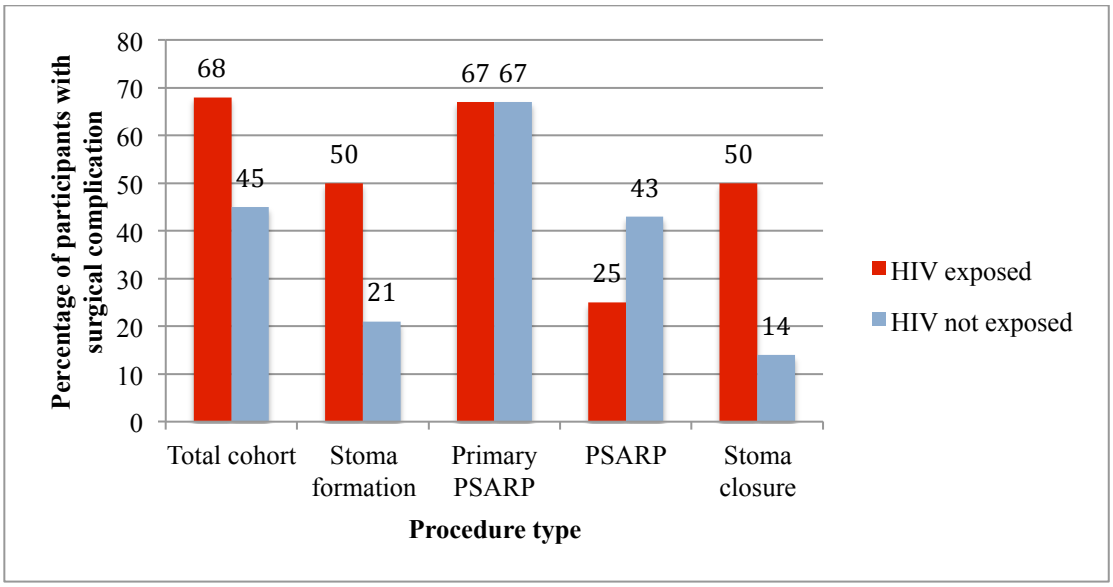


Figure 5. Percentage of complications across HIV exposed and not exposed groups

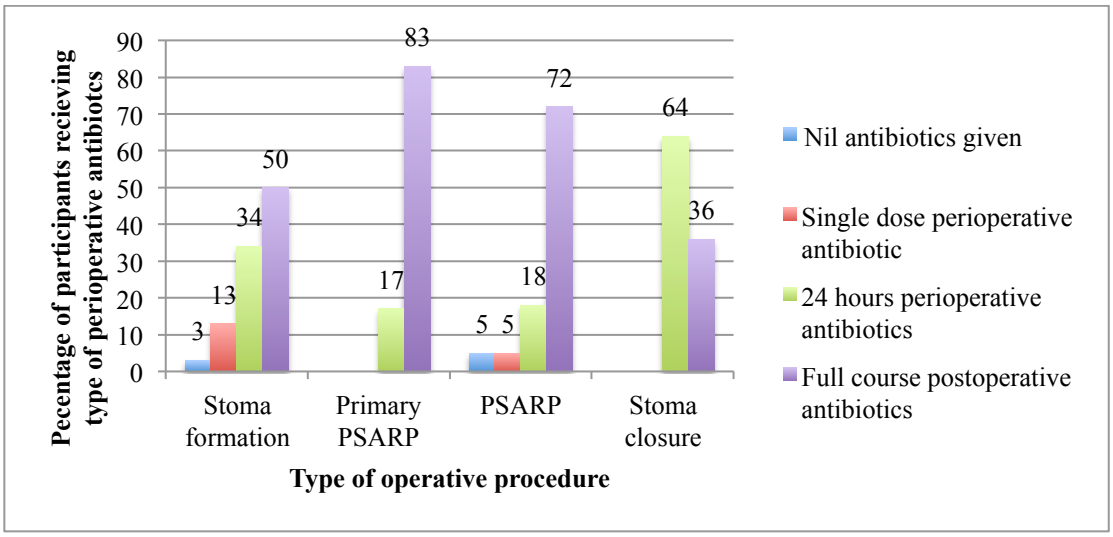


Figure 6. Percentage of participants receiving perioperative antibiotics across cohort

Six primary PSARPs were performed. There were six complications in four participants (Fig. 4). The total incidence of complications in this group was 66%. Out of the three participants who were HIV exposed, in this group, two (67%) complicated and two (67%) of the three participants who where HIV not

exposed complicated (p = 0.99) (Fig. 5). The majority of participants received a full course of antibiotic therapy (Fig. 6)

Twenty-two PSARPs were performed. There were nine complications in eight participants (Fig. 4). The total incidence of complications in this group was 36%. Out of the eight patients who were HIV exposed, two (25%) complicated and six (43%) of the fourteen patients who were HIV not exposed complicated (p = 0.66) (Fig. 5). The majority of participants received a full course of antibiotic therapy. (Fig. 6)

Eleven stoma closures were performed. There were three complications (Fig. 4). The total incidence of complications in this group was 27%. Out of the four participants who were HIV exposed in this group, two (50%) complicated and one (14%) of the seven participants who were HIV non-exposed complicated (p = 0.49) (Fig. 5). Most participants in this group received 24 hours of perioperative antibiotics. (Fig. 6)

Four deaths occurred in this cohort. Three occurred after stoma formation and one after PSARP. One death occurred within 48 hours of surgery. In this case, an ARM with a rectovestibular fistula was only referred for management on day sixteen of life. On arrival, the abdomen was markedly distended, with established peritonitis. At laparotomy it was noted that the entire small and large bowel was necrotic, secondary to abdominal compartment syndrome. The child was palliated. The other three deaths occurred in hospital but were unrelated to the initial surgery. Two patients demised due to overwhelming sepsis, one secondary to meningitis and the other to aspiration pneumonia. The fourth patient died due to complications related to perforation of the distal rectal segment during an augmented pressure distal colostogram. Of the four deaths, two (50%) occurred in HIV exposed infants and two (50%) occurred in HIV non-exposed infants.

DISCUSSION

We have gained significant insights into our own practice as a result of the outcomes of this 1-year collection of data. As expected, the vast majority of patients are referred into our institutions from surrounding referral hospitals (a large area is drained by only two centres that offer paediatric surgical services). None of the patients were antenatally diagnosed. This is very common as ARMs are difficult to detect with antenatal screening. Additionally, RSA practices Basic Antenatal Care (BANC) where ultrasound imaging in pregnancy, and referral to higher level antenatal care centres, is reserved for those patients with suspected multiple pregnancies or suspected congenital anomalies on clinical evaluation of the gravid uterus.[14] The delay in diagnosis and referral can have devastating consequences as noted in one of our patients, in whom the entire bowel was necrotic, as a result of untreated abdominal compartment syndrome from a missed anorectal malformation that was only diagnosed on day sixteen of life. This highlights one of the many areas for improvement in the South African setting, not just related to the treatment of anorectal malformations but the diagnosis, referral and treatment of all paediatric surgical patients in the country. Of note, when assessing the types of ARMs presenting to our institutions, we found that there was a very low incidence of perineal fistulas in females when compared to international literature [5] ($p = 0.006$). We propose that this is not because we actually see fewer cases of perineal fistula in our referral area but that the majority of this anatomical variant of ARM are being missed on examination and are therefore not referred for treatment at all, or only when much older when these girls present with constipation or overflow incontinence.

In 2013 the prevalence of HIV among women presenting to antenatal clinics was 28.6%, compared to 29.8% in 2009[15]. In our cohort, the prevalence of HIV infected mothers, and therefore HIV exposed children, was 38%. This is 10% higher than the previously documented prevalence in our province, and although not statistically significant ($p = 0.14$), the prevalence is still substantially higher than in the general population. HIV positive mothers were significantly older than mothers in the HIV negative group ($p = 0.026$, 30.7

years vs 26.6 years). This may be because the decreasing prevalence of HIV is occurring in the younger population, secondary to the improved rollout of ARVs or that this younger population has had fewer opportunities to contract the virus compared to their older counterparts. Another positive finding was that all mothers who were HIV positive at the time of delivery had their HIV diagnosed antenatally and all had been on ARVs for an average of 30 months prior to delivery. The result of this treatment is that the median VL of our mothers (147 IU/ml) was lower than that quoted by Venkatesh et al (> 100 000 IU/ml) which was shown to increase the risk of hospitalization and mortality in HIV exposed infants independent of their HIV status.[13]

At the time of this publication, none of the HIV exposed children in this cohort had seroconverted. This should be considered with caution as children require a polymerase chain reaction (PCR) test for HIV at birth, ten weeks and eighteen weeks of age, as well as an HIV enzyme linked immunosorbent assay (ELISA) test at eighteen months of age in order to be confirmed HIV negative post antenatal HIV exposure.[16] Many of patients in the above cohort are less than eighteen months and have, therefore, not completed all of these tests. There were no significant differences in birth weight or gestational age between those participants that were HIV exposed and those that were HIV not exposed ($p = 0.7$ and $p = 0.28$ respectively).

Complication rates in the colostomy formation and colostomy closure groups were predominantly sepsis related (superficial wound sepsis and dehiscence of the entire wound secondary to sepsis). These rates are high (32% and 27% respectively) when compared to international literature (20% surgical site infections (SSI)).[9] However, it is important to consider the complication rates in those patients who are HIV exposed compared to those who are not. In both the stoma formation and stoma closure groups, 50% of the patients in each group who are HIV exposed experienced postoperative complications compared to only 20% and 14% respectively in the groups of patients who are HIV not exposed. The complication rates in the HIV not exposed patients are similar to and lower than the international literature.[9] Although not statistically significant, because of small numbers, there tends to be far more infection-

related postoperative complications in children who are HIV exposed compared to those who are HIV not exposed (entire cohort: p = 0.11, stoma formation group: p = 0.081). Collection of higher numbers of participants may confirm this. We believe that this increased propensity to infection related complication in the HIV exposed group may be secondary to inherent immune compromise in all HIV exposed patients regardless of whether they seroconvert or not.

Although it is difficult to infer any significance from only six patients in the primary PSARP group, there was a 66% complication rate. All complications were sepsis related namely wound sepsis and wound dehiscence secondary to sepsis (with two patients requiring subsequent stoma formation). This is exceptionally high even when compared to other countries including LMICs, for example Nigeria where a complication rate of 30% was found in their cohort of primary PSARPs.[17] Although this number of patients is small it has changed our approach to performing primary PSARPs and our institution is now far more judicious with the use of colostomies in all patients regardless of the type of malformation, particularly in delayed presentations. Why the rate of complication is so high in this particular group is unknown and does not follow any trend towards HIV exposure in this small number of patients. This is an area for further research in our department to help elucidate the reasons for this trend and hopefully lead to improvement strategies to decrease the complication rate in this subset of patients.

The complication rate in the PSARP group was 38%, however the complications in this group are predominantly technical and not infectious in nature (strictures, prolapse, fistula formation, vaginal injury and post PSARP rectal necrosis). Therefore, these complications showed no predilection for the HIV exposed group as the complications were surgeon dependent rather than patient dependent. Further collection of data will clarify whether complications thought to be technical in nature (stricture and fistula formation) are increased in the HIV exposed group due to differences in wound healing when compared to HIV not exposed patients. One reason for technical complications in this group is related to the number of surgeons of different

experience levels operating on this cohort of patients, some of whom are still on the upward slope of the learning curve related to these procedures.

If one considers all complications relative to the location of the procedure at CHBAH (with its dedicated colorectal unit) and CMJAH (a general surgical unit) separately, it becomes clear that centralization of services may, indeed, be the way to improve outcomes on a broader scale. The incidence of complications in the colorectal unit was 32% compared to 48% in the general surgical unit. This proves fewer complications from the colorectal unit, although this is not statistically significant due to small numbers ($p = 0.23$). This difference cannot be accounted for on the basis of HIV exposure and, in fact, there is a higher incidence of HIV exposure (44%) at the colorectal unit when compared to the general surgical unit (33%). As such, the relative risk for developing a complication from a colorectal procedure in the general surgical unit compared to the colorectal unit is 1.5.

There was no significant association between the presence or absence of complications and associated malformations and the VACTERL association ($p = 0.37$).

We did note that choice of antibiotic prophylaxis across all surgeries was not standardized with different surgeons using different antibiotic protocols and this may have implications related to further investigation of septic complications in HIV exposed patients. Where numbers permitted, for example in the stoma formation group, there was no statistical difference between the type of antibiotic prophylaxis and the septic complication rate between the HIV exposed and not exposed groups ($p = 0.22$).

The major limitation of this study is the small number of enrolled participants, although data collection is on going and we hope to report statistically significant results in the next few years. In order to get statistically significant results, 140 patients would need to be enrolled into this study but this was unfortunately limited by the time of the study duration. This small sample size makes it difficult to calculate any statistically significant results but it remains

significant as a snap-shot into our population as a hospital sample. There was also great difficulty in contacting enrolled participants after discharge to follow them up appropriately. Apart from the limitations already mentioned, there are two aspects that must also be drawn to attention. The first is that children with trisomy chromosomes will generally complicate more than other children and therefore, their inclusion in this study may skew the results. The second is that some of the complications noted were due to iatrogenic injury. This also skews the results as these complications were independent of the HIV status of the child. Another limitation is that the follow-up period for these patients was confined to the study period and therefore, we may have some patients who complicated later that have not been added to the cohort. The number of confounding factors including the nutritional status of the child, delay in presentations and the non-protocolised nature of antibiotic practices may also skew the data.

The data suggests an increase in infection related complications in HIV exposed patients when compared to HIV not exposed patients. As such, we need to better define antibiotic protocols to ensure that we are working to prevent sepsis related complications in all patients but especially in those who are HIV exposed. We also need to better elucidate nutritional status in those patients coming for elective procedures (PSARP and colostomy closure) as this may also help improve outcomes although it is normal practice in the author's institutions not to operate on any child for an elective procedure unless they are nutritionally replete.

Further research needs to done on this subject. Once patient numbers permit better statistical analysis, interventions such as antibiotic protocols and nutritional analysis and support may be instituted to see if this helps improve our outcomes. In the interim, we need to carefully evaluate all patients who are HIV exposed and optimize management as far as possible pre-operatively to assist in preventing postoperative septic complications.

CONCLUSIONS

Anorectal malformations are not uncommon in South Africa and present a significant surgical load. HIV is also very common and, although antiretroviral rollout is adequate, there is still a higher rate of HIV infection among the mothers of children presenting with ARMs. Our prevalence of postoperative complications in HIV not exposed patients parallel those in the international literature (except for PSARPs) compared with much higher complications seen in the HIV exposed group that are primarily infection related. HIV exposure tends to increase the rate of postoperative infectious complications even when the exposed child has tested HIV negative. Therefore, children who are HIV exposed need to be optimized prior to operation as much as possible with every attempt made to decrease the risk of postoperative infection related complication. Further research is needed in this area to adequately quantify the burden of HIV exposure on paediatric surgical units across RSA.

Conflicts of interest: None

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APPENDIX A – Approved protocol

Anorectal malformations and the impact of HIV on surgical outcome

For the purpose of submission for the degree of MMed

Masters Candidate: Dr Tarryn Gabler 0200311G

Supervisors: Dr Christopher Westgarth-Taylor BSc(UCT), BSc Med Hons(UCT), MBChB(US), MRCS(England) FC Paed Surg(SA)(UCT)

Dr Andre Theron MBChB (Stell)FC Paed Surg (SA)

Abstract

Anorectal malformations (ARM's) are a spectrum of congenital anomalies of the hindgut representing a significant surgical load in tertiary paediatric surgical centres in South Africa. Surgical treatment of ARM's are often associated with postoperative complications because of the nature of major, emergency surgical procedures that are necessary to perform in the neonatal period. Postoperative surgical complications are compounded by the burden of Human Immunodeficiency Virus (HIV) in the South African setting. Demographic, clinical, surgical and management data would be collected in a prospective manner from all patients presenting to a university tertiary hospital with an ARM from 1 August 2016 – 31 January 2019. Data would be recorded in Redcap and anonymised data would be extracted and reported in tables and graphs with appropriate parametric or non-parametric tests to determine differences between complication rates in patients who are not exposed to HIV, who are HIV exposed but serologically negative and who are HIV infected. We would seek to prove that HIV exposure alone, without HIV infection increases the rate of postoperative complications in this subgroup of patients.

Literature Review

Anorectal malformations (ARM's) are a spectrum of congenital anomalies leading to an imperforate anus with or without a fistula that opens into the male urinary tract, the female genital tract or onto the perineum. The aeitiology is multifactorial and there is a low association rate in families,

although some syndromes exhibit an autosomal dominant inheritance pattern.[1] Embryologically, ARM's occur because of a deficient cloacal membrane that propagates abnormal junction between the proximal hind-gut and the fetal cloaca.[2] Because of the wide variety of possible fistula connections, an anatomical classification known as the Krickenbeck classification is used to describe the type of ARM.[1,3] (Table 1)

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

Table 1: Standards for diagnosis international classification (Krickenbeck) [3]

Wide geographical variation exists in the individual phenotypes and overall incidence of ARM's, so much so that there is even regional geographical subtype predominance.[4] The literature suggests that the incidence of ARM lies somewhere between 1:2000 to 1:5000 live births with a male predominance.[1,5] Although a low incidence of ARM's in the African population was postulated[6], a study done in South Africa (in the referral area for the University of the Witwatersrand) in 2010, showed an incidence of 1:4000.[7]

Approximately 50% of children with ARM's have associated anomalies (usually genitourinary, cardiovascular, neurological and gastro-intestinal).[5,6] A specific association of these anomalies exists, known as the VACTERL (Vertebral abnormalities, Anorectal malformation, Cardiac Abnormalities, Tracheo-oesophageal fistula, Esophageal atresia, Renal abnormalities, Limb abnormalities) association.[5,6] A child is said to have a VACTERL association if

3 or more of the VACTERL abnormalities are present. In Africa, 38-63% of patients with ARM will have an associated congenital anomaly.[4,5]

Typical management of an ARM consists of 3 operations (colostomy formation, posterior sagittal anorectoplasty (PSARP) and colostomy reversal). Some lesions are amenable to primary PSARP (without the formation of a colostomy) if the anatomical defect is favorable, the child is clinically stable, has no life-threatening associated congenital anomaly and there is absence of gross abdominal distension.[8] ARM's represent up to 67% of neonatal emergency surgical procedures[9] especially in developing countries, as children often present late, associated with abdominal distension, sepsis and dehydration.[1,5,10,11] As such, the majority of patients will require a minimum of 3 surgical procedures in the treatment of their ARM, which presents a significant clinical and surgical load.[4]

The vast majority of children presenting with ARM will undergo some surgical procedure (colostomy or primary PSARP) soon after presentation in the neonatal period. It is prudent to note that children under 1 year of age who undergo surgery already have a higher incidence of complications, and that these complications increase in number if the operation is major (e.g. entering into the abdominal cavity) or emergency in nature.[12] In 2009, Mattioli et al, reported 20% surgical site infection and 10% anastomotic leak rates in paediatric patients undergoing intra-abdominal surgery.[13] This contributes to a high morbidity if one considers this data for colostomy formation (an intra-abdominal procedure) and reversal (creation of an anastomosis). Therefore, as Oda stated in his 2013 paper which dealt with colostomy creation in neonates, "creating a stoma is a minor surgical procedure but with a potentially significant morbidity".[14]

The above should be considered in the context of HIV. South Africa (SA) is a country heavily burdened by HIV. In 2014, UNAIDS statistics reported 6.8 million people living with HIV in South Africa. 3.9 million of these people were females over the age of 15 and 340,000 children are living with the virus.[15] Much of the burden HIV infected children comes from mother-to-child

transmission of the HIV virus. In 2002, the prevention of mother-to-child transmission (PMTCT) programme began in earnest in South Africa (SA).[16] Since then, SA has improved roll-out of antiretroviral medicines to pregnant women so much so that in 2015 SA attained the Global Plan goal to provide antiretroviral drugs to more than 90% of HIV infected pregnant females.[17] This effective use of antiretrovirals in SA has decreased mother-to-child transmission of HIV to 2% in 2015.[17] However, Venkatesh et al, in 2011, proved, most notably, that infants born to HIV infected mothers with a plasma viral load of >100 000 copies/ml were at a 2 fold greater risk of hospitalisation and a 6 fold greater risk of mortality independent of infant HIV status. This illustrated the impact of maternal immunodeficiency on childhood morbidity and mortality regardless of the child's HIV status.[18]

It is known that neonates undergoing major emergency surgical procedures are at higher risk of surgical complications.[13] It is also known that HIV infected children have a higher rate of post-surgical complications.[12] With this study, we aim to quantify the number of post surgical complications in our context and to see if there is a relationship with HIV exposed but serologically negative children and increased complication rates.

Objective

To document and ascertain the incidence of postoperative complications related to surgical treatment of ARM (including colostomy, PSARP and colostomy reversal) at our university tertiary centres and to compare the incidence of these postoperative surgical complications in patients who are HIV positive, HIV negative and those who are HIV exposed but serologically negative.

Methods

This would be a prospective collection of data of all patients, under the age of 6 years old, with ARM presenting to any of the tertiary hospitals with paediatric surgery capabilities linked to the University of the Witwatersrand namely Chris Hani Baragwanath Academic Hospital (CHBAH), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and the Nelson Mandela

Children's Hospital (NMCH) once it opens. All patients would be anonymous and information would be recorded by assigning each patient to a study number. The final data would be the anonymised data.

Requirements for inclusion:

1. Referral to one of the University of the Witwatersrand tertiary hospitals for treatment of an anorectal malformation.
2. The mother of the child must give informed consent for the use of her, and her child's anonymous information in the study.
3. The child must have a recorded HIV test result.

Information for collection:

1. Required information from the mother: Contact number, address, place of delivery, hospital number, name, surname, age, race, antenatal care (ANC) booking, HIV status, CD4 count, viral load, antiretroviral (ARV) regimen, length of time on ARV's and feeding practice.
2. Required information from the child: hospital number, name, surname, Date of Birth (DOB), weight, gestational age, race, HIV exposure, PCR/ELISA result, ARV prophylaxis, VACTERL workup, ARM type, complication type and management of complication.

All data would be recorded using the Red Cap Database. The main outcome of all recorded data would be the number of postoperative complications with respect to HIV exposure and infection. We hope to collect data over 3 years from approximately 50 patients for the purposes of this Mmed.

Statistical evaluation

A sample size of 140 patients has been estimated for adequate analysis and detection of a medium effect. This should be an easily attainable number within the set time frame, however, to account for delays in data capturing and writing of exams, a minimum of 50 patients will be collected for purposes of the Mmed itself, as discussed in the protocol submission meeting on 07/09/2016.

Descriptive analysis of the data will be carried out with categorical variables summarised by frequency and percentage tabulation, and illustrated by means of bar charts. Continuous variables will be summarised by the mean, standard deviation, median and interquartile range, and their distribution illustrated by means of histograms.

The incidence of the different types of post-operative complications in the study group will be estimated with 95% confidence intervals.

A X^2 test will be used to assess relationships between categorical variables (e.g. the presence/absence of a particular post-operative complication) and the HIV group. In the event that the requirements for a X^2 test cannot be met, a Fisher's exact test will be used for 2 x 2 tables.

The relationship between continuous variables (e.g. gestational age) and HIV group (and between the VACTERL score and each post-operative complication) will be assessed by one-way Analysis of Variance (ANOVA). Where the data do not meet the assumptions of this tests, a non-parametric Kruskal-Wallis test will be used.

Data analysis will be carried out in SAS v9.4, and a 5% significance level will be used.

Benefits

No audit of this kind has ever been carried out in our unit and this information will help us to compare our postoperative outcomes to those in developed countries. It will also help us review our own practice to see if there are areas in which we can improve our care.

If the hypothesis that HIV exposure also increases postoperative complication rates is correct, it will help to better stratify our patients pre-operatively and will help us better educate our patients families, giving them a realistic expectation of the operation and its outcome. It will also help to identify those

patients who will need meticulous pre, intra and postoperative monitoring and care to ensure lowering the rate of complications.

The creation of the database for this study will continue to be used in our department allowing better tracking of our patients, maintaining follow ups and, in the future, allow us to look at the long-term outcomes of our patients, so the basis of this study also has long-term benefits.

The intention of this study is also to serve as my MMed through publication.

Costs

The primary author and colleagues will do all of the data collection. All laboratory and radiological tests necessary through out the study are standard tests and investigations that will be done on all presenting patients whether or not they agree to partake in the study so no further costs to person or government are foreseen.

Ethics

Ethics clearance has been attained from HREC. Ethics number: M160.513.

Possible limitations

The low incidence of ARM's in South Africa may lead to few numbers of patients that will not allow proper statistical evaluation over the short period of 2 and a half years.

Timeline

Process	May 2016	June 2016	August 2016 – January 2019	Feb 2019	Feb - March 2019	March 2019
Protocol Submission	X					
Protocol Assessment	X	X				
Ethics Application		X				
Collecting Data			X			
Data Analysis				X		
Writing Report					X	
Report Submission						X
Writing Paper						X

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APPENDIX B – Data collection sheet

Anorectal malformations and the impact of HIV on surgical outcome

Record ID: _____ (For investigative office use only)

Mothers details:

1. **Did mom deliver at CHBAH / CMJAH?** YES / NO
2. **What was mom's age (in years) at delivery: _____**
3. **Mom's race:** BLACK / WHITE / INDIAN / COLOURED / OTHER
4. **Was mom booked at an antenatal clinic?** YES / NO
5. **What is mom's HIV status?** POSITIVE / NEGATIVE / UNKNOWN
6. **If Mom is HIV positive…**
   - 6.1. **What was mom's most recent CD4 count? _____**
   - 6.2. **What was mom's most recent viral load? _____**
   - 6.3. **Was mom on ARV's?** YES / NO
   - 6.4. **If yes, what ARV's was mom on? _____**

     _____

     _____
   - 6.5. **How long (in months) has mom been on ARV's?_____**
7. **Is mom planning on breast-feeding or, for older children, did mom breastfeed?** YES / NO

Patient details and birth history:

1. **Birth weight in grams: _____**
2. **Gestational age at birth (in weeks): _____**
3. **Patient's race**: BLACK / WHITE / INDIAN / COLOURED / OTHER

4. **Is the child HIV exposed?** YES / NO

5. If Yes...

5.1. **Please check that a PCR was done. What was the PCR result?**

POSITIVE / NEGATIVE / UNKNOWN

5.2. **If an ELISA was done, what was the ELISA result?** POSITIVE / NEGATIVE / UNKNOWN

5.3. What postnatal prophylaxis was given? (Tick one)

None	
AZT IVI (Complete 6 week course)	
NVP PO (Complete 6 week course)	
AZT / NVP combination (Complete 6 week course)	
Incomplete course of either drug	

6. From the above info, which group does this patient fit into? (Tick one)

HIV not exposed	
HIV exposed BUT HIV negative	
HIV exposed AND HIV positive	

<u>VACTERL work up:</u>

1. **Does / did the patient have an oesophageal atresia?** YES / NO
2. **Does / did he patient have a tracheo-oesophageal fistula?** YES / NO

3. **ECHO findings:** (Tick all that apply)

Normal	
Patent foramen ovale (PFO)	
Patent ductus arteriosus (PDA)	
Atrial septal defect (ASD)	
Ventricular septal defect (VSD)	
Tetralogy of Fallot (TOF)	
Truncus arteriosus (TA)	
Transposition of the great vessels (TGV)	
Situs inversus (SI)	
Other (please specify)_____	

4. **Renal U/S:** (Tick all that apply)

Normal	
Unilateral renal agenesis (Single kidney)	
Bilateral renal agenesis	
Pelvic kidney	
Horseshoe kidney	
Unilateral hydronephrosis / hydroureter	
Bilateral hydronephrosis / hydroureter	
Vesico-ureteric reflux (VUR)	
Pelvi-ureteric junction obstruction (PUJ)	
Other (please specify)_____	

5. **Spine x-ray:** (Tick all that apply)

Normal	
Hemivertebra	
Butterfly vertebrae	
Bifid vertebrae	
Sacral dysgenesis	
Sacral agenesis	
Other (please specify)_____	

6. **Limb examination**: (Tick all that apply)

Normal	
Unilateral radial aplasia	
Bilateral radial aplasia	
Hypoplastic thumb	
Polydactyly	
Syndactyly	
Other (please specify)_____	

7. **Chromosome tests:** (Tick all that apply)

Not performed	
Normal	
Trisomy 21	
Trisomy 18	
Trisomy 13	
Abnormal XY distribution (eg. 47 XXY)	
Other (please specify)_____	

Type of anorectal malformation:

If the type of malformation is not clinically obvious (eg. Recto-vestibular fistula), this section of the form may only be filled in once the primary PSARP or distal loopogram has been performed.

1. **What is the patients gender?** MALE / FEMALE

1.1. If male, please tick 1 of the following options for type of malformation

Perineal (cutaneous) fistula	
Recto-bulbar urethra fistula	
Recto-prostatic urethra fistula	
Rectovesical (bladder neck) fistula	
No fistula	
Anal stenosis	
Rectal stenosis / atresia	
Pouch colon	
H-type fistula	

1.2. If female, please tick 1 of the following options for type of malformation

Recto-vestibular fistula	
Recto-vaginal fistula	
Perineal (cutaneous) fistula	
No fistula	
Anal stenosis	
Rectal stenosis / atresia	
Pouch colon	
H-type fistula	
Cloaca	

Surgery, complications and management:

1. **What surgery was performed on this admission?** (Tick one)

Stoma formation	
Primary PSARP (no previous stoma)	
PSARP (after previous stoma)	
Closure of stoma	

2. **If a stoma was performed, what type of stoma was done?** (Tick one)

Divided (Pena) colostomy	
End (Hartmann's) colostomy	
Double barrel colostomy	
Loop colostomy	
Ileostomy	
Other _____	

3. **What date was the surgery performed?** DD/MM/YY _____

4. **Were antibiotics given before, during of after the surgery?** (Tick one)

No	
Peri-operatively (Single dose)	
For 24 hours post operatively	
Full course (Treatment course)	

4.1. **What antibiotic was given?** _____

5. **Was there a surgical complication?** YES / NO

6. **If yes…**

6.1. Please tick ALL complications that apply to the procedure performed on THIS admission:

6.1.1. Stoma formation:

Prolapse	
Stricture	
Retraction	
Wound dehiscence	
Wound infection	
Intestinal obstruction	
Intestinal torsion	
Fistula formation	
Reversal of stoma ends	
Parastomal hernia formation	
Death	

6.1.2. PSARP:

Wound sepsis	
Stricture	
Fistula (to where? _____)	
Iatrogenic injury (to what? _____)	
Wound dehiscence	
Rectal prolapse	
Improper placement of neo-anus	
Death	

6.1.3. Stoma closure:

Superficial wound sepsis	
Intra-abdominal sepsis	
Anastamostic leak	
Anastamotic breakdown	
Anastamotic stricture	
Death	

6.2. **How was the complication managed?** (Tick one and describe management)

Operative repair _____ _____ _____	
Conservative management _____ _____ _____	

6.3. If death occurred…

6.3.1. What was the cause of death? (Tick one)

Overwhelming sepsis	
Respiratory arrest	
Cardiac arrest	
Operative complication	

6.3.2. **If an operative complication lead to death, please explain how that complication lead to death. _____**

_____

_____

_____

_____

APPENDIX C – Patient information sheet

Information Sheet

Each participant must receive, read and understand this document before any study related procedure is performed.

Study title:

Anorectal malformations and the impact of HIV on surgical outcome

Principal investigators: Dr T Gabler / Dr C West-garth Taylor / Dr A Theron

Institutions: CMJAH / CHBAH

Daytime and after hours contact: Dr T Gabler 0820540627

tarryn.gabler@gmail.com

Medical Human Research Ethics Committee details:

Chairperson: peter.cleaton-jones1@wits.ac.za

Administrators: Ms Z Ndlovu / Mr R Mkansi / Mr L Moeng

Tel: (011) 717 2700/2656/1234/1252

Email: HREC-Medical.ResearchOffice@wits.ac.za

Dear Parent / Legal Guardian,

Hello. My name is _____ (name of doctor) and I would like to ask if you are interested in allowing your child to take part in a research study. We use research to answer questions about diseases that we don't fully understand. We would like to learn more about how HIV exposure (when a mother who is pregnant has HIV) can effect the operations that we do for babies who are born with anorectal malformations (when baby is born without an anus or when the anus is in the incorrect place) in Johannesburg. The study is being conducted by Dr T Gabler (a registrar in paediatric surgery). There is no funding for this study.

- This information leaflet is to help you decide if you would like your child to participate in this study. If you have any questions, please do not hesitate to ask me.
- Before agreeing to participate, it is important that you read and understand the purpose of the study, the study procedures, benefits, risks and discomforts.
- Taking part in this study is voluntary. You can choose not to take part in the study and if you join, you may withdraw at any time. If you decide not to take part in the study, your child will still receive the usual care that he/she would have received otherwise.
- You should not agree to allow your child to take part unless you are satisfied about all the procedures involved.

- If you allow your child to take part in the study, you will be asked to sign this document to confirm that you understand the study. If you would like, you will be given a copy of this form to keep.

What is the purpose of this study?

Anorectal malformations are caused by a change in the way that the anorectal system of your baby develops while it is in the womb. The cause of this change in development is not really known. Because the baby is born with this problem, he/she needs an operation to correct the problem, which will, hopefully, allow your baby to pass stool in a normal way. Many of the babies with this problem will need more than one operation to correct the problem. Some of the babies that have these operations have different complications and we would like to know if the number of these complications is higher, the same as, or lower in babies who have been exposed to HIV in the womb compared to babies who have not been exposed to HIV in the womb.

Because anorectal malformations are a congenital problem (a problem occurring during the babies development while it is still in the womb) it may be associated with other problems in development (like problems with the heart, bones or kidneys) and these other problems will be investigated during your child's hospital admission. These problems are checked for with x-rays and ultrasound scans. Sometimes, the babies with anorectal malformations may also have a genetic problem (a problem with the chromosomes in the babies cells). If there are clinical signs that your child may have an associated genetic problem, we will pull a blood test to check for this problem. Please

note that the blood tests to check for chromosome abnormalities will be done in any case where we suspect that there may be a genetic problem and are not specific to this study.

By agreeing to participate in this study you are agreeing to let us use information about yourself (the mother) and your child, but it is very important to understand that none of the information that you give us will be able to be traced back to you or your child (it will be kept anonymous).

Benefits of the study

A study like this has never been done before in South Africa and the results will help us better treat patients with anorectal malformations and HIV exposure in the future. During the study, all the information we need form you and your child will be gathered during normal care for your child. This means that you and your child will receive the same care and will have the same investigations (e.g blood tests) that you/your child would normally receive if you were not part of the study. As part of this study, we will take blood from your baby, and possibly yourself if no previous result is available, to test for HIV. If you or your baby tests HIV positive, we will refer you to the relevant department to ensure that you receive the best care and medication for HIV. Knowing your, and your baby's, HIV status is important and will allow you to get treatment if necessary.

Risks to you or your child

There will be no added risks to you or your child if you agree to partake in this study. The care for your child will be the same and all operations that are done will be done exactly the same as if you did not agree to participate. During the study, we may need to take blood samples from you or your child and will also do some other investigations on your child which are non-invasive (this means that they do not hurt eg. x-rays and ultrasound scans). All these investigations will still need to be carried out, even if you do not agree to participate in the study and so will not add any risk to you or your child.

If you have any questions about the study please feel free to ask.

APPENDIX D – Consent forms

Consent for study participation

Informed consent for study participation:

- I confirm that I have been informed by the study staff about the nature, conduct, benefits and risks of this study.
- I have received, read and understood the study information sheet.
- I am aware that the results of the study, including personal details regarding my child's gender, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised program by Dr T Gabler.
- I can withdraw my consent and the participation of my child from this study at any time I wish, without prejudice.
- I have had sufficient opportunity to ask questions and (of my own free will) declare that I allow my child _____ to participate in this study.

Participants name and surname _____

Parent / Gaurdian:	Study Staff obtaining consent:
Name:_____	Name:_____
Signature:_____	Signature:_____
Date:_____	Date:_____

Consent for genetic testing

Informed consent for genetic testing:

- I confirm that I have been informed by the study staff about the nature, conduct, benefits and risks of genetic testing.
- I have received, read and understood the study information sheet
- I am aware that the results of the genetic testing will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised program by Dr T Gabler.
- I can withdraw my consent and the participation of my child from this study at any time I wish, without prejudice.
- I have had sufficient opportunity to ask questions and (of my own free will) declare that I allow my child _____ to have blood taken for genetic testing.

Participants name and surname _____

Parent / Gaurdian:	Study Staff obtaining consent:
Name:_____	Name:_____
Signature:_____	Signature:_____
Date:_____	Date:_____

Consent for HIV testing

Informed consent for genetic testing:

- I confirm that I have been informed by the study staff about the nature, conduct, benefits and risks of HIV testing.
- I have received, read and understood the study information sheet
- I am aware that the results of the HIV test will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised program by Dr T Gabler.
- I can withdraw my consent and the participation of my child from this study at any time I wish, without prejudice.
- I have had sufficient opportunity to ask questions and (of my own free will) declare that I allow my child _____ to have blood taken to test for HIV.

Participants name and surname _____

Parent / Gaurdian:	Study Staff obtaining consent:
Name:_____	Name:_____
Signature:_____	Signature:_____
Date:_____	Date:_____

APPENDIX E – Ethics clearance

R14/49 Dr Tarryn Gabler

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160513

NAME: (Principal Investigator)	Dr Tarryn Gabler
DEPARTMENT:	Paediatric Surgery Charlotte Maxeke Johannesburg Academic Hospital Chris Hani Baragwanath Academic Hospital Nelson Mandela Children's Hospital
PROJECT TITLE:	Anorectal Malformations and the Impact of HIV on Surgical Outcome
DATE CONSIDERED:	27/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof C Westgarth-Taylor and Dr A Theron
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	15/07/2016

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in May and will therefore be due in the month May each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX F – South African Medical Journal (SAMJ) author guidelines

The following author guidelines are quoted directly from the SAMJ website at http://www.samj.org.za/index.php/samj/about/submissions.[21] (Accessed 02 February 2018)

'**General:**

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. μ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections:
Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.

- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

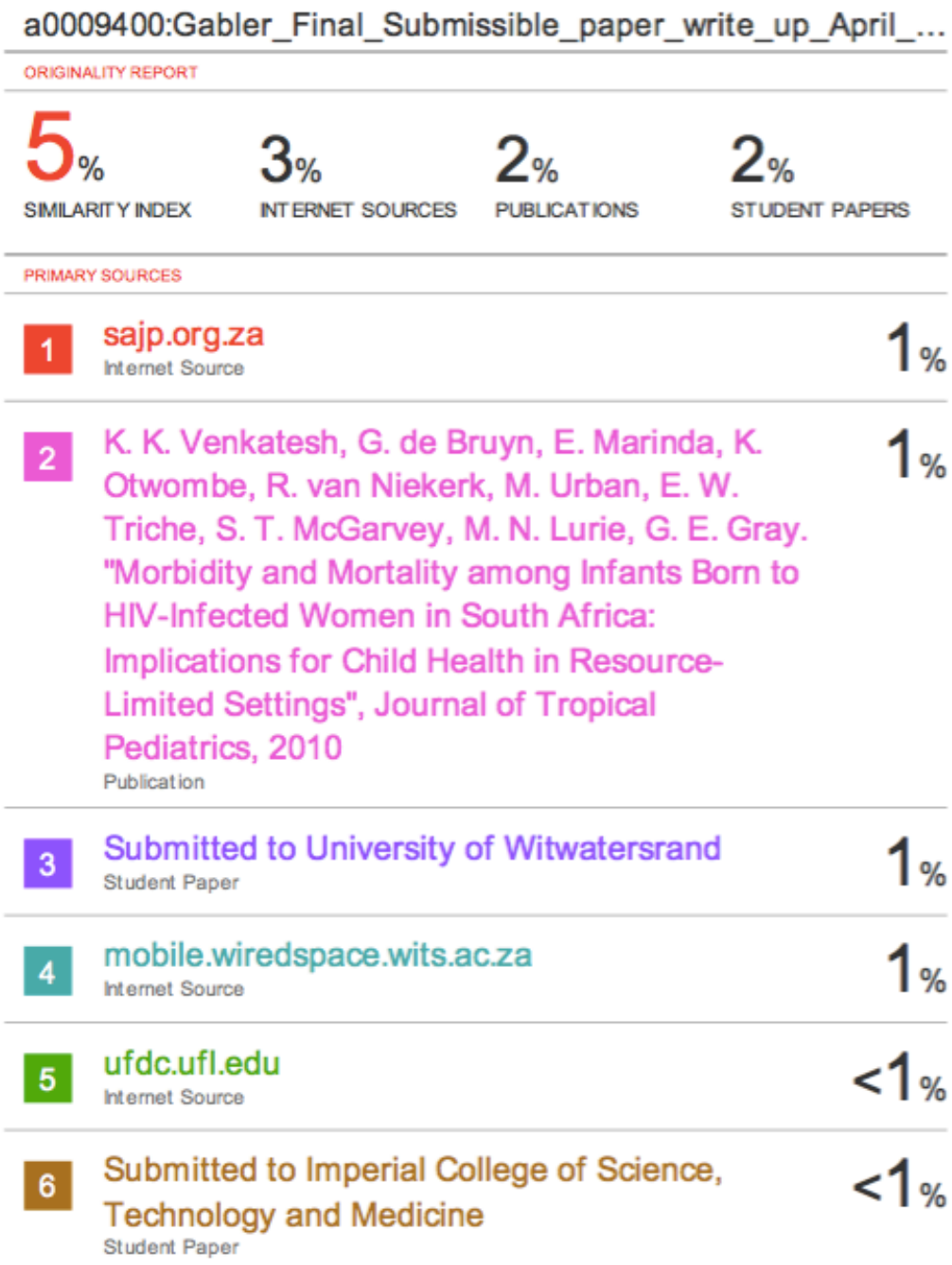
- Statement of principal findings

- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.'

APPENDIX G – ‘Turnitin’ report



a0009400:Gabler_Final_Submissible_paper_write_up_April_...

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