Prevalence of Serous Tubal Intraepithelial Carcinoma (STIC) at the Time of Postpartum Contraceptive Procedures during Caesarean Delivery

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Abstract

Background: To assess the prevalence of serous tubal intraepithelial carcinoma (STIC) in women underwent opportunistic salpingectomy at the time of caesarean delivery (CD). Methods: We conducted a retrospective cohort study (2014–2017) of women who received either bilateral total or partial salpingectomy as postpartum permanent contraception procedure during CD. We collected the characteristics of the patients, the type of CD (elective versus unscheduled), the type of surgical procedure and the related complications. We analysed surgical outcomes and calculated the point prevalence of STIC. Results: We enrolled 280 patients. Of these, 107 (38.2%) and 173 (61.8%) underwent respectively total and partial bilateral salpingectomy. Majority of CD were elective (81.8%); we did not find differences for intra- and post-operative surgical procedure-related complications. Bilateral fimbriated-part of the tube was available for analysis in 245 patients and STIC was identified in only one patient (prevalence of 0.4%). Conclusions: The frequency of STIC in patients undergoing partial or total bilateral salpingectomy during CD is extremely low, less than 1%. Total bilateral salpingectomy can be proposed as postpartum permanent contraception procedure without increasing surgical related complications. Further randomised studies are needed to confirm the benefits and safety of this procedure.

Keywords: cancer of the fallopian tube; caesarean delivery; epithelial cancer of the ovary; opportunistic salpingectomy; tubal sterilization

1. Introduction

Ovarian cancer accounts for 3.4% of all new female malignancies and causes 4.7% of female cancer deaths [1]. Epithelial cancer makes up 90% of all cases and, among them, high-grade serous carcinoma (HGSC) is the most common sub type [2]. HGSC represents 60–80% of ovarian epithelial malignancies and causes most deaths for ovarian cancer because of late-stage at the diagnosis with often bowel and upper abdomen involvement [3–5]. Regardless of the type of treatment strategy [6] and the complexity and aggressiveness of the surgical approach [7,8] the outcomes remain poor [9], even though they enhanced in recent years mainly because the introduction of targeted therapies [10,11].

The term ovarian cancer does not refer to a unique disease but to a various range of neoplasms affecting the ovary and, recent findings suggest that HGSC may originate in the fallopian tubes [12,13]. Early stage ovarian cancer is rarely diagnosed [14], since there is a lack of effective screening modalities and, therefore, any chances to reduce the risk of developing a malignancy are of utmost interest. The analysis of BRCA1 and BRCA2 mutations carriers who underwent risk reduction surgery, introduced the hypothesis that HGSC can arise from the tubal fimbra [15] and, although more rarely, from the non-fimbriated part of the tube [16]. Because the distal fallopian tube seems to be the preferred site of serous tubal intraepithelial carcinoma (STIC), irrespective of BRCA status [15,17], a protocol for sectioning and extensively examining the fimbriated end (SEE-FIM) was introduced in 2006 [18]. The frequency of incidental diagnosis of STIC among BRCA 1/2 carriers undergoing risk-reducing surgery ranges from 0.9–4.5% [19,20]; for these patients, the reduction of the risk of developing ovarian, fallopian tube or peritoneal cancer is above 80% [21]. Therefore, minimally invasive bilateral salpingo-oophorectomy is recommended in women with a BRCA1 or BRCA2 mutation between 35 and 40 years or 40 and 45 years, respectively [22]. In the general population, STIC has been found up to 68.4% of surgical specimens when HGSC was present [23] and in less than 1% of women undergoing benign surgery [24,25]. Based on the theoretical benefit in term of risk reduction for ovarian cancer development, in the last few years, salpingectomy at the time of other pelvic surgery has often proposed [26]. Caesarean delivery (CD) is, for most women, the only pelvic...
surgery during the lifespan and may be an opportunity for a concurrent definitive sterilization [27].

The aim of this study is to assess the prevalence of STIC as incidental diagnosis at the time of postpartum contraceptive procedures during CD.

2. Material and Methods

2.1 Study Design

All consecutive women underwent partial or total bilateral salpingectomy during CD at the Department of Obstetrics and Gynaecology of Spedali Civili of Brescia, a tertiary university hospital, from January 2014 to December 2017 were retrieved and included in the study. Inclusion criteria for partial or total bilateral salpingectomy during CD are maternal age >35 and at least one previous caesarean section and/or parity ≥2. Patients underwent other methods of permanent post-partum contraception, including clips and electrocauterization, were excluded. Informed consent for opportunistic salpingectomy was obtained during outpatient clinic evaluation before surgery. In the case of emergency CD, the consent obtained previously was considered valid. No informed consent concerning sterilization was obtained in emergency settings. The Institutional Review Board of our institution approved the study (reference number NP3361).

2.2 Data Extraction

We retrospectively collected all information regarding the characteristics of the patients. We collected demographic and clinical data such as maternal age, parity, number of previous CDs, BMI at the time of delivery, and rate of surgical complications related to the postpartum contraceptive procedures. The study period began when the systematic sectioning and extensively examination of the fimbrial end (SEE-FIM) was routinely applied in our pathology department.

2.3 Surgical Procedure

Elective and unscheduled (either urgent or emergent; Lucas classes 1–3 [28]) CDs were both included in the analysis. Postpartum permanent contraception procedures were performed after the closure of the uterine incision and classified as: (i) bilateral total salpingectomy, when complete transection of the tube to the corpus uteri was done; (ii) bilateral partial salpingectomy, with either segmental resection of the mid tube (Pomeroy or Parkland technique), or the middle and the end with consensual fimbriectomy. Bilateral total salpingectomy was the primary intent of the surgeons, however when intra-abdominal conditions, like widespread adhesions, did not allow it, partial bilateral salpingectomy was performed.

2.4 Pathological Findings

Fallopiian tube specimens were completely embedded for histological examination, following the SEE-FIM protocol [18] and one or multiple formalin-fixed, paraffin-embedded (FFPE) blocks, were got from each tube. A representative tissue section was considered from every FFPE block, stained with haematoxylin and eosin (H&E) and evaluated by an experienced gynecologic pathologist according to the 4th World Health Organization Classification (2014) of Female Genital Tract Tumors [29]. In addition, immunohistochemical analysis was performed on 4 µm FFPE STIC sections with specific antibodies to p53 (clone DO-7, 1:100, Thermo Scientific, Waltham, MA, USA) and Ki67 (clone 30-9, ready to use, Ventana Medical Systems Inc, Tucson, Arizona, USA) on Bond Max Automatic Immunostainer (Leica Biosystems, GmbH, Wetzlar, Germany) and BenchMark ULTRA (Ventana Medical Systems Inc, Tucson, AZ, USA).

2.5 Statistical Analysis

The sample size calculation was based on STIC prevalence in women undergoing benign surgery [17,18]. To achieve a precision of 2% in the estimation of a proportion with a normal two-tailed asymptotic confidence interval (CI) of 95.0%, assuming an overall prevalence of STIC of 1%, we estimated that we needed to consider at least 251 women in the study. We used the software SPSS Statistics for Windows version 22 (IBM; Armonk, New York, USA) for the statistical analysis. Continuous variables were analysed using the Student’s t test whereas categorical variables with the Pearson’s chi-squared test and the Fisher exact test. We defined statistical significance as a p-value of less than 0.05. We expressed the value of point prevalence as percentage with its corresponding 95% CI.

| Table 1. Baseline characteristics of patients. |
|-----------------------------------------------|
| Characteristics                               | n = 280                        |
| Maternal age in years                         | 43.5 (43–44)                   |
| Parity                                        | 2 (2–7)                       |
| Number of previous CD                        | 1.4 (0–4)                     |
| BMI (kg/m²) at delivery                      | 29 (17–59.3)                  |
| Timing of CD                                 |                                |
| Elective                                     | 229 (81.8%)                   |
| Unscheduled                                  | 51 (18.2%)                    |

Data presented as median (interquartile range) or as n (rate).

CD, caesarean delivery; BMI, body mass index.

3. Results

Two hundred and eighty patients received partial or total bilateral salpingectomy at the time of CD. Demographic and clinical characteristics are listed in Table 1. The types of permanent contraception procedures performed are shown in Table 2. No differences were noted regarding the rate of surgical procedure-related complications, regardless of the type of technique and scheduling of CD (Table 3).
Fig. 1. Histological and immunohistochemical characteristics of STIC. H&E section of the fallopian tube, showing a STIC in the lower half of the photograph represented by a pluristratified epithelium composed by highly atypical cells with marked nuclear pleomorphism in contrast to normal adjacent fallopian tube epithelium composed by ciliated cells with bland nuclei (A and B). While STIC is completely negative for p53, the normal adjacent tubal epithelium shows weak positivity for p53 (C). Ki-67 staining showing increased proliferation index in the STIC in comparison to normal adjacent fallopian tube epithelium (D). Positive area for Ki-67 is indicated with the arrows. Magnification 100×, ScaleBar 200 um (A,C,D); Magnification 200×, ScaleBar 100 um (B).

Table 2. Details of postpartum permanent contraception procedures performed at caesarean delivery.

| Postpartum contraception technique | n  = 280 |
|-----------------------------------|---------|
| Bilateral total salpingectomy      | 107 (38.2%) |
| Bilateral partial salpingectomy    | 173 (61.8%) |
| Fimbriectomy                      | 138 (79.9%) |
| Pomeroy                           | 4 (2.3%) |
| Parkland                          | 31 (17.8%) |

Data is presented as n (rate).

The types of complications are described in more detail in a larger population analysed in a previous published paper, that included the patients of the actual study [30].

Bilateral fimbriated-part of the tube was available for 245 histological samples. STIC was found only in 1 of these and the point prevalence was 0.4% (95% CI, 0.403–0.397%).

The patient was 44 years old; she had had two previous CDs and one previous endouterine fetal death at 30 weeks. She underwent bilateral fimbriectomy at the time of CD and STIC was located at the proximal part of the fimbrial end of the left tube (Fig. 1). Histologically it consisted of a thickened epithelium with loss of polarity and superficial tufting, composed of highly atypical cells with enlarged and hyperchromatic nuclei with irregularly distributed chromatin and increased mitotic and apoptotic rate. Immunohistochemical analysis showed complete loss of p53 staining (null-mutation pattern) in the presence of positive internal control and high Ki-67 proliferation index [31].

After two months she underwent staging surgery with peritoneal washing, bilateral ovariectomy and consensual resection of tubal stumps, total hysterectomy, omental and multiple peritoneal biopsies; the surgical access was laparotomic in view of the multiple previous surgeries. No macroscopic lesions were found during surgical exploration and no residual disease was found at pathological examination. Peritoneal citology failed to show neoplastic cells. After 30 months of follow-up, she was free of disease based on ultrasound imaging and CA125 levels. Unfortunately, the
Table 3. Rate of surgical procedure-related complications of postpartum permanent contraception procedures performed at caesarean delivery.

| Surgical complications | Bilateral total salpingectomy n = 107 | Bilateral partial salpingectomy n = 173 | p value |
|-------------------------|---------------------------------------|----------------------------------------|---------|
| Intraoperative          |                                       |                                        |         |
| Scheduled               | 2 (1.8%)                              | 2 (1.2%)                               | 0.66+   |
| Unscheduled             | 1 (0.9%)                              | 2 (1.2%)                               |         |
| Postoperative           |                                       |                                        |         |
| Scheduled               | 2 (1.8%)                              | 3 (1.8%)                               | 0.52+   |
| Unscheduled             | 3 (2.8%)                              | 2 (1.2%)                               |         |
| Total                   | 9 (7.3%)                              | 8 (5.4%)                               | 0.17+   |

Data is presented as n (rate).

+: Chi-Square test.

BRCA analysis was not possible due to a lack of patient compliance.

4. Discussion

The prevalence of STIC at the time of postpartum permanent contraception during CD is less than 1%, as for women who underwent other benign surgery [24,25].

There are different types of postpartum permanent contraception procedures at CD and, there is still no consensus on which one is more cost-effective; the risk reduction in of ovarian cancer and the rate of complications are the parameters that most influence the choice between these. Venkatesh et al. [32] developed a decision-analytic and cost-effectiveness model for US women who received a CD and desired a permanent sterilization in the US population. Three strategies were compared: bilateral tubal ligation, bilateral opportunistic salpingectomy, and postpartum long-acting reversible contraception, on a theoretical cohort consisting of 110,000 pregnant women. Salpingectomy and tubal ligation have both proven to be cost-effective strategies when performed at the time of CD. Salpingectomy was more cost-effective compared to tubal ligation, being also associated with a lower number of ovarian cancers diagnoses and deaths compared with tubal ligation. However, Monte Carlo probabilistic sensitivity analysis estimated that tubal ligation had a 49% chance of being the preferred strategy over salpingectomy; therefore, assuming that the risk of complication is higher for salpingectomy than for tubal ligation, and that the cancer risk reduction of salpingectomy is less than 52%, tubal ligation seems to be the preferred, more cost-effective strategy. The authors conclude that the risks and benefits of salpingectomy with CD need to be better assessed before a preferred strategy can be determined. Nezhat et al. [33] commented on this work, reiterating that a theoretical cohort demonstrating a possible increase in perioperative complications and long-term cost can’t justify the avoidance of opportunistic salpingectomy as postpartum permanent contraception; indeed, they suggested that, when clinically feasible, it should be the preferred method of sterilization at the time of CD. Furthermore, Falconer et al. [34] showed that bilateral salpingectomy was associated with a 50% decrease in risk of ovarian cancer compared with the unilateral procedure.

On the other hand, with regards to the increased risk of surgical complications of total salpingectomy, the debate is still open in the literature. Retrospective and randomized studies have shown similar surgical outcomes between salpingectomy and tubal ligation or partial salpingectomy [35–38]. This is also true for opportunistic salpingectomy performed during hysterectomy for benign pathology, where no differences in the estimated blood loss or perioperative complications were found [39]. In a previous study, we similarly demonstrated a low rate of postpartum contraception related complications and no statistically significant difference of morbidity between total salpingectomy and other approaches, neither when comparing elective and unscheduled CDs; thus, we assumed that it’s a safe procedure [30]. A recent comprehensive meta-analysis [40] showed that complete salpingectomy slightly prolonged surgical time (mean of 6 min); however, the same study reported that bilateral salpingectomy and partial salpingectomy were comparable in estimated blood loss, need for blood transfusion, surgical complications, risk of postpartum haemorrhage, surgical site infection, intensive care unit admission and, need for presentation to hospital after discharge [40]. In 2021, Mandelbaum and colleagues [41] published a population-based retrospective observational study querying the National Inpatient Sample between October 2015 and December 2018 in United States; this study included 397,260 (10.4%) and 203,400 (5.3%) women who received bilateral salpingectomy and bilateral tubal ligation, respectively, at the time of the CD. The authors noted that bilateral salpingectomy procedures increased rapidly between 2015 and 2018, replacing tubal ligation as the most common type of sterilization performed during CD; however, a in a propensity score matched model, women underwent bilateral salpingectomy were more likely to have haemorrhage, blood transfusion, hysterectomy and oophorectomy. These data were also confirmed in the no-hysterectomy group of patients, with a higher rate of haemorrhage and oophorec-
tomy for bilateral salpingectomy group [41]. The authors concluded that given the rapid shift from bilateral tubal ligation to bilateral salpingectomy, further studies are needed to correlate the increased rate of adverse surgical events with early experience [41]. In this scenario, additional data are needed to confirm the safety of opportunistic salpingectomy at the time of caesarean delivery and, the balance with benefits in terms of ovarian cancer risk reduction, in a population in which the BRCA mutation status is unknown.

The prevalence of STIC in our population is low, in line with other published data for benign surgery. STIC diagnosis after fimbriectomy supports the role of the fimbriated-part as principal site of HGSC development. Considering the data of the literature, our study cannot be exhaustive with regards to the benefit-risk balance between total salpingectomy or other sterilization procedures; however, we think that reporting the prevalence of STIC at the time of the CD in the general population can be promote further studies that can shed light on the subject.

Our study has strengths and limitations. Among the strengths of this study, we assessed the prevalence of STIC in a selected childbearing age population of patients who received tubal sterilization at the time of CD, hence excluding the older age groups for which salpingectomy could have different consequences, also in terms of menopausal symptoms [42]. Furthermore, we have also included in the study, albeit not considered for prevalence estimation, a small sample (12.5%) of patients who underwent tubal resection without fimbriectomy (Parkland and Pomeroy techniques); ideally, this group of patients can be considered as the rate of failure in providing an effective strategy for ovarian cancer prevention. The latter, together with the useful insight derived from the study results, can be used as counselling arguments before CD. Among limitations, our study was performed in a single centre and, because of the retrospective nature of the study, we cannot exclude a selection bias, especially about the choice of the surgical procedure depending on the intra-abdominal evaluation of different surgeons. The sample size calculation was at least 251 women, while we have finally included only 245 patients in our analysis. Therefore, considering the population size of the study and the finding of only one case of STIC in this, the prevalence of STIC (0.4%) in patients who underwent the opportunistic salpingectomy during CD, cannot be considered a certain data; further studies on larger populations could help to confirm the finding.

5. Conclusions

The frequency of STIC in patients who underwent partial or total bilateral salpingectomy during CD is very low (<1%). However, considering the low rate of surgical procedure-related complications, opportunistic bilateral salpingectomy can be proposed as principal post-partum permanent contraception. Accounting similar surgical morbidity and surgical time, total salpingectomy, when clinical conditions are permissive, can be performed, so it’s possible to identify the extremely rare cases in which STIC arise from the non-fimbriated part of the tube.

Further studies are needed to confirm the benefits in terms of ovarian cancer risk reduction and safety of the opportunistic salpingectomy at the time of CD.

Author Contributions

SF performed conception and design of the study, acquisition, analysis and interpretation of data and wrote the manuscript; GM performed acquisition, analysis and interpretation of data; FF wrote and revised the manuscript and gave final approval of the version to be published; LA performed analysis and interpretation of data and revised the manuscript; GV performed analysis and interpretation of data and revised the manuscript; ES and FO performed conception and design of the study.

Ethics Approval and Consent to Participate

Institutional Review Board reference number: NP3361.

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Conflict of Interest

The authors declare no conflict of interest.

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