

BJOG Mini Commentary

BJOG: 2016-SR-18361R1: Opportunistic salpingectomy for prevention of ovarian cancer

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Running Title: Opportunistic salpingectomy to prevent ovarian cancer

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Opportunistic Bilateral Salpingectomy (OBS) has been proposed and is now increasingly being undertaken as a strategy to prevent ovarian cancer (OC). Darelius et-al present a systematic literature review for impact of salpingectomy on OC-risk, surgical outcomes and endocrine function. The authors highlight and reconfirm the limited and low-quality of available evidence on level of OC-risk reduction and ovarian function (*Darelius, BJOG; 2017*). Two large retrospective studies reporting a 35%-42% OC-risk reduction following salpingectomy, suffer from indication and detection bias. The procedures were not 'opportunistic', number of OCs few, and the comparator in both these studies is no intervention at all rather than the standard surgical procedure. Tubal ligation and hysterectomy itself may offer a ~30% reduction in OC-risk. While no detrimental impact on ovarian function was found, the literature is limited by studies of small sample sizes, younger ages, use of surrogate indicators and brief follow-up. These are not predictive of onset of menopause (*Harlow, Menopause; 2012*). Long-term longitudinal assessment of hormonal function/menstrual cycle is essential to address association with premature menopause. This is critically important due to the detrimental impact of premature surgical menopause on quality-of-life/sexual function, cardiovascular, bone & neurological health, besides mortality. NNH=1:33 for cardiovascular mortality and NNH=1:8 for all-cause mortality (*Parker, ObstetGynecol; 2013*). The lack of detrimental impact of salpingectomy on complications and duration of stay is reassuring although data reportedly limited by historical controls. Should OBS become mandatory more complex procedures may be performed and the complication rate could rise? It also raises logistics for training and implementation. Cost-effectiveness of this procedure cannot be robustly established without addressing the above issues and developing salpingectomy utility-scores.

The biology of OC is complex and our understanding of the interplay between the tube and the ovary in its etio-pathogenesis is incomplete/still evolving. A number of cancers may arise outside the

tube. Precursor lesions called STICs (Serous-Tubal-Intraepithelial-Carcinomas) reportedly co-exist with HGSOC (High-grade-Serous-Ovarian-Cancer) in only 11-60% cases . There are different types of STICs, with varying biology, lag phases, progression rates and outcomes. The natural history of STICs and the rate limiting step in progression to OC remains unknown . Preliminary genomic analysis indicates that in co-existent cases, STICs may be precursors of HGSOC in only 50% cases (*Eckert,CancerDiscov;2016*). A proportion of STICs are thus metastatic. Salpingectomy is unlikely to prevent these cases.

The gaps in knowledge illustrated above raise important caveats with respect to the benefit of salpingectomy and underscore the need for prospective trials with long-term outcomes. It is important for clinicians undertaking this procedure to be aware of these issues and counsel patients appropriately. We found 50% support for introducing OBS in routine practice and 89% support for a clinical trial. A RCT with OC as the primary outcome will be challenging in terms of size, resource and time. However, menopause as the primary outcome requires 3513 subjects/arm, 5-year follow-up, for a HR=1.2 for menopause (power=90%, $\alpha=0.05$). Although incorporation of OBS into routine practice is making undertaking a RCT more challenging, recent/emerging data only re-emphasise the importance for undertaking well-designed prospective trials.

Disclosure of Interests

RM declares research funding from The Eve Appeal, CRUK and Barts and the London Charity into population based risk stratification and targeted ovarian cancer prevention, outside this submitted work.

Funding

The commentary is not funded by any charity or grant.