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Preserving fertility in pseudomyxoma peritonei, a novel approach

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Abstract

Background: Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is the gold standard treatment for patients with pseudomyxoma peritonei (PMP) but involves routine bilateral salpingo-oophorectomy. Young women wishing to maintain fertility may be reluctant to pursue this. An alternative strategy in women with low-grade PMP has been explored in the form of laparoscopic evacuation of pelvic and ovarian mucin with resection of the appendiceal tumour.

Methods: Between January 2012 and January 2015, four young women (aged 28–35 years) with PMP seeking to maintain fertility underwent laparoscopy, appendicectomy and pelvic mucinous evacuation and washout. Data regarding intra-operative and histopathological findings were collected. Endpoints were fertility-related outcomes and oncological follow-up.

Results: Infertility was a presenting symptom in three of the four women. All four had significant pelvic mucinous disease on radiological imaging and were offered CRS and HIPEC as definitive treatment, but chose laparoscopy with appendicectomy and copious irrigation and washout of the pelvis with stripping of mucinous disease off the ovarian surfaces. Postoperative histology demonstrated a low-grade appendiceal mucinous neoplasm (LAMN) in all

patients with acellular mucin or low-grade mucinous carcinoma peritonei in the peritoneal cavity. All patients successfully conceived subsequently and gave birth to healthy babies. After 12–29 months follow-up, all women are well with no radiological or laparoscopic evidence of disease recurrence.

Conclusions: In patients with low-grade PMP, initial therapeutic laparoscopy can restore fertility, whilst providing short- to medium-term disease control. This modality in young women wishing to have children appears to be a feasible alternative to immediate CRS and HIPEC.

Keywords: infertility, pseudomyxoma peritonei, therapeutic laparoscopy

Introduction

Women continue to delay completing their families, likely due to changing socio-economic roles in recent decades, primarily in Western societies. In 2014 the average age for first time mothers in England and Wales has risen to 28.5 years; also for the first time there were more live births to mothers aged 35 or over than to those under 25 years (144,181 vs 138,592 births respectively) [1]. This has imposed challenging clinical treatment decisions in young women wishing to maintain fertility and presenting with conditions such as pseudomyxoma peritonei (PMP).

Pseudomyxoma peritonei is a rare disease predominantly originating from a perforated appendiceal mucinous tumour; its annual incidence is estimated at 2–3 per million [2]. Currently, definitive treatment includes cytoreductive surgery (CRS) aimed at a complete macroscopic tumour removal, combined with hyperthermic intraperitoneal chemotherapy (HIPEC) to eliminate residual microscopic disease [3–6]. However, as the majority of women with PMP have either macroscopic or microscopic involvement of the ovaries, bilateral salpingo-oophorectomy (BSO) is considered a component of complete CRS in most cases [7, 8].

Clearly, for young women who wish to have children, the prospect of being rendered permanently infertile by CRS and HIPEC can be unacceptable, especially

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in the context of what is often a low-grade malignancy. In addition, infertility can be a presenting complaint in PMP patients as the frequent pelvic and ovarian disease itself may interfere with fallopian tube function. Infertility is therefore closely associated with PMP, both as an initial mode of presentation and as an outcome of CRS and HIPEC.

Postponing CRS and HIPEC till such time that these patients have been able to have children is often ineffective as PMP may in fact be the cause of infertility. Therefore, alternative strategies to preserve fertility in young women with low-grade PMP are sought. One such strategy is laparoscopic evacuation of pelvic and ovarian mucin. We aim to provide an initial report of the outcomes of this treatment strategy in selected patients in a large peritoneal malignancy centre.

Methods

The present report is an observational retrospective review of data prospectively collected in a dedicated peritoneal malignancy database between January 2012 and January 2015 in a main national referral centre for PMP. Institutional Review Board approval is in place for data collection in this database.

The initial study population included all female patients undergoing surgical intervention for PMP. From this group, patients undergoing a therapeutic laparoscopy aimed at assessment and treatment of ovarian and pelvic disease instead of definitive surgical management with CRS and HIPEC were selected for further review. Therapeutic laparoscopy involved staging of disease extent, appendectomy (if not performed previously) and pelvic mucinous evacuation and washout with copious irrigation. Informed consent was obtained from all patients prior to undergoing the procedure. Data regarding pre- and intra-operative assessment of ovarian and pelvic involvement and histopathological analysis of surgical specimens were extracted from surgical procedural notes and postoperative histology reports. The resected specimens were classified according to recent classification guidelines for appendix tumours and PMP [9]. The main end points were fertility-related outcomes and oncological short-term follow-up. All patients were followed up annually by abdominal radiography (either computed tomography [CT] or magnetic resonance imaging [MRI]) and serum tumour markers measurements (CEA, CA-125 and CA 19-9) [10–14]. Repeat laparoscopy was planned in case of equivocal findings on imaging.

Results

During the time period of this study (January 2012–January 2015), 271 women underwent surgery for PMP. Of these 271, four premenopausal women (1.5%) were

considered for CRS and HIPEC as definitive management for their PMP, but chose a staging and potentially therapeutic laparoscopy, for which informed consent was obtained. All four women were premenopausal and did not have any children.

An overview of these four patients is provided in Table 1. Briefly, infertility was a presenting symptom in three of women. At presentation, all were found to have pelvic mucinous disease on either radiological imaging or initial laparoscopic evaluation, with limited extra-pelvic disease in two patients. They were counselled about potential risks of disease progression associated with the decision not to undergo CRS and HIPEC. At laparoscopy, a systematic evaluation of intra-abdominal disease extent was performed, followed by an appendectomy (except in one patient who had undergone a previous appendectomy) and copious irrigation and washout of the pelvis with meticulous, blunt stripping of mucinous disease off the surface of the ovaries. At the end of the procedure, the ovaries and pelvis were completely clear of disease and macroscopically normal. Histological examination of the appendix demonstrated a low-grade appendiceal mucinous neoplasm (LAMN) in all patients; the pelvic disease consisted of acellular mucin in two patients and low-grade mucinous carcinoma peritonei in the remaining two. All four patients successfully conceived subsequently and gave birth to full-term healthy babies with only one requiring in vitro fertilisation. One patient underwent a caesarean section, at which time no pelvic disease was found. One patient underwent a repeat laparoscopy to evaluate a trace amount of pelvic fluid demonstrated on follow-up imaging; during this procedure, no intra-abdominal or pelvic mucinous disease was identified. Currently, after 12–29 months follow-up, all women are well with no radiological or (in one case) laparoscopic evidence of disease recurrence and normal tumour markers; ongoing radiological and clinical surveillance is planned.

Discussion

Infertility is an important issue facing young women with PMP. Not only is ovarian and pelvic involvement by PMP thought to be associated with infertility, but definitive treatment with complete CRS and HIPEC necessarily includes BSO, leading to iatrogenic surgical menopause and permanent infertility. Therefore, to restore or temporarily preserve fertility in those patients with active wish to have children, PMI Basingstoke has

Table 1: Clinical characteristics, surgical procedures, histology and outcomes of patients undergoing therapeutic laparoscopy.

Patient	Age, years	Presenting symptoms	Previous resections	Tumour markers	PCI	Disease extent	Laparoscopic procedures	Histology of appendix	Histology of mucin	Interval to successful delivery, months	Follow-up (interval)
1	35	None	Right oophorectomy	Normal	6	Pelvis Right diaphragm	Appendicectomy Pelvic stripping Washout	LAMN	LG MCP	17	CT: NED (25 months)
2	32	Infertility	None	Normal	6	Pelvis Right diaphragm Spleen	Appendicectomy Pelvic stripping Washout	LAMN	LG MCP	18	Laparoscopy: NED (29 months)
3	28	Infertility	None	CEA 19 ng/mL	5	Pelvis	Appendicectomy Pelvic stripping Washout	LAMN grade 1 carcinoid	Acellular mucin	10	CT: NED (12 months)
4	35	Infertility abdominal pain	Appendicectomy	Normal	3	Pelvis	Pelvic stripping Washout	LAMN	Acellular mucin	11	MRI: NED (14 months)

PCI, peritoneal cancer index; LAMN, low-grade appendiceal mucinous neoplasm; LG MCP, low-grade mucinous carcinoma peritonei; CEA, carcino-embryonic antigen; NED, no evidence of disease.

developed an alternate treatment strategy. This involves a laparoscopic procedure aimed at staging of disease extent; in cases with relatively limited mucinous disease (pelvic mucin with limited or no extra-pelvic disease), an appendicectomy is performed and the abdominal and pelvic cavity is irrigated and copiously washed out with water, with stripping of disease off the peritoneal surface of the pelvis and the surface of the ovaries, till both the pelvis and the ovaries are macroscopically free of disease.

We have shown here that this strategy has proven in carefully selected patients to be effective in permitting full-term pregnancies in all four patients and in providing at least a short- to medium-term disease control based on current follow-up. Preserving the ovaries has the additional advantage of maintaining ovarian hormonal function which when compromised can lead to significant adverse consequences such as coronary heart disease, osteoporosis and sexual dysfunction [15].

Efforts have been made to preserve and enhance fertility in young women with PMP. A recent report on a series of six women who had at least one macroscopically normal ovary preserved during CRS and HIPEC demonstrated that only one patient subsequently conceived successfully, a rate of conception much lower than that achieved with the strategy of therapeutic laparoscopy reported here [16, 17].

In addition, options such as adoption and various assisted reproductive techniques (ARTs) currently exist for women rendered infertile due to oncological treatments. These techniques include in vitro fertilisation using frozen oocytes or frozen embryo's, ovarian tissue cryopreservation and surrogacy. However, though these techniques have been offered to a proportion of patients undergoing treatment for PMP at PMI Basingstoke, none have resulted in a successful pregnancy.

It is estimated that the proportion of potential candidates for therapeutic laparoscopy as an alternative to immediate CRS and HIPEC is limited. During a 12-year period, 884 women were referred to PMI Basingstoke for treatment of PMP; 208/884 (24%) were under 45 years of age and 80 of these underwent CRS and HIPEC; 52/80 (65%) still had ovarian tissue in situ at referral and 21 of these had no children at the time. Therefore, of all women referred to PMI Basingstoke with PMP, 21 (2.5%) were under 45 years old, childless, potentially capable of having children, but highly likely to be rendered infertile due to CRS and HIPEC (unpublished data). For this subgroup of patients, therapeutic laparoscopy may be considered as an alternative to CRS and HIPEC.

Therapeutic laparoscopy is by no means to be considered an alternate definitive treatment strategy for PMP. The aim of this treatment is solely to enhance fertility whilst, by rendering patients macroscopically disease-free, postponing CRS and HIPEC till such a time that disease progression is diagnosed. However, for selected women with relatively low-volume low-grade disease, especially those struggling with infertility, laparoscopic appendectomy and evacuation of mucin may be a considered an alternative to immediate CRS and HIPEC. Careful pathological assessment of the primary appendix tumour and the extra-appendiceal disease is crucial. This strategy of therapeutic laparoscopy should therefore be discussed with and offered to young women with low-grade, low-volume PMP, who still wish to have children.

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