Should Opportunistic Bilateral Salpingectomy (OBS) for Prevention of Ovarian Cancer Be Incorporated Into Routine Care or Offered in the Context of a Clinical Trial?

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Should Opportunistic Bilateral Salpingectomy (OBS) for prevention of ovarian cancer be incorporated into routine care or offered in the context of a clinical trial?

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UM has a financial interest in Abcodia, Ltd, a company formed to develop academic and commercial development of biomarkers for screening and risk prediction. ES reports personal fees from Ethicon, and from Gedeon Richter, for training healthcare professionals, outside the submitted work. The other authors declare no conflict of interest/ competing interests.

Prof Uziel Beller

Editor in Chief

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Dear Sir,

Increasing evidence that the fallopian tube plays a central role in the origin of epithelial ovarian cancer(OC),[1] the establishment of serous tubal insitu carcinoma(STIC) as a precursor lesion and lack of mortality benefit from screening have given a huge impetus to exploring surgical prevention strategies. Opportunistic Bilateral Salpingectomy(OBS) has been recommended as an OC prevention strategy for premenopausal women who have completed their family and are undergoing tubal sterilization or benign gynaecological surgery. A number of institutions/clinicians led by the group in British Columbia[2] have changed clinical protocols to incorporate this practice. Recent guidelines from the ACOG[3] and SGO[4] recommend OBS be considered as an OC prevention strategy while at the same time highlighting the need/importance for further trials to confirm the validity and benefit of this approach.[3] Recently published retrospective analysis of Swedish[5] and Danish[6] population based data provide initial evidence of benefit from salpingectomy with a 35%-42% reduction in OC risk reported, although the confidence intervals are wide and the number of OC cases in some subgroups is small. The Swedish study was also limited by lack of control for the contraceptive pill. The biology and etiopathogenesis of OC is complex and our understanding of this remains incomplete. OBS will not prevent cancers that arise outside the tube. Only 15-60% of high-grade serous cancers (HGSC) have STIC lesions. The natural history of STICs and the trigger/rate limiting step in the development of OC is unknown. Recent data indicate the presence of different types of HGSC having different types of STICs, with different biology, lag phases, progression rates, outcomes and BRCA status.[7] Hysterectomy with tubo-ovarian conservation and tubal sterilization per-se are associated with a 30% reduction in OC risk,[8, 9] and the additional benefit from salpingectomy above this has not been precisely defined. Prospective high quality data for OBS showing a reduction in OC risk are lacking

and the long term impact of salpingectomy on health outcomes including ovarian function and menopause is unknown.

Through the RCOG we undertook a 19-item anonymised web-based survey of UK obstetricians and gynaecologists (O&Gs), regarding their views and practice of OBS. Of the 395 respondents, 53% were men and 47% women; 76.9% were consultants/post-CCT and 19.3% were trainees. 62.5% were general O&Gs, 18% were general gynaecologists and 17% subspecialists (gynaecological subspecialties). We found reasonable awareness with ~75% having heard of OBS and 61% agreeing with the tubal hypothesis. Awareness in the UK is slightly lower than reports from Canada where 90% had heard of OBS.[10] There was broad support with 33% respondents always/most of the time performing OBS and 50.2% supporting introduction into routine clinical practice. However, this was lower than levels of support reported in Canada and Ireland of 68%[10] and 74-80% respectively.[11] At the same time, 53% of UK O&Gs felt that OBS should be offered only within a clinical trial, with a high 89% respondents expressing support for a clinical trial to evaluate the benefit and short/long term outcomes. This level of support raises the possibility of prospective validation of OBS in the setting of a randomised trial in the UK. There may be greater concern in the UK regarding widespread clinical implementation with lack of data on additional reduction in OC risk (78%), RCT evidence of benefit (76%), and impact on ovarian function (65%) highlighted as leading factors limiting its introduction.

Whether OBS will lead to early menopause is unknown. Available data on ovarian function post salpingectomy are few/limited and restricted to short term outcomes of hormonal levels and ovarian blood flow indices.[12] However, these correlate with ovarian reserve in relation to fertility rates, oocyte retrieval and IVF outcomes,[13] and are not predictive of risk for premature menopause. There are no validated hormonal cut-points that predict the length of the menopausal transition or final menstrual period.[14, 15] Assessment of a longitudinal trend/change in hormonal levels (and menstrual periods) over a period of years following OBS is critically important to assess impact on menopause.

This is relevant given the detrimental impact of premature surgical menopause on cardiovascular, bone, neurological heath and mortality.[16]

Another important issue of concern is potential training implications for clinicians/O&G trainees in the UK: highlighted by 21%/49% respectively. 38% of less experienced (<8years post MRCOG) compared to 12% more experienced (>23years post MRCOG) clinicians felt they would benefit from additional training ($p<0.005$). This is higher compared to 15% Canadian O&Gs who felt additional surgical training would be beneficial.[10]

Views/practice also varies by experience and place of work. More experienced UK clinicians (63% of highest quartile vs 26% in lowest quartile) felt that OBS should only be introduced within a clinical trial($p=0.0002$). Clinicians in university/teaching hospitals (U/TH) compared to district general hospitals(DGH) were more likely to support the tubal hypothesis (66% vs 56%, $p=0.008$), perform OBS (43% vs 28%, $p=0.034$) and support its introduction into clinical practice (56% vs 44% $p=0.043$). While clinicians working at DGH compared to U/TH report greater concerns for lack of long term outcome data ($p=0.019$), RCT evidence of benefit ($p=0.011$) and implications for training for self ($p=0.035$) and trainees ($p=0.043$).

We found a significant lack of awareness regarding the reduction in OC risk associated with tubal ligation and hysterectomy itself with 72-76% respondents being unaware of this. It is possible that enthusiasm for OBS outside a study may be further tempered had these facts been better known. A 6% regret/reversal rate has been reported for women undergoing sterilization.[17] This emerged as another important issue given the irreversibility of salpingectomy compared to ligation. Paucity of cost-effectiveness data was considered a limitation by 45% respondents. A recent study from British Columbia suggests OBS may be cost-effective assuming a '50%' reduction in OC risk and 'no' detrimental impact on menopause/ovarian function.[18] However, prospective data confirming these

levels of beneficial outcomes along with utility scores for salpingectomy are lacking, maintaining uncertainty on this issue. Further prospective studies on cost-effectiveness of OBS are needed.

There is a pressing need to develop consensus on whether or not OBS should be offered primarily within a clinical trial in the UK. This may also be of relevance to other countries debating this issue. While a number of charities, patient groups and learned societies[3, 4] have advocated offering OBS, the need and importance of further trials has also been recognised,[3] with some suggesting this be offered only within a clinical trial.[19] It is important to ensure that any introduction of OBS into clinical practice does not hinder/prevent collection of prospective good quality evidence to validate its efficacy in preventing OC and understand implications on long-term health outcomes. A cohort study will not adequately answer the question of additional impact of OBS over standard surgery. A two arm RCT with OC as the primary outcome would require a multicentre international study of ~100,000 women (51,600/arm) and 10year follow-up (for a 30% difference between arms, 80% power, α=0.05, assuming annual OC incidence of 30/100,000). This will be difficult to fund. A pragmatic and plausible way forward which addresses a key issue would be a RCT with menopause as the primary outcome. A sample size of 7026 women (3513/arm) will detect a HR=1.2 or 4690 (2345/arm) a HR=1.25 (90% power, α=0.05; assuming: 20% event rate, 10% withdrawal rate). This will also address various secondary outcomes highlighted above. Moreover, it is important that all cases of OBS undertaken clinically at benign surgery be properly recorded using a separate hospital code to enable linkage for long term follow-up and data collection. The strength of the argument for change in practice needs to be driven by the magnitude of the additional benefit of OBS on OC risk, weighed against the implications for logistics of delivery, impact on training needs, potential complications, additional costs, and long-term health outcomes of early menopause and its consequences. The RCOG and its subspecialist societies as well as international bodies like ESGO and IGCS have an important role to play in this.

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