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THE SPECTRUM OF PLACENTAL PATHOLOGY IN A STATE LABORATORY VS. A PRIVATE LABORATORY PRACTICE IN GAUTENG, SOUTH AFRICA. IMPLICATIONS FOR PATIENT MANAGEMENT.

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(Student number: 300367)

A research report in 'submissible format' submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Medicine (MMed) in the specialty of Anatomical Pathology.

Johannesburg, 2020.

DECLARATION

DECLARATION

Declaration: Student's contribution to article and agreement of co-authors

I, Michael John Savage-Reid, student number 300367, declare that this research report is my own work and that I contributed adequately towards research findings in the article stated below which is included in my research report. It is being submitted in fulfilment of the requirement for the degree of Master of Medicine in the branch of Anatomical Pathology at the University of the Witwatersrand, Johannesburg. Assistance that I have received has been declared in the acknowledgments section of the article. This work has not been submitted previously for any degree or examination at this or any other university.

I certify that the protocol has been approved in accordance with the Human Research Ethics Committee (Medical) at the University of the Witwatersrand, Johannesburg (Appendix B: Ethics Clearance Certificate M180827).

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Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of his research report.

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DEDICATION

To my darling wife, Sunila

My biggest fan, best friend & greatest support

To my Lord & Saviour, Jesus Christ

Romans 11:36 (ESV)

“For from him and through him and to him are all things. To him be glory forever. Amen.”

PRESENTATIONS ARISING FROM THIS PROJECT

The findings of this research were presented at the Wits Faculty of Health Sciences Virtual Research Day and Postgraduate Expo on Thursday 15 October as an oral presentation.

PUBLICATIONS ARISING FROM THIS RESEARCH PROJECT

This paper was submitted on 03 July 2020 and published on 15 December 2020 in the South African Journal of Obstetrics and Gynaecology (SAJOG): *South African Journal of Obstetrics and Gynaecology* 2020;26(2):. DOI:10.7196/sajog.1599.

ABSTRACT

Background. Laboratory information systems have a wealth of patient and health data available for research. This data can serve to better inform health care and policies. The placenta is just one histopathology laboratory specimen that can provide such insight, particularly with regard to maternal and neonatal health care.

Objectives. To describe the spectrum of placental pathology between a private and state laboratory and to ascertain implications for improved maternal and neonatal health care and policies.

Methods. We conducted a retrospective descriptive study of placental histopathology reports from Lancet Laboratories, Richmond, and the National Health Laboratory Service (NHLS), Johannesburg over a 1-year period (August 2017 – July 2018). The reports were categorised according to the 2014 Amsterdam Placental Workshop Group Consensus Criteria and the percentages of each diagnostic entity compared between the two laboratories. These diagnostic categories included: ascending infection, maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), haematogenous infection, chronic villitis of unknown aetiology (VUE), retroplacental haemorrhage, no specific pathological changes (NSPC) and 'other.' Differences in maternal age and gestational age were also compared.

Results. There were 1 172 Lancet and 946 NHLS placentas entered into the study. MVM was the most prevalent pathology seen in both laboratories (40.6% and 47.7%; $p = 0.3193$). Mean maternal and gestational age were both higher within the private system (both p-values <0.0000).

Conclusion. Differences in placental pathology were multifactorial and reasons may include differences in socioeconomic status and resources, clinical and laboratory policies, and practices, as well as pathologist training and expertise. Clear clinical guidelines for the submission and histopathological examination of the placenta are required to better inform neonatal and maternal health care and policies. In our divided health system, collaborative medical research is not only possible between the state and private sectors but also necessary to achieve better health care and equity for the betterment of our patient population in South Africa.

ACKNOWLEDGEMENTS

Foremost, I would like to express my sincere gratitude to my supervisors, Prof. Colleen Wright and Dr. Reubina Wadee, for their patience, encouragement and immense knowledge. Their guidance has been invaluable in the completion of this dissertation.

I would also like to thank both the National Health Laboratory Service (NHLS) and Lancet Laboratories for their support in the provision of the research material that has made this possible. Too, I would be remiss not to thank the patients who use these health services and whom, as pathologists, we have little to no personal contact.

I thank our department – countless people – who have taught, encouraged and supported me in my training thus far. Thank you, Abel and Fadila, for your help with retrieving my research data.

I would like to thank my parents, Michael and Lynn, who have loved me unconditionally and have made countless sacrifices to put me in the position that I am today. A son could not ask for better parents.

To whom this dissertation is dedicated – my wife, Sunila – I thank you for your unconditional love, patience and support.

Lastly, praise be to my Lord, Jesus Christ, for His sovereignty, provision and salvation. I would not be where I am today if it were not for His saving grace in my life.

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NOMENCLATURE

AVM	Accelerated villous maturation
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CMV	Cytomegalovirus
DVM	Delayed villous maturation
EVT	Extravillous trophoblast
FVM	Fetal vascular malperfusion
HSV	Herpes simplex virus
IUGR	Intrauterine growth restriction
MDG	Millennium Development Goals
MFI	Maternal floor infarction
MPFD	Massive perivillous fibrin deposition
MTB	*Mycobacterium tuberculosis*
MVM	Maternal vascular malperfusion
NHLS	National Health Laboratory Service
NSPC	No specific pathological changes
PET	Pre-eclamptic toxaemia
SA	South Africa
SDG	Sustainable Development Goals
SNOMED CT	Systematised Nomenclature of Medicine Clinical Terms
SUA	Single umbilical artery
UN	United Nations
VUE	Villitis of unknown aetiology
WHO	World Health Organisation

1. INTRODUCTORY CHAPTER

1.1. General introduction / Background

The United Nations (UN) Millennium Development Goals (MDGs) was a commitment by one hundred and ninety-one world states to eight goals aimed at improving global health from 1990 to 2015.[1] In particular, goals four and five were aimed at reducing the under-five child mortality rate by two-thirds [2] and reducing the maternal mortality ratio by three-quarters whilst attaining universal access to reproductive health, respectively.[3]

With respect to South Africa, whilst multiple sources have had somewhat conflicting data on the estimates of maternal and neonatal mortality in the country.[4] Statistics South Africa (Stats SA) concluded the following regarding MDGs four and five: significant progress in reducing child mortality was achieved, but this fell short of the two-thirds reduction goal; the maternal mortality ratio, too, fell short of the MDG target.[5]

The world has now adopted the 2030 Agenda for Sustainable Development and its Sustainable Development Goals (SDGs) in September 2015, and whilst they are broader and have a more economic, social and environmental focus, they will undoubtedly build on any progress initially made towards achieving the MDGs in every country.[6]

According to the World Health Organisation (WHO), South Africa (SA) had a maternal mortality ratio of 138/100 000 live births, and an under-five mortality rate of 40.5 per 1000 live births in 2015. The 2030 SDG targets are less than 70/100 000 live births and as low as 25/1000 live births, respectively. In addition, cessation of all preventable deaths of newborns and children under five years of age should be attained.[7]

As a fetal organ the placenta provides invaluable insight into adverse pregnancy outcomes, both maternal and neonatal, as well as serves as a “highly pragmatic and effective means of saving on litigation payouts” in such outcomes.[8]

Thus, histopathological examination of the placenta will impact on the maternal mortality ratio and under-five child mortality rate SDG targets by both better informing acute and long-term newborn management in the case of an adverse outcome, as well as management of future pregnancies of mothers having suffered a pregnancy-related disease. These encompass vast clinical implications for prospective diagnosis, prevention, and treatment of adverse pregnancy outcomes.[9]

In addition, by providing insight into medicolegal claims for adverse pregnancy outcomes, and by having already aided in defining health policies and subsequent resource allocation,[8] histopathological examination of the placenta, too, contributes towards the overall economic dimension of the SDGs.[10]

In South Africa, the health sector comprises a private sector serving approximately 16% of the total population and a public sector serving the remaining 84%, and the former disproportionately contributes towards half of the country’s total expenditure on healthcare.[10] Whilst health outcome statistics are not always consistently reported across both sectors,[10] both sectors nevertheless contribute towards achievement of the SDGs, both individually and collaboratively.

This study is thus aimed at describing the spectrum of placental pathology across the two different hospital sectors, comparing and analysing the data and drawing possible implications for patient management and achievement of the SDGs for South Africa.

1.2. Overall research aims and individual research objectives

The aim of this study will be to describe and compare the spectrum of placental pathology across the South African public sector – by way of the National Health Laboratory Service (NHLS) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) – and private sector by way of Lancet Laboratories (Pty) LTD.

Thus, the primary objectives include:

- Record/capture the number of placental reports from each sector for the specified time period (see below).
- Categorise the diagnosis of each report according to the Amsterdam international consensus criteria.
- Calculate the percentage of each diagnostic category against the total number of reports across each health sector.
- Correlate the diagnostic categories with patient age (and gestational age, if available).
- Tabulate and graphically represent the findings of the above objectives.

As a secondary aim, the findings will be used to ascertain further implications for management of adverse pregnancy outcomes over and above that highlighted in the literature, as well as identify those more specific to South Africa's health setting (public and private health sectors).

1.3. Value of this research

To the knowledge of the authors, no such study, particularly comparing state and private sectors, has been performed in South Africa, nor elsewhere globally.

Thus, in addition to contributing towards research aimed at accelerating and improving South Africa's attainment of the SDGs, this study will better highlight the extent of different placental pathologies across both health sectors in the country, and so better guide policies and allocation of resources towards the management of both maternal and perinatal health within both health sectors.

2. Extended literature review

2.1. Brief overview of maternal and perinatal health

Maternal health is a broad term for the health of women. However, more specifically, it refers to the periods of pregnancy, childbirth and the postpartum.[11] Globally, approximately one hundred and forty million births take place annually and eight hundred and ten women die each day from preventable complications related to pregnancy and childbirth.[11] Sadly, 94% of these maternal deaths occur in low and lower middle-income countries, and 86% of these are shared between Southern Asia and Sub-Saharan Africa.[12]

The WHO defines maternal mortality as a woman dying from pregnancy-related causes during or within forty-two days of delivery. This is then expressed as a ratio to 100 000 live births.[13] Measures of maternal mortality include the maternal mortality ratio (MMR) and maternal mortality rate. The MMR is more widely used and reported and is calculated by dividing the number of maternal deaths in a given time period by the number of live births (per 100 000 live births) during that same time period. It is regarded as being high if it is greater than or equal to 300, moderate if between 100-299, and low if between 20-99 maternal deaths per 100 000 live births.[14]

The most recent global statistic available for SA's MMR is 119/100 000 live births.[14] This is down from the 138/100 000 live births in 2015 quoted in the 'Introduction' (section 1.1) above,[7] but is still considered 'moderate' by the WHO standards.

Perinatal health is closely tied to maternal health. According to the WHO, the perinatal period begins at twenty-two weeks' gestation and ends seven days after childbirth. Perinatal mortality refers to the combination of both the number of stillbirths and early neonatal (first week of life) deaths in a given population.[16]

Globally, there are approximately 2.6 million stillbirths annually, and of the 133 millions live births each year, approximately 2.8 million die with the first week of

life.[15] The pattern of the distribution of these deaths closely mimics that of global maternal mortality, that is, occurring predominantly in low and lower middle-income countries and predominantly within Southern Asia and Sub-Saharan Africa.[16]

2.2. The structure and function of the placenta

In addition to the above, prior to understanding the pathology of the placenta, a working understanding of the anatomy of the placenta is required and will be briefly described.

Initial placental development arises from cavitation of the morula which progresses to the blastocyst. The blastocyst comprises different layers of cells that each further differentiate along different cell lines with different functions. These principal layers include the outer and inner trophoectoderm and the inner cell mass. The function of the cells of the inner trophoectoderm (cells closest to the inner cell mass) are to attach to the endometrium with subsequent invasion into and below the uterine lining by the blastocyst. Thereafter, the collective trophoectoderm expands and births two cell populations, namely, the mononuclear cytotrophoblast and a multinucleated syncytium. The former leads to the development of primary and secondary villi, and the latter leads to formation of blood-filled lacunae.[17]

Anchoring villi (also called stem villi), at the basal plate, function to attach the forming placenta firmly to the decidua basalis, that is, the maternal tissues, forming anchorage points. In contrast, placental septae are extensions of the decidua basalis that project into the intervillous space. Following delivery, their former positions are what delineate the maternal surface into approximately twenty irregular segments of placenta tissue termed cotyledons.[17,18]

The cells at the proximal ends of the anchoring villi further expand and differentiate into extravillous trophoblast (EVT). Mature extravillous trophoblast cells further invade the maternal tissues as either interstitial EVT or endovascular EVT. The former extends into the decidua and/or inner third of the myometrium (that is, implantation), and the latter is responsible for the remodeling of maternal decidual vessels from high-resistance, low-capacitance spiral arterioles to low-resistance,

high-capacitance vessels, thereby continually delivering high blood volumes to the placenta and developing fetus.[17]

Together with anchoring villi, primary, secondary and tertiary villi constitute the basic functional unit of the placenta, collectively called chorionic villi. Primary villi derive from the early cytotrophoblast and secondary and tertiary villi derive from extraembryonic mesoderm of the inner cell mass.[17] Chorionic villi function to increase the surface area across which the fetal and maternal circulations communicate with one another. Maternal blood enters an area called the intervillous space, coming into contact with the chorionic villi, and thereby permitting exchange of nutrient material and gases. Once deoxygenated, this blood then leaves the intervillous space towards the decidua and thereafter enters into the endometrial veins and the maternal circulatory system.[18]

Fetal blood, in contrast, enters the placenta via the umbilical arteries which then branch into multiple chorionic arteries. These further divide as they enter the chorionic villi where they form a complex capillary system that then communicates with the maternal blood in the intervillous space via the vascular-syncytial membrane. Oxygenated blood within these villous capillary beds then returns to the foetus via the umbilical vein and enters the fetal circulatory system.[18]

Lastly, apart from the placental parenchyma, the structure of the fetal membranes also warrants brief mention. They comprise several layers, namely, the amnion with variable underlying amniotic mesenchyme, the chorion, and the decidua capsularis. The latter houses the majority of maternal vessels.[17]

Thus, with respect to the formed placenta, the fetal surface consists primarily of the chorionic plate which is surfaced by the amnion, and the maternal surface consists primarily of the decidua basalis which is continuous with the endometrium. The myometrium forms an outer boundary to the decidua basalis and is only continuous with it in pathological placental implantation states.[18,19]

2.3. Pathology of the placenta

The spectrum of pathology affecting the placenta is vast, spanning the full gamut of developmental anomalies, inflammatory conditions and even neoplasia. As such, placental pathology experts have appropriately categorised placental lesions into various categories, reflecting both their pathophysiology as well as frequency with which they are encountered. This is what is known as the Amsterdam Placental Workshop Group Consensus Statement, hereafter referred to as the Amsterdam Classification or Criteria.[20]

This classification has been adapted for this study, resulting in the following diagnostic categories of placental pathology: maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), ascending infection, haematogenous infections, villitis of unknown aetiology (VUE), retroplacental haemorrhage, no specific pathological changes (NSPC), and 'other' pathological entities.

Definitions with key diagnostic features for each of these entities and how they were applied to this study are provided. It must also be noted that the various terms and features described within each of these entities are not explored in detail in this literature review as this would go beyond the scope of this study which does not constitute a textbook on placental pathology.

Maternal vascular malperfusion (of the placental bed) goes by many other names, including but not limited to, maternal vascular underperfusion, utero-placental insufficiency and placental insufficiency. It is an entity representing a pattern of injury to the placental bed due to altered uterine and/or intervillous blood flow.[21] The exact pathophysiological is not completely understood, however, aberrations in the remodeling of the maternal spiral arterioles during placental implantation and development are intrinsic to the pathological process.[21] It is further subclassified into global/partial and segmental/complete. Global/partial MVM is characterized by accelerated villous maturation (AVM), a term describing a constellation of findings in the lower two-thirds of the placental parenchyma. These include areas of decreased villi / undergrowth alternating with areas of villous crowding with focal findings of increased perivillous fibrin, syncytial knots and villous agglutination. Segmental/complete MVM comprises placental villous infarction and/or infarction haematomas/rounded intraplacental haematomas. Infarcts comprise groups of more

than five chorionic villi showing variable representation of the following features: intervillous space collapse, karyorrhectic debris and neutrophils between the villi, ischaemic necrosis and degeneration of both the villous trophoblast and stroma. An infarction haematoma is round and comprises an organising haematomas completely surrounded by infarcted chorionic villi measuring equal to or more than five villi in diameter.[22]

Fetal vascular malperfusion is also an umbrella term encompassing a range of findings usually attributed to altered, that is, restricted, umbilical cord blood flow. It, too, can be further subclassified by patterns into segmental/complete and global/partial FVM. The features of FVM include both chorionic and/or stem fetal vessel changes and changes in the distal villi. The former includes: vascular ectasia, thrombosis, intramural fibrin deposition and stem vessel obliteration. The latter includes: avascular villi, villous stromal-vascular karyorrhexis and delayed villous maturation. Segmental/complete FVM comprises complete stem vessel obliteration or thrombotic occlusion thereof. In contrast, global/partial FVM, also referred to as intermittent obstruction, comprises lesions distributed over the majority of the placenta, namely, fetal vein vascular ectasia, intramural fibrin deposition and capillary vessel avascularity or villous stromal karyorrhexis.[23]

Two terms sometimes used and diagnosed are ‘placental compromise’ and ‘fetal compromise.’ These are broad umbrella terms whereby placental findings are non-specific and suggestive of either MVM or FVM, respectively, but fall short of the diagnostic criteria for these specific entities.

Ascending infection includes acute chorioamnionitis and subacute chorioamnionitis. Acute chorioamnionitis is defined, pathologically, as acute inflammatory cells (neutrophils) within the amnion, chorion or subchorionic space. It is most often due to an infectious aetiology arising from the ‘ascending route’ from the female genital tract to affect the amniotic fluid and placental membranes. The most commonly implicated organisms are bacteria, namely, group B streptococcus, *Escherichia coli*, enterococcus, *Listeria monocytogenes*, mycoplasma, ureaplasma and, importantly, *Treponema pallidum*. Subacute chorioamnionitis comprises a mixed infiltrate of neutrophils and mononuclear inflammatory cells that are predominantly within the

584 subamniotic tissues which is in contrast to the chorionic and subchorionic location of
585 neutrophils in acute chorioamnionitis. This is usually due to less virulent infectious
586 organisms, including Candida.[24]
587
588 Haematogenous infections are those that are blood-borne and maternally derived,
589 manifesting within the placenta as either an acute, chronic or mixed villitis. These are
590 typically an infectious villitis whereby organisms within the maternal circulation reach
591 the placenta and gain access to the villous stroma with consequent invasion into the
592 fetal vasculature and resultant neonatal sepsis. Acute villitis comprises neutrophils
593 within the villous stroma and of the many causes, the more common aetiologic
594 agents include group B streptococcus, *L. monocytogenes*, and in a South African
595 context, *Mycobacterium tuberculosis* (MTB). Chronic villitis comprises a chronic
596 inflammatory cell infiltrate within the villous stroma, that is, variable infiltration by
597 lymphocytes, plasma cells and histiocytes. When identified, these are often viral in
598 aetiology, but include numerous organisms. Cytomegalovirus (CMV), Herpes
599 simplex virus (HSV), *Toxoplasma gondii* and *T. pallidum* are among the more
600 commonly identified organisms.[24] Mixed villitis, as the names suggests, shows
601 overlapping histological features between an acute and chronic villitis.
602
603 The majority of chronic villitides, however, are non-infectious and are subsequently
604 so-named 'villitis of unknown aetiology.' Villitis of unknown aetiology, thus, is
605 diagnosed when an identifiable infectious aetiology is excluded. It manifests
606 histologically as a mainly lymphohistiocytic infiltrate within the villous stroma. Its
607 aetiology is proposed to be immune-mediated where it is most often seen in the
608 context of assisted pregnancies with donor ova. It is graded based on the number of
609 contiguous, involved villi, and grading is important as high-grade VUE is associated
610 with a 10-15% recurrence in subsequent pregnancies with associated complications,
611 including intrauterine growth restriction (IUGR).[25]
612
613 Retroplacental haemorrhage is a category here defined as haemorrhage on the
614 maternal surface as evidenced by an adherent haematoma or indentation. It is due
615 to demise in the integrity of the maternal vasculature and typically manifests clinically
616 as placental abruption / abruptio placentae. There are three subtypes, namely, acute
617 abruption, acute marginal abruption and chronic marginal abruption. Classic, acute

placental abruption is early separation of the placenta from the maternal tissues usually due to arterial haemorrhage. Causes include abdominal trauma, shearing forces (e.g. premature rupture of membranes), maternal hypertension or pre-eclamptic toxaemia (PET) or decidual inflammation ('inflammatory abruptio'). Acute marginal abruption is due to venous haemorrhage at the periphery of the placenta and is of uncertain aetiology. It has, however, been associated with abnormal placental implantation, inflammation and also trauma. Chronic abruption is also usually due to venous haemorrhage, typically at the placental periphery, and is also of uncertain aetiology. However, numerous associations have been made with the entity, including oligohydramnios, smoking of tobacco products and multiparity.[26]

'Other' entities essentially include any and all placental findings and diagnostic entities that do not fit into one of the defined categories above. That said, some of the more 'commonly' encountered 'other' diagnoses in this study will be briefly discussed. These include: chorangiosis and chorangioma, delayed villous maturation, diffuse villous oedema, chronic histiocytic intervillositis, single umbilical artery and massive perivillous fibrin deposition.

Villous chorangiosis is a fetal capillary-vascular developmental abnormality/lesion. It is defined as an increase in the number of cross-sectional profiles of capillaries within chorionic villi. This is due to dilation of the capillaries making them more readily visible in cross-section examination. Its significance lies in the fact its associations with decreased intervillous oxygen tension with normal perfusion, as well as maternal diabetes that is poorly managed. A chorangioma is another developmental anomaly that constitutes a benign vascular neoplasm comprising proliferating capillary-sized vessels with surrounding fibrous stroma. They are usually small (<2cm) and may be associated with vascular neoplasms and malformations in the neonate. If multiple or large in size (>4cm), they lead to fetal pathology in proportion to their size and/or number, including arteriovenous shunting, platelet sequestration, high output cardiac failure and subsequent stillbirths or increased risk of neonatal haemorrhage.[27,28]

Delayed villous maturation (DVM), also called distal villous immaturity, is a fetal stromal-architectural abnormality whereby there is a decreased number or absence

of terminal chorionic villi in a term placenta. The implication is that there are instead predominantly chorionic villi of intermediate size with more capillaries and poorly formed or absent vascular-syncytial membranes. As such, a better way to conceptualise this entity is as increased immature chorionic villi for gestational age. It is most commonly associated with maternal diabetes, chronic umbilical cord obstruction and even fetal mortality.[27,28]

Diffuse villous oedema constitutes oedematous villous stroma affecting mainly the immature, intermediate chorionic villi. This is usually in preterm placentas and is due to loss of integrity of the fetal vasculature whereby increased hydrostatic pressure or decreased vascular oncotic pressure result in increased villous stromal extracellular transudate fluid. This is most often due to fetal cardiac failure in the context of chronic hypoxia. The clinical associations include acute chorioamnionitis, neurological deficits in surviving infants and otherwise neonatal death.[29]

Chronic histiocytic intervillositis is defined as infiltration of the intervillous space by monomorphic, monocyte macrophages in either a patchy or diffuse distribution and devoid of a significant concomitant chronic villitis. Its aetiology is also poorly understood, but it is associated with a near 80% perinatal mortality rate whereby affected neonates are often complicated by prematurity and growth restriction. Subsequent maternal pregnancies are often complicated by recurrent miscarriages and pregnancy losses at any gestational age.[30]

A single umbilical artery (SUA) is one of many placental gross anomalies. A normal umbilical cord comprises two umbilical arteries and a single, central umbilical vein. Single umbilical artery is seen most often in pregnancies of very young or advanced maternal age, as well as multiple gestation. Clinically, it is associated with maternal tobacco use, diabetes mellitus, hypertension and seizure disorders. Whilst there are proposed pathogeneses, it is largely uncertain. In the neonate, it is associated with congenital malformations in both karyotypically normal and abnormal fetuses, particularly the VACTERL syndrome comprising vertebral anomalies, anal atresia, cardiac anomalies, trachea-oesophageal fistulae, renal and radial anomalies and other limb structural abnormalities.[28,31]

Massive perivillous fibrin deposition (MPFD) is also referred to as maternal floor infarction (MFI), yet the two terms can be histologically separated. Maternal floor infarction is defined as a "marked increase in fibrin involving the maternal floor covering at least 25% of the surface and enveloping the basal villi for ≥3mm over the entire maternal floor on at least one slide." The term MPFD is used when these lesions expand to involve at least 30% of the placental parenchyma macroscopically or at least 50% of the chorionic villi on at least one histology slide. These placentas have a distinct, band-like distribution of fibrin along the maternal floor imparting an 'orange-rind' appearance. These entities are strongly associated with increased perinatal morbidity and mortality and such neonates should be closely monitored post-delivery.[32]

Lastly, 'no specific pathological findings (NSPC)' includes any placenta devoid of both macroscopic and microscopic features to suggest underlying pathology.

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3. Published paper/s (reprint/s)

The spectrum of placental pathology in a state vs. private laboratory practice in Gauteng, South Africa.

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Abstract

Background. Laboratory information systems have a wealth of patient and health data available for research. This data can serve to better inform health care and policies. The placenta is just one histopathology laboratory specimen that can provide such insight, particularly with regard to maternal and neonatal health care.
Objectives. To describe the spectrum of placental pathology between a private and state laboratory and to ascertain implications for improved maternal and neonatal health care and policies.
Methods. We conducted a retrospective descriptive study of placental histopathology reports from Lancet Laboratories, Richmond, and the National Health Laboratory Service (NHLS), Johannesburg over a 1-year period (August 2017 – July 2018). The reports were categorised according to the 2014 Amsterdam Placental Workshop Group Criteria and the percentages of each diagnostic entity compared between the two laboratories. These diagnostic categories included: ascending infection, maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), haematogenous infection, chronic villitis of unknown aetiology (VUE), retroplacental

haemorrhage, no specific pathological changes (NSPC) and 'other.' Differences in maternal age and gestational age were also compared.

Results. There were 1 172 Lancet and 946 NHLS placentas entered into the study. MVM was the most prevalent pathology seen in both laboratories (40.6% and 47.7%; p = 0.3193). Mean maternal and gestational age were both higher within the private system (both p-values <0.0000).

Conclusion. Differences in placental pathology were multifactorial and reasons may include differences in socioeconomic status and resources, clinical and laboratory policies, and practices, as well as pathologist training and expertise. Clear clinical guidelines for the submission and histopathological examination of the placenta are required to better inform neonatal and maternal health care and policies. In our divided health system, collaborative medical research is not only possible between the state and private sectors but also necessary to achieve better health care and equity for the betterment of our patient population in South Africa.

Introduction

Health systems and policies have been compared across different countries but there has been little agreement amongst scholars with respect to assessment of the quality thereof.[1] A paper published in The Lancet Global Health in 2018 sought to do just that, giving recommendations to raise the quality of a health system.[2] One such recommendation highlighted the inability of government health ministries to accomplish improved quality alone and the necessity to partner with the private sector.[2] In South Africa, the health sector comprises a private sector serving approximately 16% of the total population and a public sector serving the remaining 84%. The former contributes disproportionately towards half of the country's total expenditure on healthcare.[3] Whilst health outcome statistics are not always consistently reported across both sectors,[3] both sectors nevertheless contribute towards overall improved quality health care in the country, both individually and collaboratively. As such, one would expect, then, a growing body of collaborative research between South Africa's two health care systems with the aim of improving quality care for all. Sadly, there is no such body of research.

Within these two healthcare systems, the histopathologist plays a pivotal role in the improvement of the quality of both population health care and health policies,[4-5] particularly because of their access to abundant patient data and laboratory results contained within laboratory information systems.[4] One histopathology specimen that offers a wealth of information and that has already been used in improving clinical health care and informing health care policies is the placenta. More specifically, the placenta is key to improving the quality of maternal and perinatal health,[6–8] especially in resource-limited settings.[7]

This study aimed to describe and compare the spectrum of placental pathology seen at Lancet Laboratories, Richmond, Johannesburg (private health sector) and the National Health Laboratory Services (NHLS) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) (state/government health sector) over a one-year period. No such comparative study exists, and very few placental pathology studies have been conducted within South African hospitals.[9–11] Our study thus adds to the growing pool of placental pathology research in South Africa and seeks to pioneer state-private collaboration with the aim of improving South African maternal and perinatal health care and policies.

Objectives

The primary objectives of our study included: capturing the number of placental reports from each sector for the specified time period, categorising the diagnosis of each report based on the Amsterdam Workshop Group Consensus Statement on the definitions of placental lesions [12] and calculating their respective percentages and comparing the differences between each sector. Secondary aims from our study included analysing these findings and ascertaining implications for the management of maternal and perinatal conditions and recommendations for subsequent health reforms and policies within South Africa's health system.

Methods

We conducted a retrospective descriptive study. Following ethical clearance (certificate no. M180827), data was collected by searching both the Lancet

Laboratories (Richmond, Johannesburg) and NHLS (CMJAH) databases using the Systematised Nomenclature of Medicine Clinical Terms (SNOMED CT) tissue codes 'placental structure' and 'entire placenta' for the period 1 August 2017 to 31 July 2018. These initial data extracts were captured into Microsoft Excel spreadsheets.

The parameters included in the searches were: hospital, patient age (years), gestation (weeks and singleton or multiple pregnancy) as well as the full placental histopathology reports with the conclusion/diagnosis. Ethnicity is inconsistently recorded on laboratory request forms and was thus not included.

Each placental histopathology report was then reviewed and based on the findings and diagnosis, placed into broader diagnostic categories according to the 2014 Amsterdam Placental Workshop Group Criteria.[12] The diagnostic categories for our study included: ascending infection (acute chorioamnionitis, funisitis, vasculitis), maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), haematogenous infection (acute and chronic villitis, acute intervillositis), chronic villitis of unknown aetiology (VUE), retroplacental haemorrhage, no specific pathological changes (NSPC) and 'other.' Cases with findings falling into more than one category were assigned multiple categories.

Cases from the NHLS data set that were designated as 'other' or otherwise could not be accurately placed into one or more of the diagnostic categories had their slides retrieved and reviewed by an experienced histopathology consultant (RW) and a senior histopathology registrar (MSR). Upon review and consensus diagnosis, each was then appropriately re-categorised into the aforementioned diagnostic categories. Any case whereby a consensus could not be reached was then reviewed by a second histopathology consultant who has years of experience in placental pathology (CW).

Only NHLS cases were reviewed due to the heterogeneity in reporting of placental specimens from this institution and difficulty in categorising the diagnosis according to the Amsterdam consensus criteria. At the NHLS, placentas are reported by different pathologists with varied placental pathology interest and expertise. In

contrast, all cases seen from Lancet during this time period were reported by one pathologist (CW) using a consistent reporting template.

Inclusion criteria were reports of complete placental specimens: umbilical cord, membranes, and placental disc(s). Chorionic disc weight was also an inclusion criterion. Where a gestational age was not available, placental weights were then used to calculate the mean gestational age using a table of reference values for single and twin placental weights in relation to gestational age.[13]

Cases were excluded if they were incomplete placental reports (absent umbilical cord and/or membranes and/or placental disc), autolysed or having severe processing artefact (precluding accurate histological assessment), as well as cases from state hospitals that were submitted to Lancet Laboratories. This kept the comparison strictly between placentas received from state hospitals reported by NHLS pathologists with that of placentas received from private hospitals reported by the pathologist at Lancet laboratories.

The final data sets for analysis were then captured onto Microsoft Excel spreadsheets in single table format. Mean percentages were calculated for patient age and gestational age, and the medians thereof also recorded. The percentage of NHLS specimens derived from academic hospitals in comparison to secondary hospitals was also captured. Gestation (singleton or multiple pregnancy) and each of the eight diagnostic categories were recorded as a percentage of the total number of cases for each of the institutions. Cases showing multiple diagnostic entities, such as MVM and FVM, had each entity included in the calculated percentages for the respective categories.

To determine any statistically significant differences between the proportion estimated from Lancet and the NHLS, we used a two-tailed Z-proportion test with significance level set at 5%. Statistical significance between average maternal and gestational ages was performed using a two-tailed independent t-test with significance set at 5%.

Results

The initial Lancet Laboratories data extract yielded 1 362 cases, of which a total of 190 cases were excluded. One hundred and thirty-five cases were excluded as originating from state hospitals. This yielded a final total of 1 172 cases from Lancet Laboratories for the period examined.

The initial NHLS data extract yielded 1 122 cases, of which 156 cases were excluded in the first round of analysis prior to reviewing of slides, leaving 966 cases remaining. Thereafter, 132 of these cases were selected for slide review, comprising 13.7% of the remaining NHLS cases, and 6.2% of the combined NHLS and Lancet cases (n=2 138). The reviewed cases comprised 29 cases classified as 'other' only and 103 cases that could not be accurately classified into a diagnostic category based on the original histopathology report. From these, an additional 20 cases were excluded from the study. Thus, a total of 946 cases from the NHLS were included for the period assessed. This is summarised in Figure 1.

Fifty-nine of the NHLS cases (6.24%) were submitted from secondary hospitals and the remainder derived from tertiary and quaternary (academic) hospitals.

Table 1 depicts the results of the mean maternal age and gestational age, as well as the number of singleton and multiple gestation placentas, across each laboratory. Both the mean maternal age and gestational age showed statistically significant differences between the two laboratories (both p-values <0.0000). The difference in number of multiple pregnancies was not statistically significant (p-value 0.7564).

Table 1: Comparison of Obstetric Parameters for Placental Samples

	Lancet	**NHLS**	**p-values**
Mean maternal age (years (median))	33.33 (34)	28.37 (28)	<0.0000
Mean gestational age (weeks (median))	32.69 (35)	27.43 (28)	<0.0000
Singleton pregnancy placentas (%)	93.69	95.35	-
Multiple pregnancy placentas: twins or triplets only (%)	6.31	4.65	0.7564

Table 2 shows that between the two laboratories FVM (p-value 0.0001), retroplacental haemorrhage (p-value 0.0000), ascending infection (p-value 0.0000) and VUE (p-value 0.0000) showed a statistically significant difference. In the remaining categories 'other' (p-value 0.6374), MVM (p-value 0.3193), haematogenous infection (p-value 0.3062) and NSPC (p-value 0.2676) were not statistically significant.

Table 2: Comparison of Placental Diagnostic Categories

Diagnostic categories	**Number and percentage of total cases**		
	Lancet (n=1172)*	NHLS (n=946)*	p-values
Maternal vascular malperfusion	476 (40.6%)	451 (47.7%)	0.3193
Fetal vascular malperfusion	271 (23.1%)	35 (3.7%)	0.0001
Retroplacental haemorrhage	568 (48.5%)	114 (12.1%)	0.0000
Ascending infection	143 (12.2%)	356 (37.6%)	0.0000
Haematogenous infection	36 (3.1%)	54 (5.7%)	0.3062
Villitis of unknown aetiology	258 (22.0%)	3 (0.3%)	0.0000
Other	130 (11.1%)	83 (8.8%)	0.6374
No specific pathological changes	57 (4.9%)	85 (9.0%)	0.2676

* Numbers do not add up to total number of cases for each institution as multiple placentas showed more than one pathological entity / diagnostic category.

The 'other' pathologies showed a broad spectrum of findings across both institutions and these individual diagnoses were not all captured. These 'other' entities included, but were not limited to, maternal floor infarction, chronic histiocytic intervillositis, umbilical cord defects (such as single umbilical artery and hypercoiling) and chorangiosis. Of interest, one case of metastatic melanoma was identified in the Lancet data set, and one case of a diffuse large B-cell lymphoma (DLBCL) was identified in NHLS data set.

Discussion

The majority of the NHLS cases came from academic hospitals, that is, where specialist obstetricians reside and train registrars. These state hospitals - and by extension, labour wards - are still largely serviced by community service medical officers and medical interns with less obstetric expertise.[14] In contrast, the private sector comprises entirely specialist obstetricians. This difference in obstetric experience may thus reflect a disparity in the awareness of criteria warranting submission of a placenta for histological evaluation. These indications can be conceptualised as fetal, neonatal and maternal indications for placental examination.[15] Some health care systems in other countries have published guidelines for histopathological placental examination,[16] however, no such guidelines exist for the South African health care system. On the other hand, as tertiary and quaternary hospitals receiving referrals for complicated pregnancies, these hospitals may also see a greater number of preterm deliveries which may also account for the lower average gestational age. Preterm delivery has numerous risk factors. Of these, hypertensive disorders in pregnancy are amongst the greatest risk factors for preterm delivery [17] and a higher frequency of MVM has already been established in the NHLS data.

There was no statistically significant difference in MVM between the two laboratories. Maternal vascular malperfusion of the placental bed is the result of trophoblast dysfunction and abnormal maternal artery remodeling during placental development.[18] Classically, this placental finding has been associated with a clinical diagnosis of preeclampsia [19] and other hypertensive disorders of pregnancy.[20] Globally, 1.4 billion people in 2010 had hypertension [21] and in South Africa at the same time it was estimated that more than 30% of adults had hypertension.[22] Prevalence of hypertensive disorders of pregnancy in South African mothers is 12.5-38% [23-24] and it causes significant maternal morbidity and mortality, accounting for 18% of maternal deaths and is currently the leading direct cause thereof in South Africa.[25] This is in keeping with the high percentage of MVM in submitted placentas from both state and private hospitals. Another placental study performed at a tertiary state hospital in South Africa showed that, in a data set of 822 cases, 32.1% of intrauterine fetal death (IUFD) cases demonstrated MVM in the accompanying

placenta.[9] Whilst not as high as the 47.7% within our state data, nor the 40.6% in our private data, this study was conducted in a different province. Lastly, regarding MVM, whilst not statistically significant, the slightly higher percentage within our state data compared to the private data may be due to the fact that tertiary and quaternary hospitals serve as points of referral for complicated pregnancies.

The private health care users' average maternal age was higher than that of the state health care system. It is proposed that this may be in part due to differences in socioeconomic status. Socioeconomic disparity between the state and private health systems in South Africa is well-documented.[26-27] A survey-based study conducted in four provinces in South Africa in 2012, including Gauteng, evaluated rates of adolescent pregnancies and contributing factors and found that 19.2% of young women reported having had an adolescent pregnancy, and unemployment and greater poverty were associated with adolescent pregnancy.[28] Another proposed contributing factor to the differences in average maternal age between the two sectors is accessibility and affordability of contraceptive use. Women with financial means may opt for their contraceptive method of choice from the private sector, whereas women using the state system – whilst contraception is free of charge – still have other financial barriers such as travel costs. Furthermore, state facilities may not always have the full repertoire of contraceptive options always available.[29]

Concerning the statistically significant pathology differences in our two data sets, the four striking differences were those in the different percentages of diagnosed VUE, FVM, ascending infection and retroplacental haemorrhage. Figure 2 highlights the key histopathological features of these diagnostic entities.

Villitis of unknown aetiology is diagnosed when an identifiable infectious aetiology has been excluded and its immune-based aetiology is largely based on its increased incidence in patients with either autoimmune conditions or those having fallen pregnant by assisted/*in vitro* fertilisation (IVF) with donor ova.[30] There is unfortunately no data available comparing the prevalence of autoimmune conditions between the two health sectors. However, IVF partly accounts for the increased numbers within the Lancet data. IVF in South Africa costs, on average, between R40 000 – R50 000 per treatment cycle [31] and is thus largely only available in the

private health care sector. Only three state/academic facilities offer IVF, namely Steve Biko, Tygerberg and Groote Schuur hospitals,[32] none of which fall within the CMJAH drainage area. What more likely explains the markedly decreased number of VUE in the NHLS data is a paucity of tissue sampling. On average, only two sections of placental parenchyma are sampled at the CMJAH NHLS laboratory per placental specimen, and this lies in stark contrast to the seven blocks of placental parenchyma per placenta sampled at Lancet Laboratories, Richmond (NHLS & Lancet, Standard Operating Procedures). At least six sections are required to detect 85-95% of cases of VUE.[33] Lastly, one study found that VUE primarily affects two main groups of pregnant women, namely, younger women of lower socioeconomic status and a history of sexually transmitted infections, and older women of higher socioeconomic status often with a history of multiple miscarriages.[34] The latter group is accounted for by the Lancet data set; however, the former group is unaccounted for in the NHLS data set and thus suggests gross under-sampling of submitted placental specimens.

The higher retroplacental haemorrhage is most likely explained by the traumatic haemorrhage associated with removal of the placenta during Caesarean section and the surgery itself.[35] Private health sector Caesarean section rates are significantly higher than the state health care system. In 2004, private sector Caesarean section rates in South Africa were estimated to be as high as 65% whereas the comparable public sector figure was then estimated between 15-20%.[36] 2017/18 rates in Gauteng were reported as 76.9% and 29.4% for the private and public health care sectors, respectively.[37]

With respect to FVM, another proposed reason for the difference is lack of awareness of or criteria for diagnosing this entity amongst state / NHLS pathologists. Fetal vascular malperfusion is a relatively new term that was introduced by the Amsterdam International consensus group of placental pathologists in 2014[38] and as such, pathologists who are not aware of these updates or see placentas infrequently may miss this entity. In addition, the use of templates and checklists in histopathology reporting is invaluable.[39] These not only aid the pathologist in making an accurate and clinically helpful diagnosis but may also aid in them effectively communicating such findings to the clinician for clinical utility and

application.[40] Within the time period of our study a reporting template for the placental histopathology reports was already in use at Lancet, whereas the NHLS laboratory based at CMJAH during that time had not yet routinely adopted a checklist for placental reports. This may further explain the lower FVM and VUE reporting in the NHLS data. An additional contributing factor, already alluded to, is the fact that the Lancet data was reported on by a single pathologist who has many years of experience in placental pathology and reports exclusively on placentas, compared to the NHLS reporting which is done by pathology 'generalists.' The specialist-generalist debate is an ongoing debate within clinical medicine [41] and has already been hinted at within the field of pathology.[42] Our study perhaps gives some evidence to argue a case for sub-specialisation within the field of pathology, where detection rates of different pathologies may then be higher. However, within the South African context, resources, training and the lack of a 'critical mass of pathologists' to support sub-specialisation within the field are barriers to this. A gross shortage of pathologists and need for increased training in Africa has already been established,[43] and where South Africa constitutes a 'concentration' of pathologists within Africa, we still have only 100 pathologists per 55 million people as of 2016,[44] of which the vast majority are practicing within the private health sector.[45]

The last significant placental pathology difference between the two sectors was the increased ascending infection in the NHLS data (37.6%). This is comparable to that found in the aforementioned South African placental study [9] where 34.5% of IUFD cases had placental evidence of acute chorioamnionitis. Risk factors for both clinically and histopathologically diagnosed acute chorioamnionitis are many. These include: prolonged rupture of membranes, prolonged labour, meconium passage, multiple vaginal examinations, epidural anaesthesia, existing genital tract infection, bacterial vaginosis, prematurity and foreign bodies such as a cervical cerclage.[46] A lower average gestational age in our NHLS data was established and the increased ascending infection in this population group may have contributed to prematurity. In a South African study based in Soweto the causes of stillbirths were found to be mostly attributed to maternal medical conditions (particularly hypertensive disorders), placental or fetal infections and pathological placental conditions. Of the fetal invasive infections, the most cultured bacterium was group B streptococcus.[24] Group B streptococci are also amongst the common bacterial causes of acute

chorioamnionitis,[47] and South Africa has a high incidence of group B streptococcal invasive disease.[48] Mothers are not routinely screened for vaginal group B streptococcus during pregnancy in the state health care system, whereas screening is more frequently performed in the private health care system (Dr Christopher Thomas, personal communication). This may also account for the higher percentage of ascending infection in the NHLS data. Numerous studies have already made compelling cases for the safety, affordability and need for group B streptococcal vaccination in pregnant mothers [24,48–50] and our study perhaps provides further evidence from a histopathological perspective.

One limitation of our study is that it only considers *submitted* placental specimens and is not a representation of all births. Furthermore, the data is representative of only one private laboratory and only hospitals that submit histopathology specimens to the NHLS CMJAH laboratory, which are predominantly academic hospitals. Thus, the data may not be truly representative of the burden of placental disease and its applicability to clinical practice across all medical facilities, especially primary and secondary care state facilities. An additional limitation regarding the privately submitted placentas is the cost to the patient. Patients on limited medical aids or who otherwise cannot afford the cost of submitting the placenta for histopathological examination will lead to a further decrease in submitted placental specimens from all private deliveries.

Nevertheless, a major strength of our study lies in that this is the first study in South Africa directly comparing data between state and private laboratories. Collaboration between these two entities is essential in South Africa's increasing progress towards achieving the Sustainable Development Goals (SDGs).

Our major recommendations from this study are threefold. Firstly, to clinicians and policymakers, it is advised that clear guidelines for submission of the placenta for histopathological examination are established in their personal practices or institutions. These should clearly lay out the fetal, maternal and neonatal indications. Placental histopathological findings will thus be of greater value in their informing current management of mother and/or neonate, as well as inform management of future pregnancies. In a litigious society, histopathological examination of the

placenta is invaluable [51] and further highlights the need for clear guidelines for submission of the placenta. Also, there is perhaps some evidence from our study to further motivate for the implementation of universal screening for prepartum group B streptococcal colonisation.

Secondly – to anatomical pathologists – awareness of these common placental pathological entities is of paramount importance. The placenta is a common specimen and the findings can have major clinical and/or legal implications. Placental pathology training workshops may serve to better equip pathologists in diagnosing placental pathology, and more focus on training at a registrar-level would be of value. Increasing the number of pathology registrar posts will also aid in addressing the shortage of pathologists and may also aid in pathologists pursuing sub-specialisations within pathology. Furthermore, important recommendations for the NHLS are to adopt a placental histopathology reporting template and to perform more extensive sampling of placental specimens to adequately detect key pathologies. Where resources may restrict this at the NHLS, carefully selecting placentas for more sampling based on the clinical history provided on the laboratory request forms (e.g. a patient with a poor obstetric history or a baby with low APGARs) may be an option.

Lastly, the authors recommend further collaboration in research between the state and private sectors. This study has illustrated the wealth of information available for research within the private laboratory sector, as well as its accessibility for researchers. There is not only a paucity of placental histopathological data within South Africa, but a great paucity in research comparing the two health systems that serve our country.

Conclusions

Histopathological examination of the placenta is an undervalued resource available to clinicians and policymakers. Apart from contributing to the understanding of the pathogenesis of different diseases, it invaluably contributes to the clinical management of mother, neonate, and future pregnancies. In a health care system divided by socioeconomic status and resources, understanding the differences in

maternal and neonatal pathology between these two health sectors is critical for informing clinical management and policymaking for maternal and neonatal wellbeing. Our study has not only provided insight into the differences in pathology between the two sectors, but the value of the placenta and the need for further private-state collaborative research.

Declaration. This study was conducted as partial requirement for MSR's MMed (Anatomical Pathology) degree.

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4. Appendices

4.1. Figure 1 – Key placental pathological diagnoses

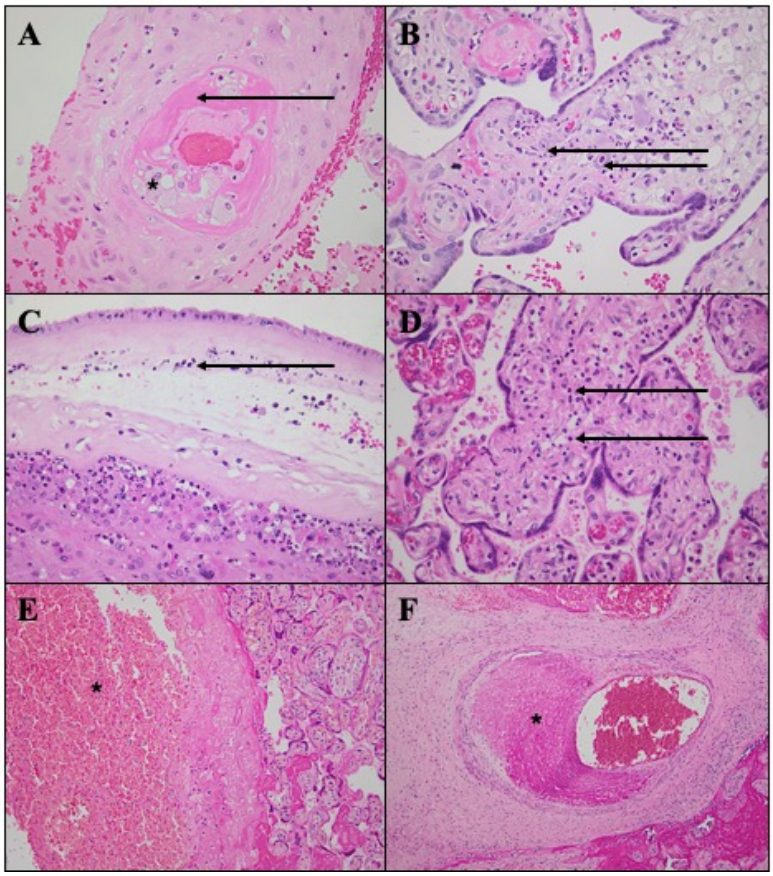

Figure 1. (A-D: Original magnification 400X; E: Original magnification 200X; F: Original magnification 100X). A: Fibrinoid necrosis (arrow) and atherosis (*) constituting maternal decidual vasculopathy in MVM; B: Villitis with Cytomegalovirus inclusions (arrows); C: Acute chorioamnionitis with neutrophils (arrow) present within the chorion; D: Numerous lymphocytes (arrows) within a villus seen in VUE; E: Retroplacental haemorrhage (*); F: Fibrin thrombus (*) in FVM.

4.2. Figure 2 – Flow diagram of inclusion/exclusion process

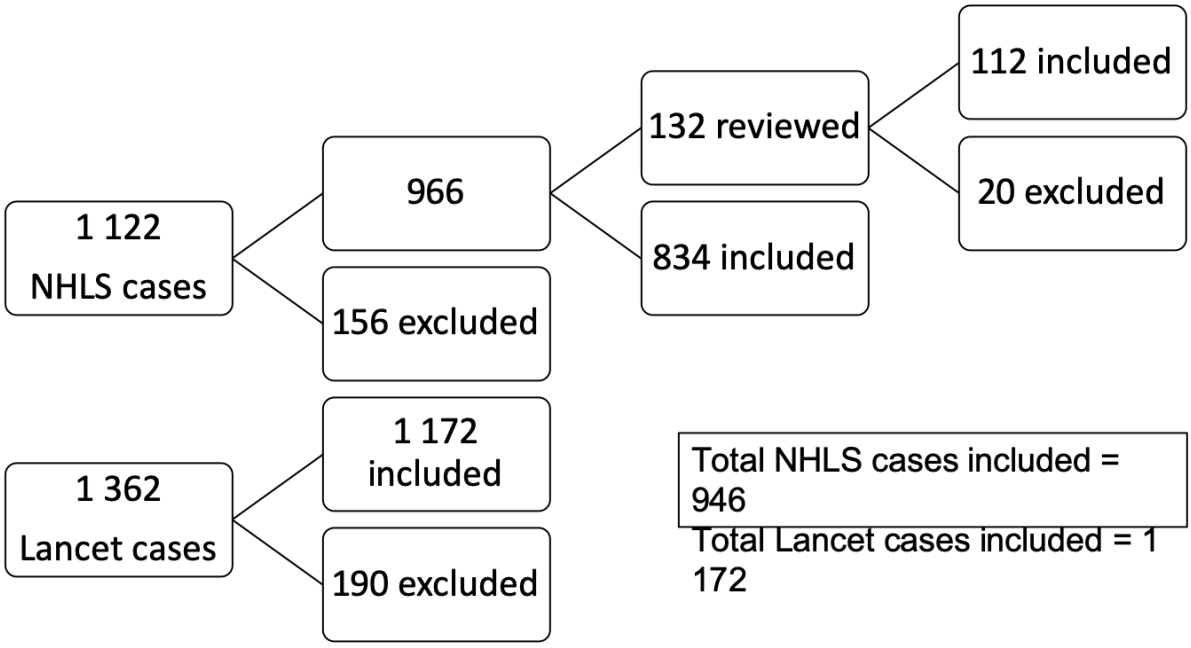

Figure 2. Flow diagram summarising the exclusion process and number of cases included from the initial data extracts from each laboratory

4.3. Research protocol

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

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DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: MMED (ANAT PATH)		
PART-TIME OR FULL-TIME		
FIRST REGISTERED FOR THIS DEGREE:	TERM: 1	YEAR: 2017
DEPARTMENT: ANATOMICAL PATHOLOGY		
TITLE OF PROPOSED RESEARCH: THE SPECTRUM OF PLACENTAL PATHOLOGY IN A STATE VS. PRIVATE LABORATORY PRACTICE IN GAUTENG, SA. IMPLICATIONS FOR PATIENT MANAGEMENT.		
CANDIDATE'S SIGNATURE:		DATE: 21/08/2018
SUPERVISOR 1 (NAME & SURNAME): PROF. COLLEEN WRIGHT		% Supervision 50%
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SUPERVISOR 3 (NAME & SURNAME):		% Supervision
SUPERVISOR'S QUALIFICATIONS		
SUPERVISOR'S ADDRESS / TEL / E-MAIL:		

SYNOPSIS OF RESEARCH (Brief summary of proposed research project; between 200-300 words only; with sub-headings: an introduction and justification for study, aim/s, proposed methodology and expected outcome/s)
[Use reverse side of this page if more space is required]

– INTRODUCTION + JUSTIFICATION ; AIMS

THIS IS A RETROSPECTIVE DESCRIPTIVE STUDY AIMED AT DESCRIBING THE SPECTRUM OF PLACENTAL PATHOLOGY ACROSS THE PUBLIC AND PRIVATE HEALTH SECTORS IN SOUTH AFRICA, AND SO ASCERTAIN RELEVANT IMPLICATIONS FOR THE MANAGEMENT OF ADVERSE PREGNANCY OUTCOMES, BOTH MATERNAL AND NEONATAL.

P.T.O

ETHICS PENDING: (Y) ETHICS APPROVED: (circle appropriate symbol)* Y		IF Y SUPPLY ETHICS CLEARANCE No:
*Please note human ethics clearance/waiver certificate or animal ethics certificate must be in the student's name		
As supervisor, I confirm that I have read the protocol which has been submitted for assessment.		
SIGNATURE OF SUPERVISOR/S:	.....	.....

SIGNATURE PG OFFICE STAFF	REGISTERED	STAMP
.....	YES X NO	21 AUG 2018

UNIVERSITY OF THE WITWATERSRAND
JOHANNESBURG

SYNOPSIS OF RESEARCH CONTINUED

THE PRIMARY MOTIVATION BEHIND THIS STUDY IS AT LEAST TWO-FOLD. FIRSTLY, IT SEEKS TO PROVIDE VALUABLE DATA TOWARDS ACHIEVING THE SUSTAINABLE DEVELOPMENT GOALS OF IMPROVED UNDER-FIVE CHILD MORTALITY AND MATERNAL MORTALITY IN SOUTH AFRICA. SECONDLY, IT WILL HELP HIGHLIGHT ANY DIFFERENCES IN PLACENTAL PATHOLOGY PROFILES ACROSS THE TWO HEALTH SECTORS AND SO BETTER INFORM ALLOCATION OF RESOURCES

PROPOSED METHODOLOGY

PLACENTAL HISTOPATHOLOGY RESULTS WILL BE COLLECTED FROM THE NHLS (AT CMJAH) AND LANCET (RICHMOND) LABORATORIES FOR THE PERIOD OF ONE CALENDAR YEAR (1 AUGUST 2017 – 31 JULY 2018). THE FINAL DIAGNOSIS OF EACH REPORT WILL BE CATEGORISED ACCORDING TO THE AMSTERDAM INTERNATIONAL CONSENSUS CRITERIA, AND THEN TABULATED BY WAY OF AN EXCEL SPREADSHEET. PATIENT AGE AND GESTATION – WHERE AVAILABLE – WILL ALSO BE RECORDED.

THE CATEGORICAL DATA WILL THEN BE REPRESENTED AS PROPORTIONS AND PERCENTAGES, AS WELL AS GRAPHICALLY. DESCRIPTIVE STATISTICAL ANALYSIS WILL ALSO BE PERFORMED FOR PATIENT AGE AND GESTATION AGAINST EACH DIAGNOSTIC CATEGORY.

EXPECTED OUTCOMES

DIFFERENCES ACROSS EACH SECTOR ARE EXPECTED, NAMELY AGE DISTRIBUTION AS WELL AS MAJORITY PATHOLOGY. UNDERPLACENTAL MALPERFUSION IS EXPECTED TO BE DOMINANT IN BOTH SECTORS, AND INFECTIONS MORE PREVALENT IN THE STATE SECTOR. DELIVERY AT EARLIER GESTATION (AVERAGE) IS EXPECTED TO BE HIGHER IN THE PRIVATE SECTOR.

2 May 2018/MP

1591

University of the Witwatersrand
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The spectrum of placental pathology in a state laboratory vs. a private laboratory practice in Gauteng, South Africa. Implications for patient management.

for the degree of a Master of Medicine (MMed) in the specialty of Anatomical Pathology

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Date: 6 June 2018

2. Introduction

The United Nations (UN) Millennium Development Goals (MDGs) was a commitment by 191 world states to 8 goals aimed at improving global health from 1990 to 2015 (1). In particular, goals 4 and 5 were aimed at reducing the under-five child mortality rate by two-thirds (2) and reducing the maternal mortality ratio by three-quarters whilst attaining universal access to reproductive health, respectively (3).

With respect to South Africa, whilst multiple sources have had somewhat conflicting data on the estimates of maternal and neonatal mortality in the country (4), Statistics South Africa (Stats SA) concluded the following regarding MDGs 4 and 5: significant progress in reducing child mortality was achieved, but this fell short of the two-thirds reduction goal; the maternal mortality ratio, too, fell short of the MDG target (5).

The world has now adopted the 2030 Agenda for Sustainable Development and its Sustainable Development Goals (SDGs) in September 2015, and whilst they are broader and have a more economic, social and environmental focus, they will undoubtedly build on any progress initially made towards achieving the MDGs in every country (33).

According to the World Health Organisation (WHO), South Africa (SA) had a maternal mortality ratio of 138/100 000 live births, and an under-five mortality rate of 40.5 per 1000 live births in 2015. The 2030 SDG targets are less than 70/100 000 live births and as low as 25/1000 live births, respectively. In addition, cessation of all preventable deaths of newborns and children under 5 years of age should be attained (7).

As a fetal organ the placenta provides invaluable insight into adverse pregnancy outcomes, both maternal and neonatal, as well as serves as a “highly pragmatic and effective means of saving on litigation payouts” in such outcomes (8).

Thus, histopathological examination of the placenta will impact on the maternal mortality ratio and under-five child mortality rate SDG targets by both better informing acute and long term newborn management in the case of an adverse outcome, as well as management of future pregnancies of mothers having suffered a pregnancy-related disease. These encompass vast clinical implications for prospective diagnosis, prevention and treatment of adverse pregnancy outcomes (9).

In addition, by providing insight into medicolegal claims for adverse pregnancy outcomes, and by having already aided in defining health policies and subsequent resource allocation (8), histopathological examination of the placenta, too, contributes towards the overall economic dimension of the SDGs (33).

In South Africa, the health sector comprises a private sector serving approximately 16% of the total population and a public sector serving the remaining 84%, and the former disproportionately contributes towards half of the country's total expenditure on healthcare (10). Whilst health outcome statistics are not always consistently reported across both sectors (10), both sectors nevertheless contribute towards achievement of the SDGs, both individually and collaboratively.

This study is thus aimed at describing the spectrum of placental pathology across the two different hospital sectors, comparing and analysing the data and drawing possible implications for patient management and achievement of the SDGs for South Africa.

To the knowledge of the authors, no such study, particularly comparing state and private sectors, has been performed in South Africa nor elsewhere globally.

In addition to the above, prior to understanding the pathology of the placenta, a working understanding of the anatomy of the placenta is required and will be briefly described.

The placenta comprises chorionic villi that arise from the chorion. These function to increase the surface area across which the fetal and maternal circulations communicate with one another. Maternal blood enters an area called the intervillous space, coming into contact with the chorionic villi, and thereby permitting exchange of nutrient material and gases. Once deoxygenated, this blood then leaves the intervillous space towards the decidua and thereafter enters into the endometrial veins and the maternal circulatory system (18).

Fetal blood, in contrast, enters the placenta via the umbilical arteries which then branch into multiple chorionic arteries. These further divide as they enter the chorionic villi where they form a complex capillary system that then communicates with the maternal blood in the intervillous space via the vascular-syncytial membrane. Oxygenated blood within these villous capillary beds then returns to the foetus via the umbilical vein and enters the fetal circulatory system (18).

Two additional anatomical structures within the placental that are important to mention are placental septae and anchoring/stem villi. The placental septae are extensions of the decidua basalis that project into the intervillous space. Following delivery, their former positions are what delineate the maternal surface into approximately 20 irregular segments of placenta tissue termed cotyledons. Anchoring/stem villi are chorionic villi that arise from the chorionic plate and attach to the decidua basalis to form anchorage points (18,19).

Thus, the fetal surface consists primarily of the chorionic plate which is surfaced by the amnion, and the maternal surface consists primarily of the decidua basalis which is continuous with the endometrium. The myometrium forms an outer boundary to the decidua basalis and is only continuous with it in pathological placental implantation states (18,19).

3. Aim and study objectives

The aim of this study will be to describe and compare the spectrum of placental pathology across the South African public sector – by way of the National Health Laboratory Service (NHLS) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)) – and private sector by way of Lancet Laboratories (Pty) LTD.

Thus, the primary objectives include:

- Record/capture the number of placental reports from each sector for the specified time period (see below).
- Categorise the diagnosis of each report according to the Amsterdam international consensus criteria.
- Calculate the percentage of each diagnostic category against the total number of reports across each health sector.
- Correlate the diagnostic categories with patient age (and gestational age, if available).
- Tabulate and graphically represent the findings of the above objectives.

As a secondary aim, the findings will be used to ascertain further implications for management of adverse pregnancy outcomes over and above that highlighted in the literature, as well as identify those more specific to South Africa's health setting (public and private health sectors).

4. Methods

This will be an observational study, namely, a retrospective descriptive study, wherein the prevalence or incidence of various placental pathologies will be collected from the two different health sectors/laboratories.

This will be ascertained from the collection and perusal of placental pathology reports from CMJAH via the NHLS TrakCare database and Lancet's database for the time period 1 August 2017 to 31 July 2018 (one calendar year). The estimated number of cases for the NHLS and Lancet for the one year period are 700 and 1000, respectively.

The findings/conclusion/diagnosis of each individual report will then be categorised according to the Amsterdam international consensus criteria for placental diagnosis (20).

In addition, parameters including age and gestation – where available - will also be recorded.

Data will be recorded in single table format using Microsoft Excel. The table layout will be as follows:

Table 1: Tabulation of data collected from placental pathology reports at CMJAH (NHLS) and Lancet Laboratories

Case number	Health sector	Patient's age	Gestation	Report diagnosis	Amsterdam diagnostic category

Below is the list of the categories from the Amsterdam international consensus criteria for placental diagnosis:

- **Maternal Vascular Malperfusion (of the placental bed)**
- **Fetal Vascular Malperfusion**
- Placental Insufficiency
- Placental Abruption
- Chorioamnionic Haemosiderosis (chronic/venous abruption)
- Subacute Fetal Hypoxia with Compensatory Response
- Ascending Infection – Chorioamnionitis
- Haematogenous Infection
- **Delayed Villous Maturation**
- **Villitis of Unknown Aetiology**
- Immunological Damage
- Small Placenta, NOS
- Within Normal Limits/No Pathological Diagnosis

5. Data analysis

Once tabulated, the categorical data will be reported as proportions and percentages across each of the different health sectors and represented graphically. This includes the final diagnostic category – as per the Amsterdam criteria – for each case.

Descriptive statistical analysis will be performed for both the patients' age and gestation against the final diagnostic category.

In addition, the percentages of each diagnostic category across the two health sectors will also be analysed for any statistical significance/difference in prevalence.

6. Ethics

Ethics issues anticipated and explained:

1. As data will be collected from both the NHLS and Lancet laboratories, there will be private collaboration.

   Nevertheless, Lancet already has an agreement with Wits University through the Wits Consortium with respect to access of private records for research purposes, and does not lay claim to any funding for assisting with research, nor for publication of the research material.

   Credit therefore will go to the authors affiliated with Wits University, where Prof. Wright will act in her capacity as an Honorary Wits Professor, and not a Lancet employee.

   However, in the case of publication, Lancet will expect affiliation with Prof. Wright on the publication or for any congress presentation purely for recognition, and not for monetary or other purposes.

   A signed form from Lancet management accompanies this proposal, confirming permission to view private reports for research intent, as well as confirming the above claims. See appendix 1 attached.

2. This study is not an audit, and as such, the slides on which the diagnosis of each report is based will not be reviewed, thus, there will be no altering of reports nor diagnoses in either sector (NHLS & Lancet).

7. Timing

	2018			2019		
	Apr-Jul	Aug	Aug-Dec	Jan-Mar	Apr-Oct	Nov-Dec
Literature review						
Preparing protocol						

Protocol assessment						
Ethics application						
Collecting data						
Data analysis						
Writing up – thesis/paper						
Submission						

8. Funding

This study is a retrospective descriptive study, and as such, no funding is required.

9. Problems

No immediate problems are anticipated.

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13. Appendices

Appendix 2 – Data Use Agreement

Lancet Laboratories and MICHAEL SAVAGE-REID (WITS UNIVERSITY) ("Recipient"), in order to make certain LANCET data ("the Data") available for purposes of research, public health, or health care operations hereby agree as follows:

1.	The Recipient agrees to use or disclose the Data only for the following purpose, and for no other purpose, except as authorized (describe, including any applicable grant or protocol identifier, if any):
2.	The Recipient agrees to use appropriate safeguards to prevent any use or disclosure of the data other than as specified in the Agreement.
3.	The Recipient will report to the Lancet Publications Committee any violation of this Agreement. The Recipient will ensure that any agents, including any subcontractors, to whom it provides the Data, agrees to the same restrictions and conditions that apply to the Recipient.
4.	The Recipient will collaborate with one or more LANCET investigators in analysing and publishing the data
5.	Authors should avoid conflicts of interest; where a relationship that presents an actual or potential conflict cannot reasonably be avoided, it should be disclosed.
6.	Approved manuscripts must use the following statement in the Acknowledgements section: "This manuscript has received the approval of the LANCET Publications Committee based on a review of its scientific content and data interpretation."
7.	Abstracts, draft manuscripts and final manuscript versions must be submitted to the Lancet Publications Committee prior to submission in the case of abstracts and drafts and a final copy on publication.

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06 August 2018

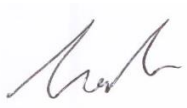
To whom it may concern,

This letter serves to confirm Lancet Laboratories (PTY) Ltd (referred to as "Lancet Laboratories") will make available anonymous unlinked pathology records for Dr MJ Savage-Reid's research study, entitled 'The spectrum of placental pathology in a state laboratory vs. a private laboratory practice in Gauteng, South Africa.

This data is made available through the signed Lancet 'Data Use Agreement' form and the candidate will have one year exclusive use of this data for publication and presentation purposes on condition that Lancet is appropriately acknowledged. This acknowledgement is for recognition and not for monetary or any other intent. Lancet lays no claim to any funding for assisting with research, nor for publication of the research material. In the instance that there are publications or any presentation of this research, Lancet Laboratories will expect to be listed as one of Prof. C Wright's centres of affiliation.

Kindly accept this letter as confirmation of the above, and please don't hesitate to contact me for any further information or confirmation.

Yours sincerely



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Professor MJ Hale MBChB (Rhodesia) FCPath (SA). LRCP, LRCS, LRCP&S (Edinburgh & Glasgow)
Professor & Head: Division of Anatomical Pathology.

5 June, 2018

Human Research Ethics Committee (Medical)
University of the Witwatersrand
Johannesburg
2000

Re: Consent for access to NHLS database

This letter serves to confirm that the Department of Anatomical Pathology at the University of the Witwatersrand and NHLS is happy to grant Dr Michael John Savage-Reid access to patient reports on the TrakCare system for his study entitled "The spectrum of placental pathology in a state laboratory vs. a private laboratory practice in Gauteng, South Africa. Implications for patient management.".

The Department of Anatomical Pathology is happy for the above research to be carried out on archived material and records in the Division of Anatomical Pathology.

With best wishes.

Yours sincerely,

Professor MJ Hale
Head: Department of Anatomical Pathology

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4.4. Ethics certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Michael Savage-Reid

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180827

NAME: (Principal Investigator)	Dr Michael Savage-Reid
DEPARTMENT:	Anatomical Pathology National Health Laboratory Service Charlotte Maxeke Johannesburg Academic Hospital Lancet Laboratories (Pty) Ltd
PROJECT TITLE:	The spectrum of placental pathology in a state laboratory vs a private laboratory practice in Gauteng, South Africa. Implications for patient management
DATE CONSIDERED:	31/08/2018
DECISION:	Approved Unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Colleen Wright and Dr Reubina Wadee
APPROVED BY:	Doctor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/11/2018

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

DECLARATION OF INVESTIGATORS

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

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1. INTRODUCTORY CHAPTER

1.1. General introduction / Background

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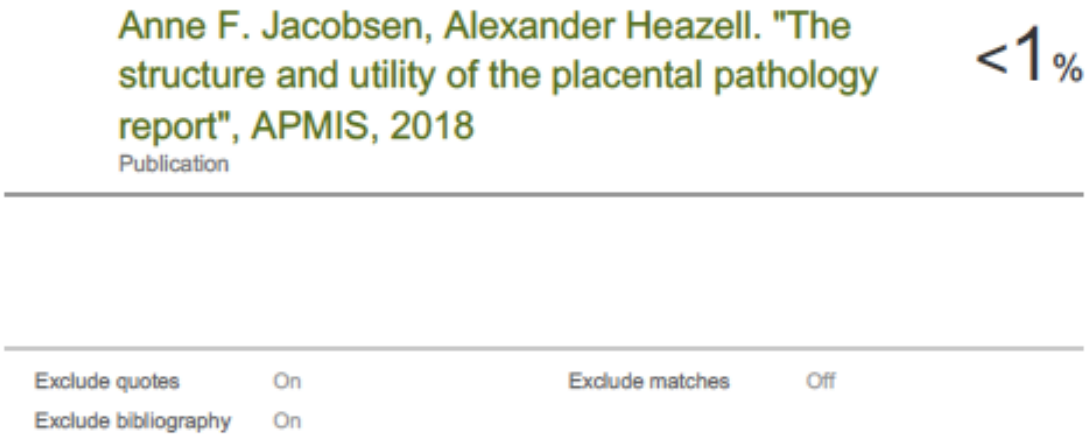

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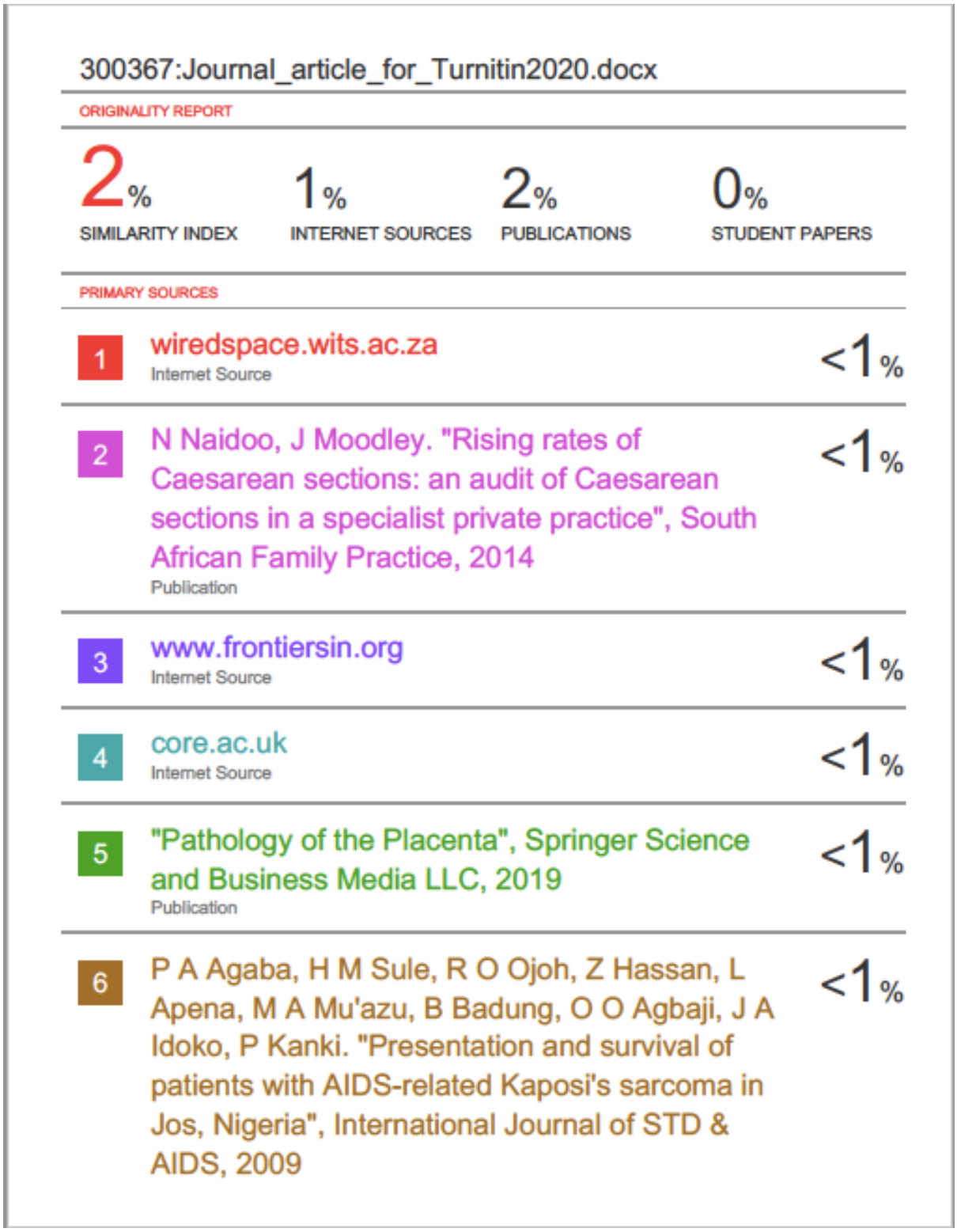

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SENATE PLAGIARISM POLICY: APPENDIX ONE

I MICHAEL JOHN SAVAGE-REID (Student number: 300367) am a student registered for the degree of MASTER OF MEDICINE (MMED) IN THE SPECIALTY OF ANATOMICAL PATHOLOGY (ANAT PATH) in the academic year 2020.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
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