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Published in:
Maturitas

DOI:
10.1016/j.maturitas.2010.03.018

Maturitas 66 (2010) 310–314

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Short-term surgical outcome and safety of risk reducing salpingo-oophorectomy in *BRCA1/2* mutation carriers

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ARTICLE INFO

Article history:
Received 4 January 2010
Received in revised form 21 March 2010
Accepted 23 March 2010

Keywords:
Risk reducing salpingo-oophorectomy
Surgical complications
Ovarian cancer
BRCA1
BRCA2

ABSTRACT

Objective: Women with a *BRCA1/2* mutation or members of a hereditary breast ovarian cancer family (HBOC) have an increased risk of developing ovarian cancer. The only effective strategy to reduce this risk is a risk reducing salpingo-oophorectomy (RRSO). The aim of this study was to evaluate the short-term surgical outcome and safety of a RRSO.
Patient and methods: Included were all consecutive women with a *BRCA1/2* mutation or members of a HBOC family who visited our Family Cancer Clinic between September 1995 and March 2006, and choose for RRSO.
Results: 159 women were included, of which 97 (61.0%) *BRCA1* and 32 (20.1%) *BRCA2* mutation carriers, and 30 women of a HBOC family (18.9%). The median age at RRSO was 42.9 years (30.3–61.1) in the *BRCA1* group, 48.4 years (33.5–66.9) in the *BRCA 2* group and 46.4 (32.8–68.7) years in the HBOC group ($p = 0.02$). The median body mass index (BMI) was 24.9 kg/m^2, 30.1% were overweighed (BMI 25–30) and 18.7% were obese (BMI > 30). The RRSO was performed by primary laparoscopy ($n = 154$) or laparotomy ($n = 5$). Intraoperatively, one (0.6%) major complication occurred and laparoscopy was converted to laparotomy. In one patient (0.6%) a minor complication occurred. Post-operatively five minor complications (3.1%) were observed. Median hospital stay was 1 day (0–13 days).
Conclusion: Laparoscopic RRSO in BRCA1/2 mutation carriers seems to be a safe procedure with a low intraoperative and post-operative complication rate (1.3% and 3.1% respectively), a low conversion rate (0.6%) and a short median hospital stay (1.0 day).

1. Introduction

Women with a *BRCA1* or *BRCA2* mutation have an increased life time risk of developing ovarian cancer. Risks at age 70 years are respectively 40% and 18% for *BRCA1* and *BRCA2* carriers compared to 1.5% in the general population [1]. Until recently, ovarian cancer screening by annual transvaginal ultrasonography and evaluation of serum CA125 was considered effective for early stage diagnosis. However, in several (retrospective) series it has been shown ineffective [2–7]. The only effective and currently available strategy is a risk reducing salpingo-oophorectomy (RRSO). Removal of the ovaries and fallopian tubes is highly effective and reduces the gynaecological cancer risk in *BRCA* mutation carriers by 85% [8].

Several reports have been published about surgical outcome after an oophorectomy for benign or malignant pathology of the ovaries. Generally, laparoscopic surgery of the ovaries is accompanied by a low complication rate, a low conversion rate, short hospital stay and fast recovery [9–11]. Little is known about surgical outcome after a prophylactic salpingo oophorectomy in a hereditary breast ovarian cancer population. Only a few studies reported limited data about surgical results in which complication rates of 5–11% are reported [12,13]. In the Netherlands, women with a *BRCA1* or *BRCA2* mutation are offered a RRSO after child bearing age. Based on age related penetrance of ovarian cancer: for *BRCA1* mutation carriers at the age of 35–40 years and for *BRCA2* mutation carriers at the age of 40–45. It is known that *BRCA1* and *BRCA2* mutation carriers with a personal history of breast cancer, aged over 40 years and parous are more likely to choose for a RRSO [14]. Despite all evidence regarding the ineffectiveness of screen-

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doi:10.1016/j.maturitas.2010.03.018

ing not all *BRCA* mutation carriers choose to undergo a RRSO. Most women who hesitate to have a RRSO are anxious for side effects and acute postmenopausal signs and symptoms [15,16]. Others are anxious because of the invasive treatment with possible intraoperative complications [16]. The aim of this prospective study was to evaluate the short-term surgical outcome and safety of a RRSO in a hereditary breast ovarian cancer population. This knowledge may improve the counseling of women who consider for RRSO. Complications were evaluated during the surgical procedure and post-operatively until 6 weeks.

2. Patients and methods

2.1. Study population

Between September 1995 and March 2006 a total of 241 new patients visited the Family Cancer Clinic of the University Medical Center Groningen. Women at increased risk of developing breast and/or ovarian cancer were counseled on screening and prophylactic surgery, based on their personal and family history and mutation status. The ovarian cancer screening included annual pelvic examination, transvaginal ultrasound and serum CA125 measurement. After one or more visits a total of 179 women decided to undergo a RRSO. Eligible for inclusion were women with a *BRCA1* or *BRCA2* mutation and those at high risk from a Hereditary Breast- Ovarian Cancer (HBOC) family without detectable mutation (yet). Participants needed to have at least one ovary in situ with normal screening results. Women were excluded if they had previously been diagnosed with ovarian cancer. All women were prospectively included in a separate anonymous, password protected database [2]. Additional data about body mass index (BMI), menopausal status, co-morbidity, surgical technique, operating time, pre- and post-operative major and minor complications and hospital stay were obtained from medical records by a structured registration form. According to the Dutch law, no further Institutional Review Board approval was needed for this study.

2.2. Surgical protocol

Surgical procedures were primarily performed by a gynaecologist and a resident. All patients received general anaesthesia and laparoscopic surgery was performed according to a standard, surgical protocol. A sub umbilical 10 mm trochar was inserted for the camera and two or three more trochars (2 mm × 5 mm, 1 mm × 10 mm) in the lower abdomen. A peritoneal washing was performed and this peritoneal fluid was send for cytological examination. After inspection of the abdomen the retro peritoneum was opened and the infundibulo-pelvic ligament sealed or coagulated with bipolar diathermia and cut, as was the ovarii proprium ligament and the fallopian tube (as close to the uterus as possible). Because of the possibility of an occult malignancy the ovaries and tubes were handled non-traumatically. After marking one side, both adnexa were placed in an endobag and removed. The wounds in the abdominal wall were anaesthetized with 10 ml bupivacaïne 0.5% and sutured with an absorbable suture. Both ovaries and fallopian tubes were examined histopathologically.

2.3. Outcome measures

The main outcome measure is the complication rate as indicator of safety of the surgical procedure. Complications are defined as minor or major complication according to CTCAE (Common Terminology Criteria for Adverse Events) version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/newadverse_2006.pdf). Complications were considered major when surgical re-intervention was needed, when the patient needed a transfusion or when there was a prolonged hospital stay due to the complication. Minor complications were described as complications with a marginal clinical relevance and required no specific medical intervention. At their follow up visit to the outpatient clinic 6 weeks after surgery, patients were asked if they had any complaints or complications post-operatively. Complications were recorded in the patient files. Secondary outcomes are conversion rate, operating time (skin–skin time) and duration of hospital stay (days).

2.4. Statistics

All results were analysed using SPSS version 16.0 software. For demographic characteristics, descriptive statistics were calculated. Descriptive values of variables are expressed as median, range and percentages. Patients were stratified according to mutation status. Differences regarding age, BMI and co-morbidity were evaluated by the Chi-square test. All *P*-values (two-tailed) <0.05 were considered to indicate statistical significance.

3. Results

3.1. Population characteristics

Between September 1995 and March 2006 a total of 179 women decided to have a RRSO of which 164 patients underwent the procedure in the University Medical Center Groningen and met the inclusion criteria. Of the patients included, 15 were operated in another hospital and from another 5 patients no medical records were available. These patients were excluded and a total of 159 women were enrolled in this study. Two patients had a history of a unilateral oophorectomy, one patient had a unilateral salpingo-oophorectomy and two patients had a fallopian tube removed because of an ectopic pregnancy in the past. Eighty-one percent of the 159 women had a proven *BRCA1* or *BRCA2* mutation: 97 patients (61%) were *BRCA1* and 32 patients (20.1%) were *BRCA 2* mutation carriers (Table 1). The remaining 30 patients were members of a HBOC family (18.9%). The median age at time of RRSO was 43.8 years (range 30.3–68.7 years) for all women, 42.9 years in the *BRCA1* group, 48.4 years in the *BRCA 2* group and 46.4 years in the HBOC family members, which was significantly different (Table 1). The median BMI was 24.9 kg/m^2 (range 18.0–48.4 kg/m^2). About a third (30.1%) of the patients were over weighted with a BMI of 25–30 kg/m^2 and 18.7% were obese (BMI > 30 kg/m^2). About two thirds (68.6%) of the patients were premenopausal at the time of RRSO and one-third (31.4%) was postmenopausal. Co morbidity requiring medication was observed in half of the patients. Four women (2.5%) had diabetes, 8.2% were known with a cardiovascular disease and 11.3% were known with an obstructive pulmonary disease. Two patients (1.3%) had a history of endometriosis, 13 women (8.2%) did have a Caesarian Section and 26 women (16.4%) had a previous laparotomy other than a Caesarian Section.

3.2. Characteristics of surgical procedure

Surgical procedures were primarily performed by a gynaecologist and a resident. A primary laparoscopic procedure was performed in 154 patients. The median operating time for a laparoscopic RRSO was 1 h and 45 min (Table 2). In 16.4% of the procedures a RRSO was combined with breast surgery mostly a prophylactic bilateral (13×) or unilateral (6×) mastectomy and a direct reconstruction. However in a few patients a new breast cancer was diagnosed shortly before the RRSO and laparoscopy was combined

Table 1
Patient characteristics.

Mutation carrier	Total patients, $n = 159$	BRCA 1, $n = 97$ (61.0%)	BRCA 2, $n = 32$ (20.1%)	HB(O)C, $n = 30$ (18.9%)	*P*
Age (years) at RRSO					
Median (range)	43.8 (30.3–68.7)	42.9 (30.3–61.1)	48.4 (33.5–66.9)	46.4 (32.8–68.7)	0.02
Age < 40	42 (26.4%)	31	7	2	
Age 40–50	78 (49.1%)	49	11	15	
Age ≥50	39 (24.5%)	17	14	7	
Body mass index (kg/m^2)					
Median (range)	24.9 (18.0–48.4)	24.4 (18.9–41.5)	25.8 (19.72–48.4)	25.2 (19.4–37.7)	*0.51*
BMI < 25	63 (51.2%)	39	11	13	
BMI 26–30	36 (30.1%)	19	8	9	
BMI ≥30	23 (18.7%)	12	7	4	
Menopausal status at RRSO					
Pre- or perimenopausal	109 (68.6%)	70	19	20	*0.34*
Postmenopausal	50 (31.4%)	27	13	10	
Comorbidity					
Yes	72 (45.3%)	44	17	11	*0.43*
No	87 (54.7%)	53	15	19	
If yes,					
Endometriosis	2 (1.3%)	2	0	0	
Caesarean section (CS)	13 (8.2%)	11	2	0	
Previous laparotomy (other than CS)	26 (16.4%)	16	7	3	
Cardiovascular disease	13 (8.2%)	8	3	2	
Diabetes mellitus	4 (2.5%)	1	1	2	
COPD	18 (11.3%)	10	4	4	
Depression/anxiety	9 (5.7%)	3	4	2	
Other	13 (8.2%)	8	2	3	
Oesophagitis		1			
Besnier Boeck disease			1		
Crohn's disease		2			
Cushings disease		1			
Ulcerative colitis		1		1	
Follicular thyroid adenoma					
Pituitary adenoma		1		1	
Migraine					
Psoriasis		1		1	
Rheumatic disease		1			
Hypercholesterolemia					
Regurgitation		1			

with a mastectomy and sentinel node procedure (2×), a lumpectomy (1×), or an axillary lymphadenectomy (1×). In two patients the RRSO was combined with a scar correction of a previous mastectomy and in one with a tattoo of the nipples after a previous mastectomy and reconstruction. In these procedures the gynecologist firstly performed the pBSO, followed by the breast surgery. The median operating time of the combined operation was 4.20 h and varied between 2.25 and 11.15 h.

Five patients (3.1%) underwent a primary laparotomy. In four patients because of a medical history with several laparotomies and massive adhesions, due to endometriosis (in two) or infectious bowel disease (one with ulcerative colitis and one with Crohn's disease). The fifth patient was very obese (BMI 40) which made the gynaecologist decide to perform a primary laparotomy. The median operating time of a primary laparotomy was 2.0 h.

Table 2
Surgical procedure.

	Total patients, $n = 159$
Surgical procedure	
Laparoscopy	154 (96.9%)
Laparotomy	5 (3.1%)
Combined	26 (16.4%)
Operating time (hours)	
Laparoscopy (range)	01:45 (00:20–04:35)
Laparotomy (range)	02:00 (00:50–02:40)
Combined surgery (range)	04:20 (02:25–11:15)
Hospital stay in days	
Median (range) RRSO combined procedure	1 (0–13) 0 (0–6) 6 (0–13)

3.3. Complications intraoperatively

In one 41-year old patient (0.6%) a major intraoperative complication occurred (Table 3). After insertion of the third trochar which ruptured the inferior epigastric artery a bleeding occurred and a haematoma developed between the peritoneum and the fascia. While proceeding it was not possible to get sufficient exposure or control of the bleeding laparoscopically. The procedure was converted to a laparotomy by a median incision. The total blood loss was 500 cm^3. The patient recovered well and was discharged after 3 days.

During one (0.6%) laparoscopic procedure a minor complication occurred intraoperatively. In a 59-year old patient, the needle broke while closing the abdominal fascia. The needle could not be found and intraoperatively an abdominal X-ray was needed to locate the needle which than could be detected under the fascia above the abdominal muscles. The needle was removed successfully. Although the operating time was prolonged with 1 h, the

Table 3
Complications.

	Total patients, $n = 159$
Complications intraoperatively	2 (1.3%)
Broken needle (minor)	1
Bleeding (<500 cm^3) *(major)*	1
Complications post-operatively	5 (3.1%)
Excessive pain *(minor)*	1
Wound infection *(minor)*	2
Haematoma *(minor)*	2

patient was discharged the same day and recovered uneventfully.

3.4. Conversions

Conversions occurred in three patients (1.9%). In two patients a conversion was performed as a consequence of inadequate exposure. In a 51-year old woman because of massive adhesions after a previous laparotomy. She had a good recovery and was discharged 4 days after the procedure. In a 53-year old woman with a previous laparotomy and severe obesity (BMI 48), the ovaries could not be exposed due to adhesions combined with her obesity. The procedure was converted to a laparotomy by a low transverse (Pfannenstiel) incision. The patient left the hospital in a good clinical condition after 6 days. In the third patient, 40 years of age, after placing the camera a brown-green fluid was observed, interpreted as possibly bowel content although without a visible bowel lesion. The procedure was converted to a laparotomy. However, even after thorough inspection of the small bowel and colon no perforation was found. After an abdominal washing the procedure was continued and both ovaries and fallopian tubes were removed. During the same anesthesia the patient underwent a mastectomy of her right breast and a scar correction of her left breast after a previous mastectomy because of breast cancer. She had an uneventful recovery after the combined surgery and she was discharged after 12 days.

3.5. Complications post-operatively

The median hospital stay was 1 day (range 0–13 days). About half of the patients were discharged the same day and a quarter the next day. The patients ($n = 26$) who underwent the procedure combined with a preventive mastectomy had a median hospital stay of 6 days. Post-operative complications during the first 6 weeks after surgery occurred in 5 (3.1%) patients. Two patients (aged 44 years and 47 years) developed a haematoma of the abdominal wall. One of these patients had a prolonged hospital stay of 2 days because of abdominal pain which was treated with paracetamol. The other patient (44 years) developed an abdominal wound haematoma after she was discharged, which she reported only 6 weeks later. No medical doctor was consulted. Two patients (42 and 48 years) developed a wound infection within 2 weeks after laparoscopy. One patient consulted the family doctor 10 days after surgery. The other patient was seen at the outpatient clinic 6 days after surgery with a serous fluid leaking umbilical wound, which was cleaned. No antibiotics were given and she recovered well. The last patient, 43 years, had excessive pain post-operatively which required one dose of 2.5 mg morphine. She stayed an extra night and was discharged the following day.

4. Discussion

The current study showed the short-term clinical data of a RRSO by laparoscopy in women with a *BRCA1* or *BRCA2* mutation or a HBOC family. The observed low intraoperative (0.6%) and post-operative complication rate (3.1%) and short median hospital stay (1 day) reflect the safety of this procedure.

This study is, to the best of our knowledge, the first prospective study on the surgical results of a prophylactic laparoscopic procedure in a selected population of *BRCA1* or *BRCA2* mutation carriers or from a HBOC family. Until now surgical outcomes in this hereditary breast ovarian cancer population have only been published as secondary data. Meeuwissen et al. [12] included 383 women, all members of a HBOC family or women with a proven *BRCA1/2* mutation. All patients entered the surveillance program and were offered a RRSO after the age of 40 years. A total of 133 women chose to undergo this procedure. In 15 patients (11.3%) complications were reported and 7 (5.3%) procedures were converted to a laparotomy. Kauff et al. [13] included 160 *BRCA 1* or *BRCA 2* mutation carriers of whom 98 women chose to undergo a RRSO. Four of the 98 procedures (4.1%) were associated with pre- or post-operative complications of and one procedure (1%) was converted to a laparotomy because of adhesions.

In this study a total of 159 RRSO procedures were performed of which 154 laparoscopically. In only two procedures (1.3%) a complication occurred of which one was major and five patients (3.1%) had post-operative complications of which all were minor.

In this University teaching hospital surgical procedures are primarily performed by a gynaecologist and a resident. Complications during surgery are registered and major complications are discussed and evaluated in a monthly complication audit by gynaecologists and residents. This setting makes it unlikely that the complication rates in our study are biased or underrated. The intraoperative complication rate (1.3%) in the current study is lower than reported in the study by Meeuwissen et al. [12] and comparable to the complication rate published by Kauff et al. [13]. In the Netherlands several studies have evaluated the gynaecological laparoscopic skills under residents [17,18]. It is known that education by a mentor traineeship is accompanied by a low complication rate and a stable conversion rate [17]. The current study, in which all patients were operated in a mentor traineeship setting, showed a low complication and conversion rate comparable to the results of Kolkman et al. [17].

In conclusion, RRSO is a safe procedure with a low incidence of complications and conversions. These findings can be used in counseling women with an inherited high risk of ovarian and fallopian tube cancer. Until more effective screening strategies are found, RRSO is the only effective preventive option which can be safely performed laparoscopically and should therefore be offered to all *BRCA1/2* carriers after child bearing age.

Conflict of interest statement

None of the authors have conflicts of interest.

Contributors

All authors have made substantial contributions to the manuscript. GHB and MJEM contributed to the design of the study. MJEM, GHB, MJAK, POE and HJGA, contributed to the acquisition of the data. All authors contributed to the analysis and interpretation of data. All authors contributed to writing and revising the manuscript and to the final approval of the submitted version.

Funding

There was no funding for this study.

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