Epithelial ovarian cancer (EOC) continues to represent one of the most lethal conditions in women in the western countries. With the constant shifting of childbearing age towards higher ages, the increasing incidence of EOC in women with active childbearing potential constitutes a therapeutic dilemma [2]. Both patients and treating physicians are being encountered with the abrupt loss of childbearing potential due to the malignant disease, while alternatives are being sought that try to preserve a last hope of fertility within the antitumor treatment [3].

With the constant shifting of childbearing age towards higher ages, the increasing incidence of EOC in women with active childbearing potential constitutes a therapeutic dilemma [2]. Both patients and treating physicians are being encountered with the abrupt loss of childbearing potential due to the malignant disease, while alternatives are being sought that try to preserve a last hope of fertility within the antitumor treatment [3].

Even though radical surgery with the primary objective of maximal tumor reduction is currently the established cornerstone in the management of advanced EOC [4], fertility-sparing techniques are being increasingly incorporated in the therapeutic strategies in early or not bulky forms of the disease. Equivalent to the nowadays established organ-preserving techniques in borderline ovarian tumors, also in early EOC, strategies like preservation of the contralateral ovary and uterus or even in highly specialized cases peritonectomy of the pelvis and uterus serosa to avoid the need of hysterectomy are being recruited [5, 6]. The subsequent systemic chemotherapy within “fertility protecting” programs where chemotherapy is being applied under the concomitant ovarian protection via substances like GnRH analog additionally induce fertility-sparing treatment and offer the affected woman a hope for conception after completion of the anticancer treatment.

Nevertheless, the inevitable question arises, whether fertility-sparing surgery (FSS) for EOC harbors life-threatening
risks, which compromise patient’s survival and set any chance for a normal family life into the background due to early and potentially chemotherapy-resistant relapse.

Since no randomized trials exist or will ever exist to prospectively evaluate and answer this question, our experience is limited to scattered, retrospective cases series. The aim of this paper is to provide an overview of the most significant hitherto reports and discuss future perspectives.

2. Current Indications for FSS in EOC

FSS for ovarian neoplasms have been traditionally adopted in early-stage malignant ovarian germ cell tumors and in ovarian sex cord-stromal tumors such as granulosa-cell tumors, Sertoli-Leydig cell tumors, ovarian dyserminomas, as well as in borderline tumors of the ovary with excellent reproductive outcomes without compromising oncologic safety [7–9]. Gold standard remains however hereby an adequate operative staging in order to unmask occult advanced disease with therapeutic consequences and impact on overall prognosis.

For invasive EOC data are much more constricted and limited to retrospective, nonrandomised series referring mainly to patients with low-grade stage IA tumors with favorable histology, while data regarding higher stages of the disease or unfavorable constellation of histologic characteristics are rather conflicting [6, 10–12]. Overall, in selecting optimal candidates for FSS, the amount of evidence has been too small to accurately estimate the risk of leaving a microscopic tumor in the contralateral ovary [13], especially in high-grade disease with positive peritoneal cytology.

According to the 2007 guidelines of the American College of Obstetrics and Gynecology (ACOG), fertility-sparing surgery for reproductive-age patients with invasive EOC is recommended for highly or moderately differentiated stage IA disease with non-clear-cell histology [14]. In an equivalent manner, the European Society for Medical Oncology (ESMO) referring in 2008 to fertility-sparing techniques in EOC identified patients with unilateral stage I tumor without dense adhesions showing favorable histology (i.e., high or moderate differentiated, non-clear-cell histology) as being the optimal candidates for this procedure [15]. However, the number of published studies concerning fertility-sparing surgery in young EOC patients is rather limited and the evaluated patient’s samples too small to allow unanimous consensus regarding the definition of the selection criteria of the optimal candidates for fertility-sparing surgery in stage I EOC. That leads to a broad variety of national guidelines regarding FSS worldwide, especially in respect to IC (iatrogenic versus not) and/or poorly differentiated disease and to clear cell histologic subtype [16]. Moreover, under additional consideration of the relatively recently emerging dualistic model theory of EOC pathogenesis, which divides EOC in type I and type II disease [17], patients selection for FSS could theoretically be performed under this perspective and hence indicated for early-stage, type I tumors, even though there is currently no evidence that would support such an approach.

Open questions remain if there should be differentiation between iatrogenic IC disease due to intraoperative tumor rupture versus IC due to tumor on ovarian surface or malignant cells in peritoneal cytology, whether patients with G3 tumors with no evidence of further metastatic disease in adequate staging are eligible of FSS and whether nonserous or non-endometrioid histologic subtypes should be a priori excluded from any organ-preserving technique.

3. Oncologic Outcomes after FSS in EOC

Data from the largest report series in the literature concerning oncologic outcome after FSS in EOC are summarized in Table 1. Zanetta et al. published in the year 1997 one of the first reports regarding this issue and was the first to systematically show that fertility-sparing surgery is a safe treatment option for early-stage patients with acceptable oncologic safety profile [12]. Various case series or case reports followed since then with a large peak in the last two years of reports mostly originating from Japan. Satoh et al. attempted for the first time in 2010 to systematically determine selection criteria for fertility-sparing surgery in stage I EOC on the basis of clinical outcomes of more than 200 stage I EOC patients who underwent fertility-sparing surgery [16]. A relapse rate as high as 8.5% was reported with 27% of the relapsed patients presenting recurrence exclusively in the remaining ovary without any distant or peritoneal metastases. Hence, the authors identified stage Ia EOC patients with favorable histology, that is, mucinous, serous, endometrioid, or mixed histology and grade 1 or 2, as the optimal candidates to safely undergo fertility-sparing surgery even without an obligatory subsequent platinum-based adjuvant chemotherapy. In case of stage Ia disease with clear cell histology or stage Ic with unilateral ovarian involvement and favorable histology, authors emphasized the need of a complete surgical staging and an adjuvant platinum-based chemotherapy, since the 5-year recurrent-free survival rate of the fifteen evaluated patients with stage Ic clear cell carcinoma was with 66.0% comparably high, while the fifteen patients with stage Ia clear cell carcinoma showed no evidence of local or distant recurrence. Concerning patients with unfavorable constellation of histological tumor type, that is, stage Ia/G3 disease or stage Ic with clear cell or G3 histology, the authors recommended their exclusion from any fertility-sparing surgical approach [16].

When collectively evaluating most published results so far, mean relapse rates are estimated to be around 10%, even in patient’s cohorts which included also Ic stage disease [12, 13, 18, 20–23]. Nevertheless, when accurately examining the characteristics of the patients who suffered from relapse, they belonged mainly to the subgroup with Ic and/or G3 tumors. Interestingly in many studies no differentiation occurs between Ic due to iatrogenic cyst rupture versus Ic due to malignant cells in the Douglas cytology or surface involvement. Kajiyama et al. [23] assessed survival after FSS separately for these two patients’ subgroups, that is, iatrogenic versus tumorbiologic Ic. He came to the conclusion that progression and overall survival of the patients with stage Ic (surface involvement/positive cytology) were significantly poorer than those of patients with stage Ia after FSS, whereas
<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Pts $N$</th>
<th>Median Age (y)</th>
<th>FIGO stage $N$ (%)</th>
<th>Grade $N$ (%)</th>
<th>Histology $N$ (%)</th>
<th>Relapse rate $N$ (%)</th>
<th>Mean PFS (mo) or 5 y DFS</th>
<th>Characteristics of pts who relapsed</th>
<th>5 y OS</th>
<th>Death</th>
<th>LND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwon et al. 2009 [18]</td>
<td>21</td>
<td>26.7</td>
<td>17 (81%) IA 4 (19%) IC</td>
<td>16 (76%) G1 3 (14%) G2 2 (9.5%) G3</td>
<td>16 (76%) muc 2 (9.5%) endom 2 (9.5%) clear cell 1 (4.7%) serous</td>
<td>1 (4.7%)</td>
<td>34</td>
<td>IC, muc</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Kajiyama et al. 2008 [19]</td>
<td>10</td>
<td>35.9</td>
<td>4 (40%) IA 6 (60%) IC</td>
<td>NR</td>
<td>10 (100%) clear cell</td>
<td>1 (10%)</td>
<td>33</td>
<td>IC, G2, clear cell</td>
<td>NR</td>
<td>1 (10%)</td>
<td>Optional</td>
</tr>
<tr>
<td>Schlaerth et al. 2009 [3]</td>
<td>20</td>
<td>27</td>
<td>11 (55%) IA 9 (45%) IC</td>
<td>14 (70%) G1 5 (25%) G2 1 (5%) G3</td>
<td>11 (55%) muc 1 (5%) serous 6 (30%) endom 1 (5%) clear cell</td>
<td>3 (15%)</td>
<td>4.3 (9–22)</td>
<td>2 IC, 1 IA</td>
<td>84%</td>
<td>3 (15%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Borgfeldt et al. 2007 [20]</td>
<td>11</td>
<td>NO</td>
<td>IA 10 (19%) IC</td>
<td>G1 2 (9.5%) G3</td>
<td>NR</td>
<td>1 (9%)</td>
<td>NR</td>
<td>IC, G3</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Schilder et al. 2002 [11]</td>
<td>52</td>
<td>26</td>
<td>42 (81%) IA 10 (19%) IC</td>
<td>38 (73%) G1 9 (17%) G2 5 (9.6%) G3</td>
<td>25 (48%) muc 10 (19%) serous 5 (9.6%) clear cell 2 (4%) mixed</td>
<td>5 (9.6%)</td>
<td>14 (8–78)</td>
<td>4 IA, G1 1 IC, G2 2 muc 2 serous 1 endom</td>
<td>98%</td>
<td>2 (4%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Kajiyama et al. 2011 [21]</td>
<td>74</td>
<td>&lt;40</td>
<td>36 (48%) IA 1 (1.3%) Ib 37 (50%) IC</td>
<td>57 (77%) G1/G2 4 (5.4%) G3</td>
<td>4 (5.4%) serous 43 (58%) muc 13 (18%) clear cell 4 (5.4%) endom</td>
<td>NR</td>
<td>87.9% 5 y DFS</td>
<td>NR</td>
<td>90.8%</td>
<td>2 (2.7%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Zanetta et al. 1997 [12]</td>
<td>56</td>
<td>29</td>
<td>32 (57%): IA 2 (3.5%): IB 22 (39%): IC</td>
<td>35 (62%) G1 14 (25%) G2 7 (12%) G3</td>
<td>18 (32%) serous 23 (41%) muc 13 (23%) endom</td>
<td>5 (9%)</td>
<td>NR</td>
<td>2 IA,G2, endom 1 IA, G3, muc 1 IA, G1, serous 1 IC, G2, serous</td>
<td>NR</td>
<td>4 (7%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Satoh et al. 2010 [16]</td>
<td>211</td>
<td>29</td>
<td>126 (60%) IA 85 (40%) IC</td>
<td>G1: 160 (76%) G2: 15 (7%) G3 6 (2.8%) clear cell: 30 (14.2%)</td>
<td>126 (60%) muc 27 (13%) serous 27 (13%) endom 10 (4.2%) Clear cell</td>
<td>18 (8.5%)</td>
<td>33.3–100% 5 y DFS</td>
<td>66.7–100%</td>
<td>5 (2.4%)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Kajiyama et al. 2011 [13]</td>
<td>41</td>
<td>&lt;40</td>
<td>27 (66%): IA 14 (34%): IC</td>
<td>NR</td>
<td>100% muc</td>
<td>3 (7.3%)</td>
<td>90.5%</td>
<td>97.3%</td>
<td>1 (2.5%)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Kajiyama et al. 2011 [22]</td>
<td>80</td>
<td>35</td>
<td>40 (50%) IA 40 (50%) IC</td>
<td>—</td>
<td>45 (56%) muc 3 (3.7%)serous 15 (19%) endom 16 (20%) clear cell</td>
<td>10 (12.5%)</td>
<td>85.5%–92.9% 5 y DFS</td>
<td>2: IA 8: IC</td>
<td>89.3%–90.5%</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Kajiyama et al. 2010 [23]</td>
<td>60</td>
<td>30</td>
<td>IA 30 (50%) IB 1 (1.7%) IC 29 (48%)</td>
<td>41 (68%) G1 7 (12%) G2 2 (3.3%) G3</td>
<td>Serous 5 (8.3%) Muc. 34 (56.7%) Endom 11 (18%) Clear cell 10 (17%)</td>
<td>8 (13%)</td>
<td>89.8%</td>
<td>2 IA, 1 IB</td>
<td>89.8%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>580</strong></td>
<td><strong>26–35.9</strong></td>
<td><strong>333 (57%): IA 4 (0.7%): IB 234 (40%): IC</strong></td>
<td><strong>334 (57%): G1 39 (6.7%): G2 20 (3.4%): G3</strong></td>
<td><strong>300 (52%): muc 51 (9%): serous 128 (22%): clear cell 65 (11%): endom</strong></td>
<td><strong>50 (8.6%)</strong></td>
<td><strong>33.3–100% 5 y DFS</strong></td>
<td><strong>66.7–100%</strong></td>
<td><strong>18 (3.1%)</strong></td>
<td><strong>Yes</strong></td>
<td></td>
</tr>
</tbody>
</table>

muc: mucinous; endom: endometrioid.
this was not the case when comparing survival rates of patients after FSS with Ia versus iatrogenic Ic disease, that is, after intraoperative tumor rupture.

In the study of Zanetta et al., none of the women undergoing bilateral oophorectomy had microscopic foci of cancer in the normal-looking contralateral ovary. The rate of bilaterality is congruent with the previous observations of other authors who reported an extremely low rate of contralateral involvement for mucinous tumours [12].

In two very recent studies originating also from the same authors group by Kajiyama et al., the authors assessed the feasibility of fertility-sparing surgery in patients with clear cell or mucinous carcinoma of the ovary, two histological types which have been associated in various reports with a rather less favorable prognosis [16, 22]. In both analyses the authors concluded that FSS in presence of these two histological subtypes was not necessarily associated with a poorer prognosis than after radical surgery and hence feasible. Data are shown in Table 1. This can be possibly attributed to the fact that the negative impact of unfavorable histology on survival has mainly been established for advanced-stage disease III and IV [24, 25]. Underlying theories are mainly based on an increased chemotherapy resistance to the conventional carboplatin and paclitaxel regimens of mainly mucinous cancers resulting in emerging attempts to treat these types similar to intestinal cancers with oxaliplatin and capcitabine ± bevacizumab within randomized trials [24]. In early stage Ia, however, no adjuvant treatment is necessary, with complete resection and adequate staging consisting a sufficient treatment plan.

When attempting to identify a recurring profile of the patients who relapsed after FSS, then no specific pattern can be identified, since in various series also Ia patients tend to recur, whereby here one has to consider the possibility of occult more advanced disease after inadequate staging. One of the major limitations of the existing studies is that not all of the cases underwent an obligatory systematic lymphadenectomy, in which case there might occur an up-staging of some patients [10, 16]. Reported death rates are ranging between 2 and 15%.

4. Reproductive Outcomes after Fertility-Sparing Surgery in EOC

The issue of impaired fertility in young cancer survivors represents a therapeutic dilemma for both treating physicians and affected patients. Systemic and operative oncologic treatments consistently compromise the ovarian function, often resulting in infertility and premature menopause [26–28].

Data regarding reproductive outcome after FSS in EOC are summarized in Table 2. Literature data concerning the rate of women with successful conception after FSS accounts approximately 30% of all patients however, if one takes into consideration only the women with childbearing wish who actively tried to conceive, then rates of successful conception are substantially higher and range from 66% to 100%, indicating that no relevant reproductive impairment exists after FSS. Also, where reported, only the minority of patients required assisted reproductive techniques for a successful conception and pregnancy [3, 10–12, 16, 18, 29].

When evaluating the incidence of spontaneous abortions, then rates range between 11% and 33%. No evidence is however given regarding details about the gestational week, the onset of symptoms, and whether there was a habitual recurring modus, so that no conclusions can be extracted about the cause of the abortions and their pathophysiology.

In the recent evaluation by Satoh et al. [16], there are even details given regarding the restoration of the menstrual cycle after completion of oncologic treatment. A hundred and eighty two patients (96.8%) of the overall 188 who gave information on their menstruation had almost the same cycle of menstruation as before treatment. However, six (5.0%) of the 121 patients who received platinum-based chemotherapy presented a persistent secondary amenorrhoea up to 224 months after completion of 4–6 cycles of systemic chemotherapy. Details about the reproductive outcome of this population are given in Table 2. Five (9.1%) of the 55 patients who successfully conceived have been stated to receive an infertility treatment before pregnancy. Interestingly, the authors report four (9.4%) of the 53 patients who gave birth to children having undergone completion surgery after childbearing, consisting of hysterectomy and contralateral salpingo-oophorectomy.

Wherever reported, none of the patients who successfully conceived and gave birth presented any relevant, cancer-related clinical problems during the perinatal period. Also no higher rates of congenital malformations or abnormal fetal outcomes have been reported in the current literature [11, 16, 32].

5. Hormonal Support Options for Ovarian Protection in Chemotherapy-Induced Gonadotoxicity

It is well known that the number of oocytes decreases as a normal process from the fetal life up to menopause. At 20 weeks of gestation, female infants have about six to seven million oocytes, newborns only one to two million, and women at the age of 37 have only about 25,000 oocytes left. Chemotherapeutic agents, which act cytotoxic by interrupting the normal cell cycle and inducing apoptosis do also negatively affect the highly endocrine-active ovarian tissue. Cisplatin and its analogues, that is, agents which play a highly significant role in the management of ovarian cancer, have been proven to present a risk factor for ovarian failure by an estimated odds ratio as high as 1.77 [28]. In order to decrease chemotherapy-induced gonadotoxicity on young women after FSS, hormonal protection is being recruited to force the ovarian tissue by pituitary downregulation to enter into a state of inactivity and so to make it less susceptible to cytotoxic agents. Various agents have been applied such as GnRH agonists or antagonists, oral contraceptives, or even in a newly setting the selective estradiol receptor tamoxifen. The protective effect of GnRHs against chemotherapy-induced gonadotoxicity is still under debate [33]. The reason is mainly the lacking of large prospectively evaluated
Table 2: Relevant case series reports in the literature concerning fertility-sparing surgery in epithelial ovarian cancer: reproductive outcome.

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Patients (N)</th>
<th>Mean age (years)</th>
<th>FIGO stage N (%)</th>
<th>Childbearing wish N (%)</th>
<th>Successful conception N (%)</th>
<th>Abortions N (%)</th>
<th>IVF N (%)</th>
<th>Delivery modus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwon et al. 2009 [18]</td>
<td>21</td>
<td>26.7</td>
<td>17 (80.9%) : IA 4 (19.04%) : IC</td>
<td>5 (23.8%)</td>
<td>5 (100%)</td>
<td>0</td>
<td>0</td>
<td>Spontaneous</td>
</tr>
<tr>
<td>Schlaerth et al. 2009 [3]</td>
<td>20</td>
<td>27</td>
<td>11 (55%) : IA 9 (45%) : IC</td>
<td>6 (30%)</td>
<td>6 (100%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Borgfeldt et al. 2007 [20]</td>
<td>11</td>
<td>27.5</td>
<td>30 (88%) : IA 1 (3%) : IIa</td>
<td>NR</td>
<td>7</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Morice et al. 2005 [29]</td>
<td>34</td>
<td>27</td>
<td>3 (8.8%) : Ic 1 (3%) : IIa</td>
<td>NR</td>
<td>9</td>
<td>1 (11.1%)</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Schilder et al. 2002 [11]</td>
<td>52</td>
<td>26</td>
<td>42 (80.7%) : IA 10 (19.2%) : IC</td>
<td>24 (46.1%)</td>
<td>17 (71%)</td>
<td>5 (29%)</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Morice et al. 2001 [30]</td>
<td>25</td>
<td>24</td>
<td>19 (76%) : IA 6 (24%) : Ic Ia,G3 : 2 (20%)</td>
<td>4 (16%)</td>
<td>4 (100%)</td>
<td>1 (25%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Raspagliesi et al. 1997 [31]</td>
<td>10</td>
<td>22.7</td>
<td>Ic : 2 (20%) IIIa : 2 (20%) IIIc : 4 (40%) 32 (57%) : IA 2 (3.5%) : IB 22 (39%) : IC 126 (60%) : IA 85 (40%) : IC</td>
<td>5 (50%)</td>
<td>3 (60%)</td>
<td>1 (33%)</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Zanetta et al. 1997 [12]</td>
<td>56</td>
<td>29</td>
<td>NR</td>
<td>20</td>
<td>4 (20%)</td>
<td>0</td>
<td>15 (75%): vaginal 2 (10%): caesarean sections</td>
<td></td>
</tr>
<tr>
<td>Satoh et al. 2010 [16]</td>
<td>211</td>
<td>29</td>
<td>84 (40%)</td>
<td>55 (66%)</td>
<td>10 (18%)</td>
<td>5 (2.4%)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>440</td>
<td>28</td>
<td>279 (63.4%) : IA 4 (1%) : IB 141 (32%) : IC</td>
<td>127 (29%)</td>
<td>22 (17.3%)</td>
<td>5</td>
<td>Mainly spontaneous</td>
<td></td>
</tr>
</tbody>
</table>

NR: not reported.
randomized studies to confirm and establish the protective effect of such agents. In a recent phase II study by the German Hodgkin Study Group, young women with advanced-stage Hodgkin lymphoma were randomly assigned either to receive daily OC or monthly GnRH-a during escalated combination therapy with bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc). The trial had to close prematurely after an interim analysis which showed that in both arms the ovarian follicle preservation rate was 0% with a 95% confidence interval ranging between 0% and 12% [34]. To demonstrate the protective effect of the GnRH analogue triptorelin, on chemotherapy-induced ovarian gonadotoxicity, Tan et al. applied different doses of triptorelin in combination with the alkylating agent busulfan in sexually mature, virgin, female mice. Results have demonstrated a dose-dependent protective effect against gonadotoxic chemotherapy of a GnRH analogue on ovarian reserve, thus suggesting a novel application of GnRH analogues in fertility preservation [35].

Almost all clinical studies assessing the protective effect of GnRH agents have been conducted in patients with haematologic malignancies, breast cancer, or even nonmalignant diseases which however require a cytotoxic treatment like lupus erythematoses [36]. Reviewing of all published studies using GnRH-a or oral contraceptives, data clearly demonstrate that they are too limited to provide conclusive statistical evidence concerning the reduction of premature ovarian failure, even though most studies analyzing the effect of hormonal protection during chemotherapy have shown a reduction of POE in patients receiving GnRH-a or OC during systemic chemotherapy [36].

Recently, also the combination of GnRH antagonist and analogue has been recruited to reduce time for therapy [36].

References


[38] L. Lotz, M. Montag, H. van der Ven et al., “Xenotransplantation of cryopreserved ovarian tissue from patients with ovarian tumors into SCID mice - No evidence of malignant cell contamination,” Fertility and Sterility, vol. 95, no. 8, pp. 2612–2614.e1, 2011.
