**Title page**

**Title:**

**Standardising the Surgical Management of Benign Ovarian Tumours in Children and Adolescents:**

**A Best Practice Delphi Consensus Guideline**

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**Abstract**

**Aim**

No widely agreed international consensus protocols exist for the management of benign ovarian tumours (BOT) in children. As a result this presents a substantial risk for suboptimal management in young female patients. We therefore aimed to generate a multi-specialty Delphi consensus statement to clarify ( i ) perioperative controversies, ( ii ) standardise surgical management and ( iii ) provide clear after care surveillance guidance in those patients who have had benign ovarian tumours (BOTs).

**Methods**

A Two-round confidential Delphi Consensus Survey was distributed to a multi-specialty expert panel (Paediatric Oncology Surgeons, Paediatric Oncologists, Adolescent Gynaecologists), concluded by two semi-structured videoconferences. Results were summarised into the Consensus Statement.

**Results**

Consensus was generated for these Core Outcomes Sets: Pre-operative, intra-operative management (elective and emergency presentation); follow-up; referral to adolescent gynaecology. Main consensus results: (1) Females with BOTs should receive a robust care pathway as those patients with potentially neoplastic lesions, which must include a full pre-operative discussion at a paediatric oncology multi-disciplinary tumour board meeting for risk stratification categorization and management by health professionals with expertise in ovarian-sparing surgery and minimally invasive surgery.; (2) Ovarian-sparing surgery for BOTs should be performed wherever possible to maximise fertility preservation.; (3) Ovarian mass lesions detected during emergency diagnostic laparoscopy/laparotomy should be left in situ and investigated later appropriately (imaging/tumour markers) prior to planned definitive resection ; (4) After care surveillance should be vigilantly undertaken for all female patients after BOT resection, with regular ultrasound imaging (US). All patients should be later referred to adolescent gynaecology services once post-pubertal status is achieved to discuss implications on future fertility / fertility preservation.

**Conclusion**

This best practice Delphi consensus emphasises the key importance of managing female paediatric patients harbouring BOTs with a well defined oncological MDT strategy to optimise their risk stratification preoperatively and allow fertility preservation by ovarian-sparing surgery wherever possible.

**Key words:**

Ovarian tumour; ovarian teratoma; ovary sparing operations ; fertility preservation;surveillance; paediatric ; Delphi survey

**Manuscript**

**Introduction**

In contrast to most other paediatric tumours there are no widely agreed treatment or working consensus protocols for female children with benign ovarian tumours. Optimal management remains a matter of wide international debate. [1] Although some effort at offering brief guidance has been published by the UK Children’s Cancer and Leukaemia Group (CCLG), the British Association of Paediatric and Adolescent Gynaecologists (BritSPAG) and the Royal College of Obstetrics and Gynaecology (RCOG), robust evidence on key areas such as operative approach, management of unexpected intraoperative findings of an ovarian tumour, and follow-up management is distinctly lacking. [2, 3, 4] Little is known about the true natural history of benign ovarian tumours, risk(s) of recurrence, metachronous disease, and the long-term consequences on fertility are also poorly understood. [5] Existing guidelines leave much room for perplexing interpretation. [2, 3, 4] This was illustrated recently by a national survey of United Kingdom (UK) consultant paediatric surgeons, which showed great heterogeneity in the approach to BOTs in all areas of clinical practice including pre-operative imaging, operative strategy and follow-up management in particular, all of which were determined by individual surgeon’s preference. [1]

In a 10-year multi-centre study of patients with BOTs from 12 UK CCLG oncology centres tumour recurrence or metachronous disease occurred in 5% of children. [5, 6] Other retrospective studies, smaller in size suggest an even higher risk of metachronous disease ranging from 6% - 23%. [7, 8, 9] Until recently paediatric surgical management of female children with benign ovarian tumours was unilateral oophorectomy as this was considered to offer curative therapy. In case(s) of metachronous tumour or ovarian torsion index patients were therefore at significant risk of losing the contralateral ovary and being rendered infertile. [5]

Population-based cohort studies have now demonstrated additional long-term health implications of oophorectomy on both psychological and hormonal health, including a significantly increased risk of premature ovarian failure, even after unilateral oophorectomy alone. [10, 11, 12] Added complexity may result from the fact that girls with ovarian tumours can present in a variety of health care settings, ranging from an outpatient referral office visit , to a surgical emergency via a district general hospital admission or a specialist paediatric surgical unit. Patients may be managed by a variety of different specialties notably general surgeons, paediatric surgeons, paediatric oncology surgeons and gynaecologists all with varied management strategies. This current lack of a unified management guidance pathway presents a potential risk for suboptimal surgical and long-term management.

The objective(s) of the current study was therefore to create a multi-specialty best practice consensus to establish better guidance on pre- and intraoperative management and after care follow-up of paediatric female patients with benign ovarian tumours.

**Methods**

A consensus study was conducted in accordance with previously published guidance with a prospective protocol [13-15]. A multi-specialty Delphi panel was activated that included UK CCLG Paediatric Oncology Surgeons, UK CCLG Paediatric Oncologists representing the CCLG Germ Cell Tumour Group, and the CCLG Late Effects Group, and Paediatric Gynaecologists representing the British Association of Paediatric and Adolescent Gynaecologists (BritSPAG), with specific expertise in fertility preservation and reproductive medicine.

The ovarian masses / tumours included were those defined as: mature teratoma, mucinous cystadenoma, serous cystadenoma, large (> 5cm) ovarian cysts. Small simple functional ovarian cysts, endometriomas, and haemorrhagic ovarian cysts as identified on imaging as well as neonatal ovarian cysts were excluded.

A broad themed literature search was undertaken and existing guidelines on the theme(s) from other national specialty groups were critically reviewed to generate a defined core outcome set:

- Pre-operative management

- Intra-operative management – emergency presentation

- Intra-operative management – elective admission and presentation

- Follow-up management

- Referral to Adolescent Gynaecology Services

A two‐round confidential e‐Delphi survey was distributed to the Delphi panel using a validated online survey tool [16]. Participants were asked to then anonymously score a list of statements for importance using a 9‐point Grading of Recommendations Assessment, Development and Evaluation (GRADE) Likert Scale: Scores 1 to 3 – do not agree with statement / statement of limited importance; 4 to 6 – important but not critical; 7 to 9 – fully agree with this statement / of critical importance. [17] Participants were thereafter invited to add comments and suggest additional relevant outcomes using free‐text responses.

The criteria for consensus were agreed a priori. ‘Consensus in’ (Statement to be accepted into the guideline) required 60% or more of the Delphi participants to score outcome(s) as being critically important (score 7-9) and less than 15% of participants to disagree with the statement (score 1-3). ‘Consensus out’ (Statement not to be included) required 60% or more of participants to disagree with the statement, and less than 15% of participants to agree (score 1-3). Outcomes that did not meet any of these criteria were defined and labelled as ‘no consensus’. These set thresholds have been used successfully in other studies, and were utilised in order to ensure that the majority of expert panelists regarded the outcome(s) as very important, with only a small minority considering items to have little or no importance. [14, 18]

In Round 1 all statements were scored. In Round 2 outcomes having ‘no consensus’ were scored, as well as additionally suggested outcomes. The Delphi process was then finalised in two subsequent semi-structured video conferences to generate the consensus statement guidelines.

**Consensus Statement**

Definition of a benign ovarian tumour: Imaging in keeping with a benign ovarian tumour (no immature features, no obvious finding of endometrioma or haemorrhagic ovarian cyst), negative serum tumour markers, no signs of precocious puberty, no other clinically concerning features.

**Pre-operative investigations for a child referred with a suspected benign ovarian tumour:**

1. Any patient with a complex ovarian lesion or an ovarian cyst > 5cm should undergo an ultrasound (US) imaging scan as the first line investigation.
2. For further assessment of the mass, the patient should ideally have an abdomino-pelvic magnetic resonance imaging (MRI) scan. [19, 20, 21]
3. Any patient with a complex ovarian lesion or simple ovarian cyst > 5cm should have the serum tumour markers alpha Fetoprotein (AFP) and beta human chorionic gonadotropin (beta-HCG) assayed. In a postpubertal female patient the serum cancer antigen marker 125 (Ca125) should be added.
4. Additional tumour markers such as Inhibin, LDH, CEA and Ca19.9 may be useful and can be obtained in addition to the above at the discretion of the treating clinician, but there is currently insufficient evidence to recommend their routine use in the assessment of a suspected benign paediatric ovarian tumour. [22, 23, 24]
5. The management of a female paediatric patient with a suspected ovarian mass should always be discussed in the oncology multi-disciplinary tumour board meeting (MDT) prior to surgical intervention. The MDT should aim at risk stratifying the tumour preoperatively (benign/ malignant) and determine and assess if the tumour is amenable to ovarian-sparing surgery. [25]

**Intraoperative management**

**(I) Emergency management: Finding of an ovarian mass / ovarian torsion**

1. In the case of intraoperative findings of ovarian torsion, the ovary should be detorted and left in situ. [26]
2. In the case of incidental intraoperative finding of a mass suspicious for an ovarian tumour, the lesion should be not be excised and left in situ until tumour markers and further imaging are later obtained. The patient should be referred to a paediatric oncology surgeon and an MDT opinion thus obtained prior to further surgery.
3. If required, subsequent tumour resection should be planned on a semi-elective basis following MDT tumur board discussion.
4. Management of large ovarian cysts by aspiration / fenestration only should be avoided wherever possible due to the risk(s) of cyst recurrence and spillage of tumour contents in the case of a neoplastic lesion. [27]

**(II) Elective management: elective resection of a benign ovarian tumour**

1. Preservation of ovarian tissue should be of paramount importance to the surgeon and ovarian-sparing surgery should be performed whenever feasible in all paediatric benign ovarian tumours regardless of size of the lesion. [28, 29, 30]
2. Ovarian-sparing surgery and adherence to oncological principles takes precedence over operative strategy (minimally invasive surgery [MIS] vs open). [31]
3. If an ovarian mass is amenable to MIS but the surgeon does not feel sufficiently skilled to perform the procedure she / he should consider referral to a colleague who can offer minimally invasive ovarian-sparing surgery.
4. A MIS ovarian-sparing approach should especially be the preferred route of surgery in an obese female patient in order to reduce the potential risk(s) of wound dehiscence from a Pfannenstiel / laparotomy wound. Minimally invasive ovarian-sparing surgery should also be considered the ideal approach of choice in small benign ovarian tumours that are <7cm in diameter. [32, 33]
5. Intraoperatively [2]:
	1. The contralateral ovary should always be inspected.
	2. The abdominal cavity should be carefully explored intraoperatively for suspicious lesions / deposits.
	3. Suspicious peritoneal and omental lesions should always be biopsied and peritoneal fluid sent for cytology.
	4. Intraoperative spillage of tumour content should be managed by careful washout of the peritoneal cavity with sterile water or normal saline and this event must be documented in the operation note(s).

**Follow-up after resection of a benign ovarian tumour**

**(I) Duration**

1. Follow-up should be undertaken for all female children and young adults following excision of a benign ovarian tumour. [5]
2. Follow-up appointments should include a pelvic US scan.
3. The initial post-operative follow-up for female children and young adults following excision of a benign ovarian tumour should ideally be performed within 3 months post-operatively with an US scan to ensure complete lesion resection and as a baseline imaging assessment for future follow-up.
4. After the initial follow-up appointment, the next follow-up appointment should be scheduled ideally at 2 years post-operatively with a surveillance US scan.
5. Thereafter, follow-up US scanning should be scheduled every 2 years until the patient reaches the age of 16 years. The young person should then be referred to an adolescent gynaecologist for fertility assessment (see below). This approach allows ready identification of recurrence and metachronous disease, when tumours are likely still small, and more amenable to repeat ovarian-sparing surgery.
6. If a suspicious ovarian lesion is identified on follow-up US, further imaging should be obtained with an MRI scan. The case should be discussed at the oncology MDT tumour board prior to further surgery being undertaken.
7. Tumour markers should be assayed at follow-up visit(s) if they were elevated pre-operatively. If tumour markers are elevated or remain elevated at follow-up, the patient should be re-discussed at the oncology MDT tumour board and pathology fully reviewed.

**(II) Referral to Adolescent Gynaecology Services**

1. Patients who have undergone resection of an ovarian tumour should be offered referral to an adolescent gynaecologist to discuss health with regard future well being and fertility preservation. This is especially important in females following unilateral oopherectomy (or more extensive surgery), as these patients are considered to have an increased risk of premature ovarian insufficiency. [10, 11]
2. The referral for fertility assessment should take place once the young person has completed puberty; by the age of 16 years at the very latest. If the patient has been discharged from surgical follow-up before they reach this age, the General Practitioner (Family Doctor, GP) needs to be informed at the point of hospital discharge from surgical follow-up to ensure a timely referral is made later. In prepubertal female children a formal fertility assessment with blood tests and internal US (antral follicle count) is not considered helpful. [34, 35]

**Discussion**

The natural history of benign ovarian teratoma (which constitutes the majority of non malignant ovarian tumours in children) remains poorly described. The tumours are considered relatively rare and hence various clinical specialties may be involved in primary management. With the aim(s) to generate a better health care pathway for female paediatric patients we undertook a Delphi consensus to yield new guidelines on the surgical management of benign ovarian tumours. To do this we assembled experts from the main UK paediatric specialty groups notably oncology surgeons, medical oncology and adolescent gynaecologists, seeking unified endorsement from health care professionals. Following the Delphi consensus a number of key points emerged as being of outstanding importance, which are discussed now in further detail.

***Multi-disciplinary management***

It is vital that female children with a benign ovarian mass receive the same expertise and clinical management as other young paediatric patients with potentially neoplastic lesions. Pre-operative discussions in the oncology multi-disciplinary tumour board meeting (MDT) allows risk stratification, to determine pre-operatively where possible if the ovarian tumour is likely to be benign and thus amenable to ovarian-sparing surgery.

Selection of patients with non malignant disease suitable for ovarian-preserving surgery requires a combined informed interdisciplinary discussion of the patient’s characteristics, imaging studies and serum tumour marker results best undertaken in an MDT meeting. Whilst full histological analysis of the resected lesion ultimately determines if an ovarian tumour is benign or malignant , the small but undeniable possibility of later confirmation of a malignant tumour should always be discussed with the patient’s family pre-operatively. Discussion of all female children harbouring BOTs at the oncology MDT tumour board will facilitate in the rare scenario where a malignant lesion is identified on histology that the patient is already well known to relevant specialists teams where they can receive timely management as per the current guidelines for malignant lesions [2].

***Ovarian-sparing surgery***

Outcomes following resection of a benign ovarian tumour are generally excellent. Regrettably emerging this widespread clinical practice female patients have been traditionally managed by total unilateral oophorectomy. However, over the last decade, a number of important studies have been published in the adult literature providing good evidence to show that unilateral oophorectomy can lead to premature ovarian insufficiency. Yasui et al ( Japan ) analysed comprehensive data of some 24152 women enrolled in the Nurses’ Health Study using Kaplan-Meier survival curves and convincingly showed that unilateral oophorectomy was an independent risk factor for premature ovarian insufficiency. [10] Similar findings were published from the HUNT2 survey involving a retrospective cohort study of 23580 women. This compelling study showed that women having had prior unilateral oophorectomy entered menopause at least one year earlier than healthy women without oophorectomy. The crude relative risk of menopause was 1.28 (95% CI: 1.15-1.42), and these data remained even after adjustment for other risk factors. [36] Several further studies have also demonstrated the potential risks for other significant long-term health after unilateral oophorectomy. [11, 12, 37 - 39].

Astonishingly, no such long-term follow-up data is currently available in the paediatric population, but it should be assumed that the risk(s) of early menopause through depletion of the total oocyte pool must similarly apply to this young patient cohort. Ovarian-sparing surgery for benign ovarian tumours should therefore be performed wherever possible in female children with BOTs, in order to maximise fertility preservation and to minimise late health effects notably premature ovarian insufficiency.

***Follow-up and fertility preservation***

Following unilateral oophorectomy female paediatric patients are at an irrefutable risk of losing their solitary contralateral ovary from torsion or metachronous disease. [5, 7-9] Where unilateral oopherectomy may already result in significant long-term health consequences bilateral oopherectomy will be catastrophic for the patient. rendering them sterile. Existing evidence to accurately determine if or when the risk of lesion recurrence and metachronous disease decreases is currently unavailable.

Follow-up surveillance should therefore always be recommended for all female children following resection of a BOT as published studies report risk(s) of recurrent and metachronous disease.

In this Delphi study we aimed to generate robust follow-up protocol(s) that would be (I) safe, (II) easy to follow and (III) facilitate transitional care to adult services for fertility assessment at appropriate timepoints. Such guidelines of course do not exclude earlier referral to paediatric gynaecology services for individual counselling purposes as per patient request.

Following the initial US scan undertaken at 3 months post operatively to check for completeness of lesion resection the multispeciality care group agreed ‘ on a minimum ‘ of at least 2 yearly US scanning intervals up to the age of 16 years, as some 95% of females patients will have completed pubertyby this stage and a fertility assessment at this point .deemed appropriate, In view of the reported life time risk(s) of metachronous ovarian disease, we strongly believe that immediate discharge after primary resection is not safe.

***Treatment and speciality disciplines***

Many girls with ovarian tumours still undergo operation by surgeons without a speciality interest in paediatric oncology or ovarian gynaecology surgery. In an era where it has become evident that increasing subspecialisation in surgery is linked with better patient outcomes, we strongly advocate that surgery for ovarian tumours in female children and adolescents should be undertaken by accredited specialists ie. paediatric oncology surgeons or paediatric and adolescent gynaecologists both skilled at performing ovarian-sparing surger including access to minimally invasive operations.

**Conclusion**

This Delphi multi-speciality best practice guideline is a contemporary summary statement based on current best available evidence. It will hopefully serve as a key first step towards better health care management of all female paediatric patients with benign ovarian tumours.

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