

1 **A case of prepubertal ovarian tissue cryopreservation in metachronous**  
2 **bilateral mature ovarian teratoma requiring bilateral oophorectomy**

3 Authors: Tom Malik; Juliet Gray; Nigel J Hall

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5 The potential for metachronous contralateral should be considered at index  
6 operation and a decision made regarding resectional strategy. Ovarian tissue  
7 cryopreservation should be discussed in a multidisciplinary setting and with careful  
8 consideration of the risks and benefits guided by best available evidence.

## 9 Introduction

10 Mature teratoma is the commonest benign ovarian tumour affecting children.<sup>1</sup> Arising  
11 in multiple germinal layers, mature ovarian teratomas are characterised by the  
12 presence of ectopic tissue and display a preponderance for ectodermal proliferation.<sup>2</sup>  
13 Treatment requires surgical excision, either ovarian sparing or by oophorectomy.<sup>3</sup>  
14 Though complete resection is associated with a good prognosis there remains a risk  
15 of metachronous contralateral disease, the magnitude of which is uncertain (reported  
16 at 4-23% in several European studies<sup>4-6</sup>). Girls with mature ovarian teratoma in the  
17 United Kingdom (UK) undergo regular post-operative surveillance with ultrasound  
18 scan to identify contralateral metachronous disease<sup>3</sup>. If this occurs then infertility is  
19 an inevitable sequel when bilateral oophorectomy is required. Whilst ovarian sparing  
20 surgery would likely preserve fertility in these rare cases, it may not be possible. This  
21 could be due to concern of a malignant tumour prior to excision, prompting  
22 oophorectomy as a safe oncological procedure, or due to it being impossible to  
23 identify any macroscopically normal ovarian tissue at the time of surgery. Indeed  
24 oophorectomy is the recommended treatment for any ovarian mass for which the  
25 diagnosis is uncertain.<sup>7</sup>

26 For children with cancer, the UK National Institute for Health and Care Excellence  
27 (NICE) advises considering options for fertility preservation before treatment is  
28 started.<sup>8</sup> The only method available for prepubertal girls is ovarian tissue  
29 cryopreservation (OTC).<sup>9</sup> This involves retrieval of ovarian tissue (by ovarian biopsy  
30 or oophorectomy) which is then frozen. If the patient is rendered infertile by their  
31 oncological disease or its treatment (chemo/radiotherapy, bone marrow transplant or  
32 surgery) and later wishes to attempt a biological pregnancy, the tissue can be

33 thawed and autotransplanted into the ovarian medulla or an adjacent peritoneal  
34 window.

35 Evidence concerning the efficacy and morbidity of OTC in prepubertal girls is limited.  
36 For girls with certain types of cancer and those undergoing bilateral oophorectomy  
37 for other reasons, however, it offers the only hope of fertility preservation. We  
38 present a case of oophorectomy and OTC for the treatment of metachronous  
39 bilateral mature ovarian teratoma in a prepubertal girl. The challenges which have  
40 emerged following analysis of the case are discussed.

41

## 42 **Case report**

43 A premenarchal 11 year old girl presenting with abdominal pain was found to have a  
44 left iliac fossa mass. Ultrasonography demonstrated a 7.3cm left adnexal mass with  
45 a central cystic component and peripheral rim of soft tissue (Figure 1), associated  
46 with a small volume of free fluid in the pelvis. Alpha-fetoprotein, human chorionic  
47 gonadotropin, CA-125 and lactate dehydrogenase were normal.

48 Contrary to pre-operative clinical and radiological findings, laparoscopy identified a  
49 right ovarian mass comprising cystic and solid components with no normal ovarian  
50 tissue visible (Figure 2). The reason for discrepancy between pre- and intra-  
51 operative findings was not clear, other than that the anatomy was distorted by the  
52 presence of the large mass. Inspection of the left ovary, left fallopian tube and uterus  
53 revealed no abnormality and no other intra-abdominal pathology was evident. The  
54 mass was delivered through a muscle-sparing Pfannenstiel incision and excised,  
55 with presumed en masse resection of the right ovary. Histopathology demonstrated a

56 completely excised mature ovarian teratoma with no malignant features. There was  
57 no normal ovarian tissue visible on microscopy, save for a small amount of  
58 haemorrhagic and oedematous ovarian stroma. Given the risk of metachronous  
59 disease, annual follow-up was arranged with pelvic ultrasonography at each  
60 appointment.

61 At follow-up one year after surgery, routine ultrasound revealed a 1.7cm area of  
62 increased echogenicity concerning for calcification in the left ovary. Magnetic  
63 resonance imaging (MRI) demonstrated a multi-cystic left adnexal lesion containing  
64 fat (Figures 3 & 4). Tumour markers were again normal. The patient received  
65 multidisciplinary input from consultants in Paediatric Oncology, Paediatric Surgery  
66 and Reproductive Medicine alongside a fertility counsellor. A decision was made to  
67 attempt ovarian sparing excision of the tumour in order to preserve fertility. It was,  
68 however, agreed pre-operatively that OTC would be performed if oophorectomy  
69 became necessary.

70 At laparoscopy, the left ovary appeared pathological but intra-abdominal inspection  
71 was otherwise normal. The previous Pfannenstiel incision was re-opened and the left  
72 adnexal structures were delivered through the wound. The tumour's limits were  
73 difficult to discern, with no macroscopically normal ovarian tissue visible, therefore  
74 oophorectomy was performed. Following resection, the specimen was dissected ex-  
75 vivo and a sample of apparently normal ovarian tissue was sent for cryopreservation.  
76 Histopathology demonstrated a mature ovarian teratoma with clear margins and no  
77 malignant characteristics.

78 Multidisciplinary care continued post-operatively. There were no oncological or  
79 surgical concerns and hormone replacement therapy was commenced. The patient

80 received counselling and was reviewed by a dietitian as her weight remained static  
81 during a six-month period post-surgery. She continues to be followed up by a  
82 general paediatrician and paediatric endocrinologist. Her frozen sample of ovarian  
83 tissue is now stored securely and will be made available if she wishes to attempt  
84 pregnancy at a later date.

85

## 86 **Discussion**

87 We have described a case of bilateral metachronous oophorectomy and OTC to  
88 treat metachronous bilateral mature ovarian teratoma in a prepubertal girl. This is a  
89 rare condition, but has been reported in up to 23% of girls with mature ovarian  
90 teratoma <sup>4-6</sup>. The case highlights important challenges for those caring for girls with  
91 this pathology.

92 It is believed that the ideal method of fertility preservation in children with mature  
93 ovarian teratoma is to perform ovarian sparing tumour excision in order to preserve  
94 healthy ovarian tissue. The desire to preserve fertility must, however, be balanced  
95 against the need to perform an oncologically safe resection. Adherence to the  
96 principles of oncological surgery entails complete tumour dissection, staging and  
97 avoiding tumour spillage.<sup>10</sup> In cases of suspected mature ovarian teratoma, the  
98 surgeon must still respect these principles as the true nature of the disease cannot  
99 be known until histopathological examination has been performed. In their series of  
100 children with mature ovarian teratoma, Chabaud-Williamson et al. demonstrated  
101 complete resection in all cases of ovarian sparing surgery ( $n=10$ ).<sup>5</sup> They  
102 recommended that this technique be reserved for tumours suspected to be localised

103 mature ovarian teratoma. This view is supported by recent guidance from the  
104 Children's Cancer and Leukaemia Group (CCLG), which states that an attempt at  
105 ovarian sparing resection is acceptable if mature teratoma is strongly suspected.<sup>3</sup> In  
106 addition, a clear plane of dissection between tumour and normal ovary must be  
107 visible intra-operatively.<sup>11</sup> In this case, ovarian sparing surgery was not possible for  
108 either side. This resulted in the unfortunate position of a girl rendered infertile  
109 following surgical treatment of what ultimately was found to be benign disease.

110 For situations such as this, OTC represents the only option for a future biological  
111 pregnancy. However, the sparsity of evidence concerning the efficacy and safety of  
112 prepubertal OTC presents a challenge to those considering its undertaking. Limited  
113 reports exist regarding the efficacy of OTC when tissue has been harvested  
114 prepubertally, although this is a rapidly developing field. Two cases of successful  
115 pregnancy have been reported following prepubertal OTC<sup>12,13</sup> and induction of  
116 puberty has been reported following autotransplantation of prepubertally  
117 cryopreserved ovarian tissue<sup>14,15</sup>. Whilst generally a safe procedure, harvesting of  
118 ovarian tissue may require additional surgery with the inherent associated risks. Due  
119 consideration of these risks should be made in particular in cases where laparoscopy  
120 would otherwise not be required and the risk of gonadal failure (usually related to  
121 treatment of oncological or haematological disease) may be difficult to quantify<sup>16</sup>.  
122 There is currently no standardisation of service provision for OTC in prepubertal girls  
123 in the UK. At our centre, it is considered in individual cases at high risk of infertility  
124 secondary to treatment for benign or malignant disease.

125 In conclusion, the possibility of metachronous contralateral disease necessitating  
126 bilateral oophorectomy should be considered in all children with mature ovarian

127 teratoma. Ovarian sparing surgery should be considered at index operation, and  
128 regular ultrasound surveillance should be undertaken. The efficacy of prepubertal  
129 OTC remains uncertain and it is important to engage full multi-disciplinary team  
130 discussion prior to its undertaking. Informed consent regarding resectional strategy  
131 and OTC mandates full disclosure of the associated benefits and risks, guided by the  
132 best available evidence.

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### 134 **Conflict of Interest**

135 The authors have no conflicts of interest to declare.

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185 **Figure captions**

186 Figure 1: Ultrasonography demonstrating a sagittal view of suspected left adnexal  
187 mass. Laparoscopy confirmed that the tumour was in fact associated with the right  
188 ovary.

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190 Figure 2: Laparoscopic view of the right-sided mature ovarian teratoma.

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192 Figure 3: MRI demonstrating an axial view of the metachronous left ovarian teratoma  
193 pre-operatively.

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195 Figure 4: MRI demonstrating a sagittal view of the metachronous left ovarian  
196 teratoma pre-operatively.