Opportunistic bilateral salpingectomy (OBS) for the prevention of ovarian cancer should be offered in the context of a clinical trial FOR: There is lack of clarity on a number of key issues

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BJOG DEBATE

Opportunistic Bilateral Salpingectomy (OBS) for prevention of ovarian cancer should be offered in the context of a clinical trial? (FOR the motion)

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Running Title: Opportunistic Salpingectomy for Ovarian cancer prevention

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Increasing evidence and acceptability of the role of the tube in the etiopathogenesis of ovarian cancer has led to Opportunistic Bilateral Salpingectomy(OBS) being considered as an ovarian cancer prevention strategy for premenopausal women (who have completed childbearing) undergoing tubal sterilisation/benign gynaecological surgery. Some clinicians/jurisdictions (e.g. British Columbia) have incorporated this into routine practice. Recent American College of Obstetrics & Gynaecology and Society of Gynaecological Oncology guidelines recommend OBS be considered for ovarian cancer prevention but also highlight the need/importance for further trials to confirm the validity and benefit of this approach.

The arguments for a clinical trial are based on lack of clarity on a number of key issues. (1) The size of ovarian cancer risk reduction: While a 35%-42% reduction was recently published on retrospective analysis of Swedish (*Falconer,2015*) and Danish (*Madsen,2015*) data, the confidence intervals were wide, number of ovarian cancer cases in salpingectomy subgroups small and the Swedish analysis was not adjusted for contraceptive pill use. The biology/etiopathogenesis of ovarian cancer is complex and our understanding remains incomplete. OBS will not prevent cancers arising outside the tube. 15-60% of high-grade serous cancers are reported to have precursor Serous-tubal-insitu-carcinoma(STIC) lesions. The natural history of STICs, and the trigger/rate limiting step in development of ovarian cancer is unknown. There are different types of high-grade serous cancers with different types of STICs, having different biology, lag phases, progression rates and outcomes (*Howitt,2015*). (2) Impact over and above hysterectomy with tubo-ovarian conservation and tubal sterilization per-se, which provide a ~30% reduction in ovarian cancer-risk is unknown. (3) The long-term impact on ovarian function is unknown: This issue is of major relevance given the detrimental impact of premature surgical menopause on cardiovascular, /bone/neurological heath, quality-of-life/sexual function, and mortality (NNH=33 for cardiovascular and NNH=8 for all-cause mortality (*Parker,2013*). Available data are restricted to short term hormonal levels/blood flow indices, which

correlate with fertility rates/IVF outcomes, and are not predictive of risk of premature menopause. Only long-term longitudinal assessment of hormonal levels/menstrual cycle can clarify this issue as there are no validated hormonal criteria that predict duration of menopausal transition/final menstrual period (*Harlow,2012*) (4) Cost-effectiveness in the UK: Levels of beneficial outcomes andsalpingectomy 'utility-scores' assumed in a Canadian analysis (*Kwon,2015*) are unconfirmed, maintaining uncertainty on this issue (5) Training implications for clinicians/ trainees when salpingectomy is undertaken at tubal sterilisation.

Our anonymised web-based survey of UK obstetricians & gynaecologists found broad support (33% performed, 50% supported introduction) for OBS. Simultaneously 53% UK obstetricians & gynaecologists felt OBS should only be offered within a clinical trial, and 89% expressed support for a clinical trial. Lack of data on ovarian cancer-risk reduction(78%), RCT evidence of benefit(76%), and impact on ovarian function(65%) were leading factors limiting its introduction. A randomised trial with ovarian cancer as the outcome maybe challenging in terms of resource and time. Approximately 51,000 subjects in each arm would be required to compare OBS with not undertaking such surgery, with subsequent development of ovarian cancer as primary outcome. A randomised trial with menopause as the primary outcome will require 3513 subjects/arm, with 5 year follow up, for a HR=1.2 for menopause (at 90% power and α=0.05). This will addresses key issues of menopause/ long-term health outcomes and is feasible. The argument for change in practice needs to be driven by the magnitude of 'additional' benefit of OBS on ovarian cancer-risk, weighed against logistics of delivery, implications on training needs, potential complications, cost-effectiveness, impact on menopause and long-term health outcomes. Well-designed trials are needed to achieve this.

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