**Manuscript**

**Title: Operative management of pediatric ovarian tumors - the challenge of fertility-preservation. Results from the UK CCLG Surgeons Cancer Group Nationwide Study**

1. **Introduction**

Ovarian tumors in children are rare. Overall incidence is estimated at 2.6 per 100 000 girls, but varies depending on patient age and histological diagnosis. [1,2,3] 90% of paediatric ovarian tumors are classed as benign. Mature ovarian teratoma, a slow-growing tumor with the potential for malignant transformation, constitutes the most common benign prepubertal ovarian neoplasm. [2] Prognosis is thought to be excellent following complete resection and for a long time, total unilateral oophorectomy has been generally performed in these cases. [4]

Little is known on the true incidence of recurrence and metachronous disease in benign ovarian tumors. Most studies on this subject are retrospective and only include few patients. Nevertheless, they all suggest that there is a risk of metachronous disease occurring in the contralateral ovary; reported incidence varying between 5.7% - 23%. [5 - 7] These findings suggest that children undergoing unilateral oophorectomy for an ovarian tumor are at significant risk of losing the contralateral ovary in case of a metachronous tumor.

More evidence has become available on the detrimental impact of oophorectomy on female fertility and hormonal health. Ovary-sparing surgery and use of minimally invasive surgery have therefore gained increasing popularity. The literature shows however, that these techniques are much more commonly employed by adolescent gynaecologists than pediatric surgeons. [8]

A recent national survey amongst UK pediatric surgeons demonstrated that – unlike other tumors – ovarian tumors are frequently treated by non-oncology surgeons. This may partially be explained by the fact that children with ovarian tumors more commonly present out of hours, in an emergency situation with acute abdominal pain or suspicion of ovarian torsion. The survey also showed that most non-oncology surgeons treat less than two ovarian tumors per year and raises questions if this really is best practise management for these children. [9]

We therefore aimed to investigate in a UK nationwide multicentre study if children with ovarian tumors who presented as emergency(s) were more likely to undergo total oophorectomy and conventional open surgery, than patients who were referred and managed on an elective basis by speciality surgical services.

1. **Methods**

A nationwide study facilitated through the Surgical Specialty Group of the UK Children’s Cancer and Leukaemia Group (CCLG) was performed. The study was registered as Audit 7705 with the Royal Manchester Children’s Hospital as Lead coordinating centre. Participation was open to all pediatric surgical oncology centres in the United Kingdom (UK) on a voluntary basis.

A standardised data collection form was distributed amongst participating centres (Figure 1). Female patients <16 years with an index diagnosis of ovarian tumor from 2006 - 2016 were included. Patients with functional cysts and neonatal ovarian cysts were excluded. For statistical analysis, cumulative tables were created using Microsoft Excel®. Statistical significance was determined using the online tool “Social Science Statistics®” Calculator [22] employing the two-tailed Mann Whitney test, and the Fisher’s exact test respectively, as indicated.

1. **Results**

Twelve out of the 22 UK CCLG registered pediatric surgical oncology centres participated in the study, resulting in a response rate of 55%. Three-hundred and ten patients were identified who underwent resection of an ovarian tumor between 2006 - 2016.

One hundred and forty-eight (47.7%) patients presented as surgical emergencies, meaning the child presented to the emergency department with acute symptoms. 160 (51.6%) cases had elective presentation. Elective presentation was defined as General Practitioner referral to hospital outpatient clinics. Mode of referral was unclear in 2 patients.

Median age at surgery was 11 years [IQR 8 – 14 years]. Most common diagnoses were mature teratoma (57%, 176 cases), immature teratoma (11%, 34 cases) and serous cystadenoma (7.7%, 24 cases). [21]

Overall, 70% (217) of cases were performed as conventional open procedures. 30% (94) of children underwent minimally invasive surgery (MIS). Out of these cases 11% (10) were commenced as laparoscopic procedure(s) and subsequently converted to an open operation.

Mode of presentation – i.e. whether a patient presented as an emergency or was referred electively – did not significantly influence the choice of surgery. 37.2% of all MIS cases were emergency procedures, and 31.5% of all open cases were emergency procedures (p=0.35; Fisher’s exact test).

Tumors were smaller in children who underwent MIS. Median tumor size in the laparoscopic group was 6cm [IQR 5.7; 10], compared to 11cm [IQR 7; 19] in the open group (Graph 1). This result was statistically significant (p < 0.00001; Mann Whitney test, two-tailed). Overall children who underwent MIS were significantly more likely to have ovary-sparing surgery (p < 0.00001; Fisher’s exact test); (Graph 2).

21% (22) of children who presented as an emergency had ovary-sparing surgery, compared to 23% (48) of children that were treated on an elective basis. This was not significant (p=0.77; Fisher’s exact test).

1. **Discussion**

The main challenge for the pediatric surgeon in the management of ovarian tumors lies in finding the right balance between optimal tumor resection and maximal fertility preservation. Recent large population-based cohort studies have demonstrated significant long-term health implications of oophorectomy on female fertility as well as psychological and hormonal health. [10]

Detrimental effects can be seen following both unilateral or bilateral oophorectomy. Yasui et al showed that unilateral oophorectomy increases the risk of premature ovarian failure and early menopause (ie. menopause under the age of 45 years). [10] Estrogen deficiency in the first decades of life increases the risk for cardiovascular disease, and it is well-established that early menopause results in increased risk for osteoporosis and bone fractures. [11], [12]

In addition, a recent meta-analysis confirmed that oophorectomy is associated with an increased overall mortality, which is not solely due to ischaemic heart disease. [13]

Interestingly, oophorectomy has also been shown to effect cognitive function, and is associated with an increased risk for dementia and Parkinson’s disease. [14] The overall effects on quality of life, psychological well-being and sexual function are less well researched, but one can imagine that these are effected, too. Of further concern, only some (but not all) of the above negative outcomes can be influenced by estrogen replacement therapy. [14]

These findings demonstrate that preservation of healthy ovarian tissue must be of great importance to surgeons dealing with ovarian pathology. Only 22% of children in our study underwent ovary-sparing surgery, regardless of mode of presentation. Previous studies have shown that adolescent gynaecologists are more likely to undertake ovary-sparing surgery, and total oophorectomy is more common in children under 14 years. [8]; [15] Management of germ cell tumors in the United Kingdom (UK) is facilitated by the Children’s Cancer and Leukaemia Group’s (CCLG) guidelines, yet – in terms of managing mature teratoma – these are open to varied interpretation. CCLG guidance advises that “in strongly suspected ovarian mature teratoma it is reasonable to attempt fertility preserving surgery with resection of tumor only, rather than oophorectomy.” [16] No recommendation is provided whatsoever on the use of minimally invasive surgery – hence it is not surprising that the vast majority of cases in our study underwent conventional open surgery. Guidelines by the Royal College of Obstetricians and Gynaecologists clearly favour minimally invasive surgery because of decreased post-operative morbidity, shorter patient recovery time and earlier hospital discharge. [17] However it is wholly acknowledged that minimally invasive surgery may be of little benefit, or not even feasible in large ovarian neoplastic lesions. This is the case for example in slim, prepubertal girls with large solid lesions, where a reasonable sized incision is required at the end of the procedure to extract the tumor, whether or not the main part of the procedure was performed laparoscopically. [17], [18]

Chemical peritonitis as a consequence of intraoperative tumor spillage following ovarian teratoma resection has been of concern for a long time. [19] However, when reviewing the literature more closely, it must be acknowledged that there is very little evidence available, most of which stems from the adult literature. [20] A systematic review including 14 studies of minimally invasive surgery ovarian teratoma resection with notably high spillage rates concluded that overall the risk for chemical peritonitis lies at 0.2%. [20] More research is therefore clearly required to establish the true impact of intraoperative spillage in surgery for mature ovarian teratoma.

In this study the total number of cases treated by minimally invasive surgery, and the total number of cases undergoing ovary-sparing surgery were small compared to the group of female patients who underwent open surgery and total oophorectomy. This was not influenced by the mode of clinical presentation of the patient. In view of the impact of total oophorectomy on a girl’s future fertility and hormonal health and the possibility of late occurrence of metachronous disease, it is time to review current surgical practice and agree an evidence based ‘best practice’ strategy. In the emergency setting, we recommend the following approach, which may aid pediatric surgeons without special interest in paediatric surgical oncology in their decision making, should they be faced with a girl presenting in the setting of potential ovarian torsion out of hours. The safest approach, if a large black ovarian mass is discovered, is simple derotation of the torted ovary and closure. In case of a simple torsion, this allows for preservation of any viable ovarian tissue, in case of an ovarian tumor it allows time for an adequate work-up, including tumour markers, possibly further imaging and subsequent management by a paediatric surgical oncologist.

Considering the recent evidence on long-term effects of oophorectomy, we think it is imperative to raise awareness of the importance of ovarian preservation amongst paediatric surgeons. Similar to other tumours, we recommend that these cases should be managed by surgeons with an expertise in ovary-sparing surgery. This will also aid the pre-operative counselling to allow a meaningful and frank discussion with patient(s), family(s) and the surgeon. The conversation should weigh up the risks of recurrence/ metachronous disease and implications of oophorectomy, in order to agree a personalised management strategy for each patient.

**Conclusion**

This UK nationwide study demonstrates that ovary-sparing surgery and minimally invasive surgery are still infrequently deployed by pediatric surgeons in the UK. In view of the clear implications on fertility and hormonal health caused by unilateral oophorectomy, we need to review current practice. Ovary-sparing surgery by trained surgical specialists taking appropriate precautions to avoid tumor spillage should be performed in benign ovarian disease wherever possible.

**Legends for graphs/ tables:**

Figure 1: Data collection form

Figure 2a: Tumors were significantly smaller in children who underwent MIS. Median tumor size in the MIS group was 6cm [IQR 5.7; 10], compared to 11cm [IQR 7; 19] in the open group. This result was statistically significant (p< 0.00001; Mann Whitney test, two-tailed). [MIS = minimally invasive surgery]

Figure 2b: Patients who underwent MIS were significantly more likely to have ovary-sparing surgery (p < 0.00001; Fisher’s exact test) (Graph 2). [MIS = minimally invasive surgery]