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A fifteen-year retrospective review of surgically managed ovarian masses in children at Charlotte Maxeke Johannesburg and Chris Hani Baragwanath Academic Hospitals

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A fifteen-year retrospective review of surgically managed ovarian masses in children at Charlotte

Maxeke Johannesburg and Chris Hani Baragwanath Academic Hospitals

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the Master of Medicine (MMed) in Paediatric Surgery degree. Written in the submissible format according to JPSO guidelines.

Johannesburg, 2024

DECLARATION

I, Nkhensani Mashaba, declare that this Research Report is my original work. It is being submitted for the Master of Medicine (MMed) in Paediatric Surgery degree at the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination at any other university previously.



Signed on the 4th day of July 2024 in Johannesburg

DEDICATION

First and foremost, I am profoundly grateful to my beloved grandmother, (Maria Masingi). Her wisdom, patience, and endless encouragement have been a guiding light throughout my academic pursuits. Her unwavering belief in my abilities has been a source of strength.

To my mother (Carol Masingi), my sons (Molatelo and Motumi) and my helper (Tlou Manala)—I offer my deepest appreciation. Their unwavering support has been a constant source of strength and inspiration. I am profoundly grateful for their presence in my life and their role in my academic achievements.

PRESENTATIONS

1. South African Association of Paediatric Surgeons (SAAPS), Cape Town, May 2023, 10 minutes oral presentation
2. The International Society of Paediatric Oncology (SIOP Africa), Johannesburg, June 2024, 10 minutes oral presentation

ABSTRACT

Background and objectives

Existing literature on ovarian masses necessitating intervention in children by pediatric surgeons and gynecologists in Low- and Middle-Income Countries is sparse. Therefore, this study seeks to assess the range of ovarian masses presenting to these two specialties and to explore variations in management.

Methods

A retrospective review of surgically biopsied or excised ovarian masses at two academic hospitals in Johannesburg.

Results

We identified 288 patients, six with bilateral disease hence 294 ovarian masses. Mean age of 13.3 years (SD ± 5.1). The most common presentation was abdominal pain 149/288 (52%); 117 patients (41%) were from pediatric surgery and 171 (59.4%) from gynecology departments. There were 127/288 (44.1%) non-neoplastic and 161/288 (56%) neoplastic lesions, of which 110/161 (68.3%) were benign and 51/161 (32%) malignant. The neoplastic lesions consisted of 107/161 (67%) Germ cells, 28/161 (17.4%) Surface epithelial-stromal and 26/161 (16.1%) Sex cord-stromal tumors. Ovarian-sparing surgery was done in 56/288 (19.4%) patients, 22/117 (19 %) in pediatric surgery, and 34/171 (20%) in gynecology. Laparoscopy was done in 57/288 (20%) patients, 24/117 (21%) in pediatric surgery,and 19/171 (19.3%) in gynecology. Malignancy survival was 86.3%.

Conclusion

The findings underscore the importance of considering ovarian lesions in girls with abdominal pain. With most masses being benign, preserving fertility, preferably via minimally invasive surgery, is crucial.

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I would like to thank the Research Unit of the Department of Paediatric Surgery at the University of the Witwatersrand for their input throughout the study. I am grateful to the Department of Gynae-Oncology at Christ Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital for allowing me to include their department in this research.

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LIST OF ABBREVIATIONS

BEP: Cisplatin-etoposide-bleomycin regimen

CDW: Central Data Warehouse

CHBAH: Departments at Chris Hani Baragwanath Academic Hospital

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

COG: Children Oncology Group

DSD: Disorders of sexual differentiation

FIGO: International Federation of Gynecology and Obstetrics

JEB: Carboplatin-etoposide-bleomycin regimen

NHLS: National Health Laboratory Service

PCOS: Polycystic ovarian syndrome

SD: Standard deviation

INTRODUCTION

Ovarian lesions are the most common genital tract lesions in female children, making up to 60 – 70% of gynecologic lesions, and are mostly benign [1]. They are also the least common tumors in children, accounting for around 1% of all tumors with an incidence of 2.6 per 100 000 girls per year, and only 10% of these are malignant [1–3]. Diseases of the ovary are divided into two categories: non-neoplastic and neoplastic lesions. Non-neoplastic diseases includes functional cysts, inflammatory and non-inflammatory lesions. Neoplastic lesions include benign, borderline, and malignant tumors [1,4,5]

The incidence, clinical presentation, and histology of ovarian lesions in children differ from the adult population [6]. Children may present with non-specific symptoms, ranging from abdominal pain to a distended abdomen. Some children may be asymptomatic, with an incidental finding of an abdominal mass [6]. Little is known about pediatric ovarian masses in developing countries, where late presentation, unavailability of facilities, and low index of suspicion lead to delayed diagnosis, advanced presentation, disease progression, and complications of the disease, leading to a reduced survival rate [7,8].

Historically, the management of ovarian masses in children has been through surgical removal; however, the current advanced radiologic imaging and identification of tumor markers allow for more conservative management. Unlike in adults, where the management of ovarian tumors is oophorectomy, the management approach in children aims to preserve ovarian tissue to spare gonadal function and fertility [9–11].

With little research and little known about pediatric ovarian lesions, their diagnosis, and management in South Africa and Africa as a whole, this study aimed to describe the profile and surgical management of ovarian masses in children 18 years and younger at two academic hospitals in Johannesburg from 1 January 2007 to 31 March 2022, in preparation to standardize surgical management at a national level.

MATERIALS AND METHODS

The study was a retrospective review of surgically biopsied or excised ovarian masses. It was conducted in the Pediatric Surgery and Gynecology Departments at Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). CHBAH is a 2 680-bed central academic hospital, and CMJAH is a 1 200-bed central academic hospital, both affiliated with the University of the Witwatersrand. The study was approved by the University of the Witwatersrand Human Research Ethics Committee (Medical) (M220536). It was a record review of children 18 years and younger who presented and were surgically managed for ovarian masses at CHBAH and CMJAH between 01 January 2007 to 31 March 2022. Patients were excluded if they had no surgical intervention, were treated but not operated on at the two study hospitals, if the specimen were pregnancy-related specimens or involved disorders of sexual differentiation (DSD), and those cases with missing records.

The following data were collected regarding the patient profile: age, clinical presentation (presenting complaint, signs of precocious puberty and associated syndromes), investigations (radiological and tumor markers), histo-pathological diagnosis, and 5-year survival outcome of malignant lesions. The surgical management data included: the treating surgical department, type of surgical intervention and approach, intra-operative staging, and chemotherapy.

The data were collected by one author (NM). Pathology reports were retrieved from the Central Data Warehouse (CDW) and the National Health Laboratory Service (NHLS) databases. The pathology reports were reviewed to compile a list of patients that were reviewed for inclusion in the study. Additional data were obtained from patient files, the pediatric surgical oncology database, and the hospitals' Picture Archiving and Communication System.

Data were analyzed using STATA version 14 (StataCorp. 2015. Stata Statistical Software: Release *14*. College Station, TX: StataCorp LP). Age was described using means and standard deviations. The remainder of the data were described as frequencies and percentages where applicable.

RESULTS

The sample realization is shown in Figure 1. Of the 288 patients, 117 (41%) presented to pediatric surgery and 171 (59.4%) to gynecology. Pediatric surgery treated patients ranging from 0 to 16 years of age, while gynecology treated patients between the ages of 9 and 18 years. The overall mean age of the cohort was 13.3 years (SD ± 5.1). Specifically, the mean age in pediatric surgery was 12.5 years (SD ± 5.1), whereas in gynecology, the mean age was 13.4 years (SD ± 5.1). The mean age (SD) for non-neoplastic lesions was 13.4 (± 5.1), 13.4 (± 5.1) for neoplastic benign, and 13.4 (± 5.1) for malignant disease. Fifty-one (18%) had malignant disease; of the patients with malignant disease, 14 (28%) were ten years and below, and 37 (73%) were eleven years and above. Table 1 shows a summary of the patient's clinical presentation. Two patients had Peutz-Jeghers syndrome, and four had Polycystic ovarian syndrome (PCOS). Ten patients had associated precocious puberty.

Ultrasound imaging done in 212 (74%) patients, reported 199 (94%) to have unilateral disease and 13 (6.1%) bilateral disease. CT scan was done in 121 (42.0%) patients and only 11 (7.4%) of the 13 initially reported by sonar to have bilateral disease had bilateral disease. Tables 2 and 3 show radiological investigations and malignant tumors with associated tumor markers respectively. The surgical intervention, surgical approach, and histopathological diagnosis are shown in Tables 4 and 5.

Of the 51 patients presenting with malignant tumors, pediatric surgery had 38/51 patients. A documented staging report was found in 18/38 patients. Pediatric Surgery used the Children Oncology Group (COG) staging system. Two patents were COG stage 1, 3 were stage 2, 9 stage 3, and 4 stage 4. Out of the 38 patients, 21 received chemotherapy of which 9 received a neo-adjuvant carboplatin-etoposide-bleomycin regimen (JEB), 8 adjuvant therapy JEB, and 4 received cisplatin-etoposide-bleomycin regimen (BEP).

Gynecology had 13/51 patients with malignant lesions, a documented staging report was found in 13/13 patients. Gynecology used the International Federation of Gynecology and Obstetrics (FIGO) staging system. Seven were FIGO stage 1, 4 stage 2, and 2 were stage 4. The 2 patients with stage 4 disease presented critically ill and demised without getting chemotherapy.

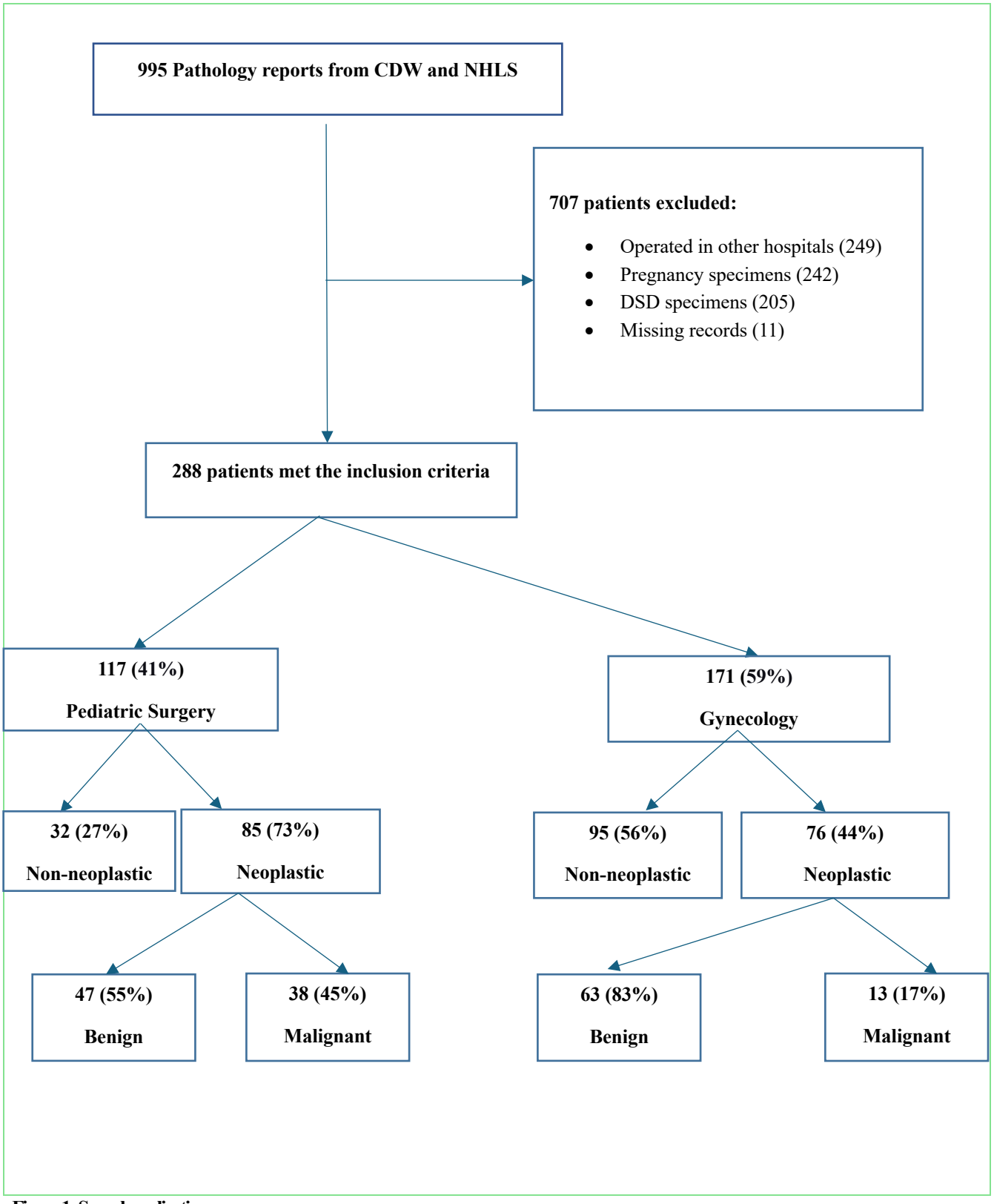


Figure 1: Sample realization

CDW (Central Data Warehouse)

NHLS (National Health Laboratory Service)

DSD (Disorders of Sexual Differentiation)

Table 1: Clinical presentation

Clinical presentation (N=288)	*Presenting Symptom*	*N*	*%*	*Lesion*	*N*	*%*
Main presenting complaint	Abdominal pain	149	52	Non- neoplastic	98	66
				Neoplastic benign	30	20
				Malignant	21	14
	Abdominal mass	135	47	Non- neoplastic	27	20
				Neoplastic benign	78	58
				Malignant	30	22
	Other	4	1	Non neoplastic	2	50
				Neoplastic benign	2	50
				Malignant	0	0
Associations N=16	Precocious Puberty	10	4	Non-neoplastic	0	0
				Neoplastic benign	0	0
				Malignant	10	100
	Peutz-Jeghers syndrome	2	1	Non-neoplastic	0	0
				Neoplastic benign	0	0
				Malignant	2	100
	Polycystic ovarian syndrome	4	1.4	Non-neoplastic	3	75
				Neoplastic benign	1	25
				Malignant	0	0

Table 2: Radiological investigations

Radiological investigation	*Type of lesion*	*Cystic only*		*Solid only*		*Mixed*	
		N	%	N	%	N	%
U/S N=212	Non neoplastic	63	61	22	21	19	18
	Neoplastic benign	25	32	5	6	49	62
	Malignant	3	10	8	28	18	62
CT N=121	Non neoplastic	10	37	9	33	8	30
	Neoplastic benign	14	24	3	5	42	71
	Malignant	3	9	8	23	24	68

The 5-year survival analysis revealed no mortality among patients with non-neoplastic and neoplastic benign lesions, and there was no loss to follow-up in the malignant cohort. Seven (14%) of the 51 patients with malignant lesions demised and hence the overall survival rate in the malignant cohort was 44/51 (86%). Five deaths were from Pediatric Surgery, and two were from Gynecology. In pediatric surgical patients, 1 patient with advanced yolk sac tumor died ten days post-surgery from overwhelming sepsis secondary to necrotic bowel post-surgery, 2 deaths were from neutropenic sepsis post-chemotherapy in patients with yolk sac tumors and 2 deaths were from patients diagnosed with advanced dysgerminoma and Sertoli Leydig cell tumor with lung metastasis. The 2 patients from Gynecology who demised had stage 4 yolk sac tumors and mesothelioma respectively.

Table 3: Malignant Tumors and associated markers

Type of malignant tumor N=51	**Total number of patients diagnosed**	**AFP**	**β-HCG**	**CA 125**
		Number of patients positive/ tested	**Number of patients positive/ tested.**	**Number of patients positive/ tested.**
Germ cell tumors				
Yolk sac tumor	15	15/15 (100%)	5/11(46%)	3/3 (100%)
Dysgerminoma	7	0/5 (0%)	6/7 (86%)	3/4 (75%)
Choriocarcinoma	2	0/2 (0%)	2/2 (100%)	0%
Immature teratoma	2	2/2 (100%)	0/2 (0%)	0/2 (0%)
Mixed germ cell tumor (Embryonal and yolk sac)	5	5/5 (100%)	3/5 (60%)	1/3 (75%)
Sex Cord–Stromal Tumors				
Granulosa cell tumors	10	0/6 (0%)	0/3 (0%)	3/5 (60%)
Sex cord stromal tumor with annular tubules	2	2/2 (100%)	0/2 (0%)	1/2 (50%)
Sertoli-Leydig cell tumor	6	1/5 (20%)	1/5 (20%)	4/6 (67%)
Epithelial-Stromal Tumors				
High grade epithelioid	1	0	0/1 (0)	1/1 (100%)
Other (Mesothelioma)	1	1/1 (100%)	1/1 (100%)	1/1(100%)

Table 4: Surgical intervention and approach

Open Surgery N=224 (78%)		Benign		Malignant	
		N	%	N	%
Pediatric Surgery N=91	Oophorectomy	41	77	38	100
	Ovarian sparing	12	23	0	
Gynecology N=133	Oophorectomy	99	81	11	100
	Ovarian sparing	23	19	0	0
Minimal Invasive Surgery (MIS) N=57 (20%)					
Pediatric Surgery N=24	Oophorectomy	14	58	0	0
	Ovarian sparing	10	42	0	0
Gynecology N=33	Oophorectomy	20	65	2	100
	Ovarian sparing	11	35	0	0
Unspecified surgical approach N=7 (2%)					
Pediatric Surgery N=2	Oophorectomy	2	100	0	0
	Ovarian sparing	0	0	0	0
Gynecology N= 5	Oophorectomy	5	100	0	0
	Ovarian sparing	0	0	0	0

Table 5: Histo-pathological diagnosis

Class of lesion N=288	Type of lesion	Pediatric surgery		Gynecology	
Non-neoplastic N=127		**N=32**	**%**	**N=95**	**%**
	Follicular cyst of ovary	11	34	8	8
	Corpus luteum cyst	6	19	31	33
	Other unspecified ovarian cysts (simple cyst)*	8	25	25	26
	Pelvic inflammatory masses	3	9	14	15
	Torsion ovary	4	13	17	18
Neoplastic benign N=110		**N=47**	**%**	**N=63**	**%**
	Surface epithelial–stromal tumors	7	15	20	32
	Sex cord–stromal tumors	4	9	3	5
	Germ cell tumors**	36	76	40	63
Neoplastic malignant N=51	**Surface epithelial–stromal tumors N=1**	**N=0**	**%**	**N=1**	**%**
	• High grade epithelioid	0	0	1	100
	Sex cord–stromal tumors N=18	**N=9**	**%**	**N=9**	**%**
	• Granulosa cell tumors (adult and juvenile)	4	45	6	67
	• Sertoli-Leydig stromal tumors***	3	33	3	33
	• Sex cord stromal tumor with annular tubules***	2	22	0	0
	Germ cell tumors N=31	**N=29**	**%**	**N=2**	**%**
	• Yolk sac tumors	14	48	1	50
	• Dysgerminomas	6	21	1	50
	• Immature teratomas	2	7	0	0
	• Mixed germ cell tumors	5	17	0	0
	• Nongestational choriocarcinoma	2	7	0	0
	Miscellaneous tumors N=1	**N=0**	**%**	**N=1**	**%**
	• Mesothelioma	0	0	1	100

* *Three patients with unspecified cysts had polycystic ovarian syndrome*

** *One patient with Mature cystic teratoma had polycystic ovarian syndrome*

*** *Two patients with sex cord stromal tumors had Peutz-Jeghers syndrome*

DISCUSSION

In this study, 288 cases were operated in 15 years, surpassing the expectations set by the authors and findings reported in other African literature and high-income countries. For instance, in South-Western Nigeria, only 24 cases were documented over 22.5 years [12], while Tunisia reported 98 cases in 15 years [13], and Australia recorded 244 cases over 19 years [14]. However, contrasting figures were observed in Shanghai, China, with 521 cases documented over 9 years [4], and in Texas, where 752 cases were reported over 10 years [15]. The variance between the findings of this study and those of the Shanghai study might be attributed to differences in population size, while Texas's higher case count could be linked to a more robust record-keeping system. These disparities highlight the importance of considering regional factors and healthcare infrastructure when interpreting and comparing research findings.

Children diagnosed with ovarian lesions may seek treatment from either pediatric surgery or gynecology departments, leading to potentially differing management approaches. In the hospitals studied, the majority of patients 171/288 (59%) were seen by the gynecology department. This contrasts with findings from a study by Xac et al., where 68.3% of patients were seen by pediatric surgeons [15]. The variation in departmental presentations can be attributed to several factors. Before COVID-19, the pediatric surgery department at CHBAH had an age limit of ten years, which later increased to 14 due to bed shortages in adult wards. Additionally, it's possible that in Johannesburg, there's a prevailing assumption among clinicians that gynecologists exclusively manage ovarian pathology. In some cases, 4/288 (1%) patients presented to general surgical departments with symptoms suggestive of bowel obstruction or appendicitis, prompting intra-operative involvement of gynecologists for management.

Non-neoplastic and benign neoplastic lesions are more prevalent among pediatric patients than malignant ones, according to literature [1], This study also observed that non-neoplastic and benign neoplastic lesions are the most common ovarian lesions in children. It further noted that the risk of malignancy rises with age, with the majority of patients diagnosed with malignancy being older than 10 years, consistent with findings from a Nigerian study [6].

Contrasting observations exist; in Tennessee, USA, a higher risk of malignancy was reported among younger patients [16], whereas Zhang et al. [4] found no variation in age distribution. In low-to-middle-income countries, a low index of suspicion and delayed referrals may contribute to later presentations [7].

A review conducted by Heo et al. [6], concluded that clinical manifestations in children are generally nonspecific, but frequently include abdominal pain, abdominal distension, and the presence of a palpable mass. This aligns with our study's findings, where abdominal pain emerged as the most prevalent symptom 149/288 (52%). Patients with non-neoplastic lesions predominantly presented with pain, while those with neoplastic benign and malignant lesions commonly exhibited an abdominal mass. Notably, Zhang et al. [4] reported that only 6% of patients with malignant lesions presented with a palpable mass. However, in our study, 135 patients exhibited a palpable abdominal mass. This discrepancy may be attributed to the presence of more advanced disease in our study cohort compared to that reported by Zhang et al.

Precocious puberty and its related syndromes were uncommon in this study, consistent with findings from other research [14,17]. Patients diagnosed with sex cord-stromal tumors may exhibit precocious puberty, as evidenced by the ten cases in our study, all of which involved sex cord-stromal tumors (specifically granulosa cell tumors). Additionally, two patients (1%) diagnosed with Peutz-Jeghers syndrome in our study presented with sex cord-stromal tumors (one Leydig cell tumor and one sex cord-stromal tumor with annular tubules), a linkage extensively documented in the literature [18–20]. Al Harbi et al. reported a 36% association between Peutz-Jeghers syndrome and sex cord-stromal tumors with annular tubules [21].

While some studies hypothesized a potential link between PCOS and ovarian cancer due to increased androgen exposure [22]; others found no association [23,24]. Our study did not find any correlation between PCOS and ovarian cancer; among the four patients with PCOS, three had unspecified simple cysts, and one had a cystic ovarian teratoma.

Ultrasound is utilized to characterize masses and assess for malignancy. Manegold-Brauer et al. noted a low specificity and sensitivity of ultrasound in children [25]; however, How et al. found ultrasound to be moderately effective in detecting malignancy [14]. According to Heo et al. [6], ultrasound, CT, and MRI can aid in distinguishing between benign and malignant tumors, with radiological findings guiding treatment decisions. In our study, ultrasound was conducted on 212 out of 288 patients (74%), revealing that non-neoplastic lesions were predominantly cystic, neoplastic benign lesions exhibited a mixed (cystic and solid) composition, and malignant lesions appeared solid or mixed. These findings align with existing literature [6] and confirmed on CT. Ultrasound detected bilateral disease in 13 patients, yet only 11 were confirmed on CT scans. Intraoperatively, only 5 of these cases were pathologically confirmed. Both ultrasound and CT scans facilitated diagnosis and informed potential treatment modalities for patients in our study.

Tumor markers play a vital role in screening, diagnosing, prognosticating, and monitoring treatment [26]. When combined with age, they can offer valuable diagnostic insights [27] and aid in providing a differential diagnosis [6]. However, in this study, not all patients underwent tumor marker testing due to the inclusion of emergency cases requiring immediate surgical exploration before further investigations. Nonetheless, for those tested, tumor markers assisted in formulating a differential diagnosis and guiding management decisions. Additionally, these markers confirmed that certain ovarian tumors can exhibit atypical hormonal activity, as evidenced by the ten patients with granulosa cell tumors who presented with associated precocious puberty.

In this study, follicular cysts of the ovary were the most prevalent non-neoplastic lesions among patients treated by pediatric surgeons, contrasting with corpus luteal cysts, simple cysts, and pelvic inflammatory masses more frequently observed in gynecology patients. Mature cystic teratoma emerged as the most common benign neoplastic lesion in both departments, aligning with findings from studies conducted in Nigeria [12], Tunisia [13], and Texas [15].

Germ cell tumors surpassed Sex cord and Surface epithelial-stromal tumors in prevalence across both departments, although older patients treated by gynecologists exhibited a higher incidence of Surface epithelial-stromal tumors compared to those seen by pediatric surgeons. Yolk cell tumor and dysgerminoma were the most frequent malignant lesions among patients aged ten and younger, differing from reports in other studies; Burkitt's lymphoma in Nigeria [12], juvenile granulosa cell tumors in Tunisia [13], and mixed germ cell tumors in Texas [15]. Sertoli-Leydig cell tumors were predominantly observed in patients older than 10 years.

The preferred approach for patients with benign lesions and normal serum tumor markers, or when the diagnosis is uncertain, is laparoscopy [6]. This minimally invasive technique is known to reduce morbidity, postoperative complications, pain, hospital stay duration, and total hospital costs [11]. However, in our study, laparoscopy was performed on only 57 out of 288 patients (20%), with 24 out of 117 (21%) in pediatric surgery and 33 out of 171 (19%) in gynecology. The low utilization rate may be attributed to factors such as limitations in funding for laparoscopic equipment, the hierarchical structure of surgical care, and the expertise required for laparoscopic procedures, as noted by Choy et al. [28]. All patients who underwent minimally invasive surgery (MIS) in pediatric surgery had benign diseases, while those with suspected malignant lesions underwent laparotomy.

Two patients from gynecology, both with Juvenile granulosa and adult granulosa cell tumor FIGO 1A, underwent MIS as they required emergency explorations before further investigations. However, for malignant diseases, the gold standard is complete removal without rupture of the malignant lesion, preferably through laparotomy. Zhang et al [4] reported that as many as 82% of their patients underwent laparoscopic surgery. Their study involved patients aged 9 to 19 years, while ours included patients aged 0 to 18 years. Additionally, their higher rate of pediatric laparoscopic surgeries suggests a more developed pediatric laparoscopic surgery program.

Eskander et al [10] and Xac et al [15] found that patients treated by gynecologists are more likely to undergo ovarian-sparing surgery. In our study, ovarian-sparing surgery was performed in 56 out of 288 patients (19%) with non-neoplastic and benign neoplastic lesions across both disciplines, with 22 out of 117 (18.80%) in pediatric surgery and 34 out of 171 (20%) in gynecology. All patients with suspected malignancy preoperatively or intraoperatively from both departments underwent oophorectomies. Zhang et al. [4] conducted ovarian-sparing surgery in 82% of cases with benign lesions and cautioned against ovarian cystectomy in malignant lesions due to the high recurrence rate.

Bilateral tumors of the ovary are relatively uncommon, with an estimated incidence ranging from 0.7% to 2%, and the majority are reported to be malignant [29]. They can occur synchronously or metachronous and may range from benign to malignant, presenting considerable challenges in management [30].

These tumors can exhibit the same or different histology, simultaneous occurrence of two tumors with different histology is uncommon [31]. In this study 1 patient had non-gestational choriocarcinoma in the left ovary and mature cystic teratoma in the right ovary, 2 patients had bilateral benign ovarian teratomas, and 3 had bilateral atypical serous tumors.

Management of bilateral ovarian masses can be challenging, if malignancy is suspected, bilateral oophorectomy is acceptable [32].The patient diagnosed with non-gestational choriocarcinoma and mature cystic teratoma showed elevated B-hCG levels and underwent laparotomy followed by bilateral oophorectomy. The two patients with bilateral mature cystic teratoma underwent bilateral oophorectomy, one via open surgery and the other through minimally invasive surgery (MIS). Majority (50%) of serous tumors are benign, 15% are borderline, while 35% are malignant [31]. The three patients diagnosed with atypical serous tumors had no documented tumor markers before surgery, and all underwent bilateral oophorectomy via open surgery.

Two patients from the gynecology department were diagnosed with stage 4 pulmonary disease at 18 years old and passed away during the same admission. One patient was HIV positive but not yet undergoing treatment and was diagnosed with advanced mesothelioma. The other patient was diagnosed with a yolk sac tumor.

Among the five patients from pediatric surgery, all passed away within two years of diagnosis. The youngest was 18 months old and had a yolk cell tumor, while the oldest was 13 years old and had a stage 4 Sertoli Leydig cell tumor with lung metastasis.

A limitation of this study is its contextual nature, conducted solely in two academic hospitals in Johannesburg, which may limit the generalizability of the results to other hospitals.

Conclusion

This study revealed that most ovarian masses were benign, while malignant lesions were more prevalent in patients aged ten and above. It underscores the importance of thoroughly investigating ovarian pathology through tumor marker assessment and radiological studies before resorting to surgical intervention. These steps are essential for guiding the decision-making process regarding ovarian-sparing surgery.

The authors advocate for a heightened awareness of ovarian lesions in girls experiencing abdominal pain. They propose that utilizing a laparoscopic approach in conjunction with ovarian-sparing techniques should be regarded as the preferred method for treating benign lesions, with the aim of enhancing patient outcomes.

Pediatric surgeons and gynecologists are urged to increase their efforts in enhancing their proficiency in laparoscopic surgical techniques. This proactive approach is crucial for ensuring optimal outcomes and preserving ovarian function in young patients.

Furthermore, the authors suggest the implementation of an educational program aimed at clinicians working in lower-level hospitals. This initiative would aim to raise awareness and suspicion of ovarian pathology in young girls, thereby reducing delays in referrals. Such proactive measures have the potential to mitigate both the morbidity and mortality associated with the disease process itself and complications stemming from treatment

Conflict of interest

The authors declare no conflict of interest.

Author contributions

NM, LM, DH, TO, and EM conceptualized, designed, and drafted the initial manuscript. They also conducted reviews, edits, and ultimately approved the final version for submission.

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APPENDIX 1

A fifteen-year retrospective review of surgically managed ovarian masses in children at Charlotte

Maxeke Johannesburg and Chris Hani Baragwanath Academic Hospitals

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BACKGROUND

Diseases of the ovary are divided into two categories: non-neoplastic and neoplastic lesions. Non-neoplastic lesions include functional cysts, and inflammatory and non- inflammatory lesions. Neoplastic lesions include benign, borderline and malignant tumours. Most ovarian tumours in childhood and adolescence are benign; the most common non-neoplastic lesions are functional cysts. The neoplastic benign category includes mature teratoma, fibroma, borderline cystadenoma and gonadoblastoma. (1–3)

The World Health Organisation classifies ovarian tumours according to their histological features (4). This classification categorises tumours according to their cell of origin, which may be surface epithelial, germ cell, or stromal. Germ cell tumours (GCTs) are the commonest ovarian tumours in children, whereas surface epithelial and stromal tumours are commoner in adults (1).

Ovarian lesions are the commonest genital tract lesions in children, making up 60-70% of gynaecologic lesions in this age group (2). The estimated incidence of ovarian tumours in children is 2.6 per 100 000 girls per year, and only 10% of these are malignant (2). However, they are the least common tumours in children, accounting for less than 1% of all tumours in children (2)

There is a paucity of data on the prevalence of ovarian pathology in the paediatric population in Africa and in the South African population. A retrospective review of 521 Chinese children published in 2014 reported that 91% presented with benign disease, and Germ cell tumours were the commonest malignancy between the ages 9 and 19 years. The study had a mean presenting age of 16 years. Their findings are similar to those reported in a study from Ghana by Akakpo, where 65,7% of tumours found in children between 0 and 19 years were Germ cell tumours. (7)

Sex cord-stromal tumours (SCST) account for 5.7% to 17% of childhood/adolescent ovarian neoplasms (3). According to the South African children's cancer study group by Hendricks et al, conducted between 1990 and 2015, twenty-three patients were diagnosed with sex cord stromal tumours (SCSTs) across nine oncology centres in South Africa. Thirteen/twenty-three had Granulosa-Theca stromal tumours. Fourteen (60.9%) had stage 1 tumours. Nighty one point three percent had surgical resection with no reported morbidity and mortality, and an overall survival rate of 82.1% was reported. Most of these children had recognized standardised chemotherapy except 2 (5). This study shows that most patients presented early, which could be the reason for the good survival rate.

Granulosa cell tumours (GCT) (juvenile type) are the commonest SCSTs. They may be functional, presenting with precocious puberty or virilization. Ovarian epithelial neoplasms account for 20-30% of ovarian tumours in females under 20 years of age. They occur after menarche and are mostly benign. They may show mucinous, serous and endometroid differentiation. (3)

Tubo-ovarian abscess is an inflammatory condition which involves the ovary and fallopian tubes. It is usually a complication of pelvic inflammatory disease (6) and is uncommon in both paediatric and adult populations (8).

In 2017, Risser reported that the true incidence of pelvic infections in the United States was unknown because these infections are not notifiable. According to this study, these infections are more common in children over 15 years and are attributed to sexually transmitted infections (9).
The incidence of ovarian inflammatory conditions and infections in Africa and South Africa is explicitly not reported.

The incidence, clinical presentation, and histology of ovarian lesions in children differ from the adult population. (10)

Children may present with non-specific symptoms, ranging from abdominal pain and distended abdomen, to a palpable pelvic or abdominal mass that may be mobile. Other symptoms include nausea, vomiting, poor appetite, weight loss, anaemia, weakness, diarrhoea or constipation, and urinary frequency depending on the type and size of tumour. Some patients may be asymptomatic, with the mass being an incidental finding. (10)

Zhang et al reported that 9% of patients with malignant lesions (n=47/521) presented with abdominal distension and pain compared to 73.3% with benign lesions (n=382/521) which mainly presented with menstrual abnormalities (1). The presence of abdominal or pelvic tenderness might be a sign of ovarian torsion, haemorrhage or rupture of an ovarian mass.

Some patients may present with endocrine abnormalities like enlargement of breasts, abnormal vaginal bleeding, early development of pubic and axillary hair, whereas adolescent girls, may have abnormal menstruation, acne, deep voice and hirsutism (11)

Ovarian masses can be located outside of the pelvis and should be a differential diagnosis when a mobile abdominal mass is palpated, irrespective of abdominal location. It is essential to diagnose and treat early to prevent complications of a benign mass and the spread of a malignant one.

Shanbhougue et al. reported that patients might atypically present with clinical syndromes associated with ovarian tumours e.g hyperthyroidism, hyperestrogenism, and virilization. Knowledge of these clinical syndromes is critical for the efficient diagnosis of ovarian pathology (11). Other syndromes associated with ovarian pathology include Peutz-Jeghers syndrome, Maffucci syndrome, and Chediak- Higashi syndrome (3)

Trans-abdominal ultrasound is the initial imaging of choice because it is readily available, has no radiation, and does not require sedation (10). It is able to estimate the size of the tumour and identifies whether the mass is cystic, solid, or complex (10).

CT/MRI can be performed to get additional information regarding the nature and extent of the tumour. They may also predict the biological potential of the mass. Malignant masses tend to be more extensive and solid compared to benign masses (10)

Tumour markers can be used in preoperative risk stratification of malignant ovarian Masses but no single tumour marker provides enough reliability. Serum AFP levels are usually elevated in germ cell tumours, immature teratomas, embryonal carcinoma and mixed GCTs with yolk sac elements.
B-H CG is elevated in choriocarcinomas. CA-125 is mostly elevated in ovarian epithelial tumours.LDH can be elevated in dysgerminomas. CA-125 is not routinely done in children as epithelial-stromal tumours are rare compared to adults. Negative tumour markers do not, however, exclude a malignancy because tumour markers are only positive in 54% of cases (12)

Historically, the management of ovarian masses in children has been surgical removal, however the current advanced radiologic imaging and identification of tumour markers allows for more conservative management (13). There is also a wide variability in surgical management, and surgical approaches including open laparotomy and laparoscopy. Unlike in adults, where the management of ovarian tumours is oophorectomy, the management approach in children aims to preserve ovarian tissue to spare gonadal function and fertility.

In a Japanese study by Oue, the pre-operative indication for ovary-sparing surgery depended on a size smaller than 15cm. Intra-operatively, the decision was made by the degree of ovarian torsion and the ability to find a dissecting plane between the tumour and the ovary (14)

A study by Ozcan et al., they opted for ovary-sparing surgery based on absence of Lymphadenopathy or metastasis, normal tumour markers, and the existence of calcification on CT scans as a sign of teratoma. (15). If a lesion looks malignant, an oophorectomy must be performed after a full inspection of the other ovary (3). The contralateral ovary should be saved if it looks and feels normal. If it looks suspicious for malignancy, a Salpingo-oophorectomy should be performed after malignancy is confirmed histologically by biopsy.

The laparoscopic approach is preferred in patients with cystic lesions and normal Serum tumour markers or in cases where the diagnosis is unclear (10). A meta-analysis by Qazi et al. looking at 44 studies on the management of ovarian masses in children found that laparoscopic management was generally advocated for benign lesions. Those with a suspicion for malignancy were treated with more caution. This systemic review concluded that there was insufficient evidence to suggest that the laparoscopic approach had better outcomes when it comes to operating time, blood loss, or hospital stay. (16)

In developed countries, the survival rate is nearly hundred percent because of the availability of advanced imaging facilities amongst other things (17). The actual incidence of ovarian masses in developing countries is unknown and late presentation, unavailability of facilities and low index of suspicion leads to mismanagement and progression or complication of the disease, reducing survival rate (17)

RATIONALE

There is a scarcity of data regarding ovarian pathology in children in South Africa

and Africa in general, due to a lack of documentation and reporting of these conditions.

AIM OF STUDY

To determine the epidemiology and clinical outcome of surgically managed ovarian masses in children below 18 years of age at Charlotte Maxeke Johannesburg (CMJAH) and Chris Hani Baragwanath Academic Hospitals (CHBAH) between January 2007 and 31st December 2021

STUDY OBJECTIVES

1. To describe the demographic profile (age and race) of children with ovarian pathologies
2. To determine the clinical presentation, work-up, pre-operative and, pathological diagnosis and surgical management of children with ovarian masses.
3. To determine the prevalence and outcomes of malignant ovarian tumours in children below 18 years of age at CMJAH and CHBAH between January 2007 and 31st December 2021

METHODOLOGY

a) **Design:** This will be a retrospective observational study looking at the incidence, demographic, types, size, treatment and post-surgical outcomes of ovarian pathology in children treated at CMJAH and CHBAH between January 2007 to December 2021

b) **Site:** CMJAH and CHBAH Department of Paediatric Surgery, Gynae-Oncology and Anatomical pathology

c) **Study population:** Children from 0-18 years of age with ovarian pathology operated by Paediatric Surgery and Gynae-Oncology from 1 January 2007 to 31 December 2021 at CMJAH and CHBAH

d) Sampling

1. i) **Inclusion criteria:** All paediatric, surgically excised or biopsied ovarian lesions from the Paediatric surgery and Gynaecology Units at CMJAH and CHBAH with an available pathology report on the LabTrack and/or Central data warehouse(CDW) system of the National Health Laboratory Service system between 1 January 2007 to 31 December 2021

2. ii) **Exclusion criteria:**

   - Missing medical records: Data will be extracted from Labtrack, CDW, Paediatric surgery online patient database and Gynae-Oncology files.

   Where some data on a case is missing, it will be excluded from analysis of that parameter.

   - All cases referred to CMJAH or CHBAH after ovarian surgery

e) A pilot study will not be required as a retrospective study has already been performed at Chris Hani Baragwanath Academic hospital looking at ovarian paediatric surgical oncology between 2007 and 2016(18); the study reported 15 surgically managed paediatric ovarian masses in a 10 year period; together with the average 3-4 cases seen per year at CMJAH, provides sufficient information with regard to expected sample size.

f) Sources of bias

- Loss of follow up that may affect outcome data

- Missing medical records

g) Sample size: Estimated sample size is 50-60 cases based on the reported case numbers from the 10 year retrospective review of ovarian paediatric surgical oncology cases at CHBAH and the 3-4 cases seen annually at CMJAH (personal communication - Dr. Ellen Mapunda:Head paediatric Surgery)

h) Outcome: Three year overall and five year overall survival

DATA COLLECTION VARIABLES

Presenting age (in years)									
Main Presenting complaint		Abdominal pain:							
		Abdominal mass:							
		Other:							
Signs of precocious puberty		Present:							
		Absent:							
		Unknown							
Associated Syndromes									
Palpable abdominal mass		Yes:							
		No:							
		Unknown							
Tumour markers		Ca125	AF P	hCG	Ca19-9	CEA	LDH	Other	
Clinical diagnosis									
Ultrasound findings	Unila t	Bilat	Thick wall	Thin wall	Septa t	Solid	Cystic	Projecti	High colour doppler	Ascites
CT scan Findings	Unila t	Bilat	Thick wall	Thin wall	Septa t	Solid	Cystic	Projecti	High colour doppler	Ascites
Distant metastasis at diagnosis	Yes									
	No									
Neoadjuvent therapy		Yes						Regimen:		
		No								
		Not Applicable								
		Unknown								
Open/Minimal invasive(MIS)/MIS assisted									
Intra-operative findings									
Ovarian-Sparing Surgery		Yes							
Intra-Operative staging		No							
Histological Diagnosis									

Staging (malignant neoplasms)		
Type of staging(FIGO/COG)		
Adjuvant therapy (if malignant)	Yes	Regimen
	No	
Presented to:	Paediatric Surgery	
	Gynaecology	

DATA ANALYSIS

Data will be extracted from anatomical pathology data base: LabTrack and Corporate Data Warehouse (CDW) and files of all specimens will be traced back to retrieve clinical information including age at presentation, clinical presentation, pre- operative diagnosis, post-operative diagnosis, pre and post-operative management. Microsoft Excel 2010® will be used to store data as a spreadsheet. Abstracted data will include the following: age, presenting symptoms and signs, palpable abdominal mass, tumour markers, sonographic findings, CT findings, pre-operative diagnosis, intra-operative findings, histological findings, neo-adjuvent and/or Adjuvent therapy.

Data will be cleaned, coded and prepared for a statistical analysis software/tool. A P value of <0.05 will be regarded as significant. Statistical analysis of the data will be

performed using STATISTICA 13.0. Statistical analysis of data will use simple descriptive statistical methods including reporting of medians with their inter-quartile ranges for continuous variables such as age, and for dichotomous variables, proportions with their 95% confidence intervals will be reported.
Correlation of the histological subtype with the pre-operative diagnosis, presentation and management outcome will be done using Pearson test.

ETHICS

Before commencing with data collection, the study will await approval by the Wits Human Research Ethics Committee (HREC). The study will also be registered with the National Health Research Database. Permission to access data and to conduct the study will be applied with the Head of Departments of Gynaecologic Oncology and Paediatric Surgery as well as the Office of the CEO of Charlotte Maxeke Johannesburg and Chris Hani Baragwanath Academic hospitals.

The participant's anonymity will be maintained at all times. No personal identifiers will be used. Each participant will be allocated a unique study number. Data will be kept confidential at all times. All data collected and analysed will be stored on a secured hard drive stored in a locked room with regular backup on to a secure cloud server. Data transfer will be via managed access controls. Only the primary investigator and supervisors will have access to the data. No participant consent will be required as this will be a retrospective study.

FUNDING

There will be no funding for the study. All costs including those of travel, printing and copying, will be borne by the primary investigator.

ESTIMATED COST OF THE STUDY

Stationary	R500
Sundry	R200
Total	R700

TIMING

2021	**June**	**July**	**Aug**	**Sept**	**Oct**	**Nov**	**Dec**		
Literature Review	**x**								
Preparing Protocol		**x**	**x**	**x**	**x**	**x**	**x**		
2022	**March**	**April**	**May**	**June**	**July**	**Aug**	**Sep**	**Oct**	**Dec**
Protocol Assessment	**x**	**x**							
Ethics Application			**x**						
Data Collection				**x**	**x**	**x**	**x**		

Data Analysis								**x**	**x**
2023	**Jan**	**Feb**	**March**	**April**	**May**				
Writing up	**x**	**x**	**x**						
Report				**x**	**x**				

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APPENDIX 2

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO:	Dr N Mashaba School of Clinical Medicine Department of Surgery Division of Paediatric Surgery Medical School University E-mail: drmashaba@yahoo.com
CC:	Supervisor: Dr L Mbodi <mlangi2005@yahoo.co.uk> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252 E-mail: Iain.Burns@wits.ac.za
DATE:	2022/07/28
REF:	R14/49
PROTOCOL NO:	**M220536** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	*A fifteen year retrospective review of surgically managed ovarian masses in children at Charlotte Maxeke Johannesburg and Chris Hani Baragwanath Academic Hospitals*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr N Mashaba

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220536

NAME: (Principal Investigator) Dr N Mashaba

DEPARTMENT: School of Clinical Medicine
Department of Surgery
Division of Paediatric Surgery
Medical School
University

PROJECT TITLE: *A fifteen year retrospective review of surgically managed ovarian masses in children at Charlotte Maxeke Johannesburg and Chris Hani Baragwanath Academic Hospitals*

DATE CONSIDERED: 2022/05/27

DECISION: Approved unconditionally

CONDITIONS:

NOTE: If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>

SUPERVISOR: Dr L Mbodi

APPROVED BY: CB Penny
Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 2022/07/28

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **May** and therefore reports and re-certification will be due in the month of **May** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

APPENDIX 3

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

30 January 2024
Person No: 2534420
PAG

Dr NC Mashaba
276 Pine Avenue
Unit 15 The Village
Ferndale
2194
South Africa

Dear Dr Nkhensani Mashaba

Master of Medicine in Surgery: Approval of Title

We have pleasure in advising that your proposal entitled *A fifteen-year retrospective review of surgically managed ovarian masses in children at Charlotte Maxeke Johannesburg and Chris Hani Baragwanath Academic Hospitals* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX 4

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ORIGINALITY REPORT

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APPENDIX 5

About the journal

Aims and scope

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Original Research Articles are preferred and should be in the format of Introduction, Methods, Results and Discussion. Original articles must include a structured abstract of 250 words or less and should not exceed 5,000 words of text and 50 references. Combined number of figures and tables are limited to 6 (see below for detailed information). Submissions reporting an observational cohort, case-control, or cross-sectional study must include the relevant completed STROBE Checklist. Additional information can be found on the STROBE website.

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Manuscripts on operative technique should be submitted as original research articles. These manuscripts should focus on novel or innovative approaches to established or new surgical approaches to surgical conditions. Those focusing on established techniques will not receive strong consideration.
Case Series of more than 5 patients with excellent scientific and educational values will be considered. The format of these should follow that of original research articles.
Case Reports with fewer than 5 patients, can be submitted to the journal's companion title Journal of Pediatric Surgery Case Reports

Experimental or animal research articles are also encouraged, so long as they are relevant to the field of pediatric surgery. These manuscripts should not exceed 4000 words, with a combined total of five figures and tables, and 30 references. Additional material over and above these instructions could be published as supplementary material.

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All authors should have made substantial contributions to all of the following:

1. The conception and design of the study, or acquisition of data, or analysis and interpretation of data.
2. Drafting the article or revising it critically for important intellectual content.
3. Final approval of the version to be submitted.

All authors should agree to be accountable for all aspects of the work to ensure that the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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- Only in exceptional circumstances will the journal editor consider the addition, deletion or rearrangement of authors post acceptance.
- Publication of the manuscript may be paused while a change in authorship request is being considered.
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- Honoraria
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- Grants or any other funding

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The resulting Word document containing your declaration should be uploaded at the "attach/upload files" step in the submission process. It is important that the Word document is saved in the .doc/.docx file format. Author signatures are not required.

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Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants, scholarships and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

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There is no single, universally agreed-upon set of guidelines for defining sex and gender. We offer the following guidance:

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We advise you to read the Sex and Gender Equity in Research (SAGER) guidelines and the SAGER checklist (PDF) on the EASE website, which offer systematic approaches to the use of sex and gender information in study design, data analysis, outcome reporting and research interpretation.

For further information we suggest reading the rationale behind and recommendeduse of the SAGER guidelines.

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We ask authors to define how sex and gender have been used in their research and publication. Some guidance:

- Sex generally refers to a set of biological attributes that are associated with physical and physiological features such as chromosomal genotype, hormonal levels, internal and external anatomy. A binary sex categorization (male/female) is usually designated at birth ("sex assigned at birth") and is in most cases based solely on the visible external anatomy of a newborn. In reality, sex categorizations include people who are intersex/have differences of sex development (DSD).
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The equator network has guidelines covering CONSORT:

- Read the CONSORT guidelines.
- Follow the CONSORT checklist.

Writing and Formatting

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We ask you to provide editable source files for your entire submission (including figures, tables and text graphics). Some guidelines:

- Save files in an editable format, using the extension .doc/.docx for Word files and .tex for LaTeX files. A PDF is not an acceptable source file.
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You are required to provide a concise and factual abstract. The abstract should briefly state the purpose of your research, principal results and major conclusions. Some guidelines:

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When your artwork is finalized, "save as" or convert your electronic artwork to the formats listed below taking into account the given resolution requirements for line drawings, halftones, and line/halftone combinations:

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To foster transparency, you areencouraged to state the availability of any data at submission.

Ensuring data is available may be a requirement of your funding body or institution. If your data is unavailable to access or unsuitable to post, you can state the reason why (e.g., your research data includes sensitive or confidential information such as patient data) during the submission process. This statement will appear with your published article on ScienceDirect.

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[3] W. Strunk Jr., E.B. White, The Elements of Style, fourth ed., Longman, New York, 2000.

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[4] G.R. Mettam, L.B. Adams, How to prepare an electronic version of your article, in: B.S. Jones, R.Z. Smith (Eds.), Introduction to the Electronic Age, E-Publishing Inc., New York, 2020, pp. 281 - 304.

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[5] Cancer Research UK, Cancer statistics reports for the UK. http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/, 2023 (accessed 13 March 2023).

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[6] M. Oguro, S. Imahiro, S. Saito, T. Nakashizuka, Mortality data for Japanese oak wilt disease and surrounding forest compositions [dataset], Mendeley Data, v1, 2015. https://doi.org/10.1234/abc12nb39r.1.

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[7] E. Coon, M. Berndt, A. Jan, D. Svyatsky, A. Atchley, E. Kikinzon, D. Harp, G. Manzini, E. Shelef, K. Lipnikov, R. Garimella, C. Xu, D. Moulton, S. Karra, S. Painter, E. Jafarov, S. Molins, Advanced Terrestrial Simulator (ATS) v0.88 (Version 0.88) [software], Zenodo, March 25, 2020. https://doi.org/10.1234/zenodo.3727209.

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