International Journal of Gynecological Cancer

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

--Manuscript Draft--

Manuscript Number:	
Full Title:	Should Opportunistic Bilateral Salpingectomy (OBS) for prevention of ovarian cancer be incorporated into routine care or offered in the context of a clinical trial?
Article Type:	Letter to the Editor
Keywords:	ovarian cancer; opportunistic bilateral salpingectomy; high grade serous carcinoma; salpingectomy; risk reduction; fallopian tube
Corresponding Author:	Ranjit Manchanda, MD, MRCOG, PhD Barts Health NHS Trust, Barts Cancer Institute London, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Barts Health NHS Trust, Barts Cancer Institute
Corresponding Author's Secondary Institution:	
First Author:	Ranjit Manchanda, MRCOG, PhD
First Author Secondary Information:	
Order of Authors:	Ranjit Manchanda, MRCOG, PhD
	Dhivya Chandrasekaran
	Ertan Saridogan
	Matthew Burnell
	Robin Crawford
	Elly Brockbank
	Jatinder Kalsi
	Davor Jurkovic
	Usha Menon
Order of Authors Secondary Information:	
Manuscript Region of Origin:	UNITED KINGDOM

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

Ranjit Manchanda[1,2*], Dhivya Chandrasekaran[4], Ertan Saridogan[5], Matthew Burnell[2], Robin Crawford[6], Elly Brockbank[1], Jatinder Kalsi[2], Davor Jurkovic[4], and Usha Menon[2]

[1]Department of Gynaecological Oncology, St Bartholomew's Hospital, London, UK, [2]Department of Women's Cancer, EGA Institute for Women's Health, University College London, London, UK, [3]Barts Cancer Institute, Charterhouse Square, London, UK, [4]Department of Obstetrics and Gynaecology, Northampton General Hospital, Northampton, UK, [5]Department of Gynaecology, University College London Hospital, London, [6]Department of Gynaecological Oncology, Addenbrookes Hospital, Cambridge, UK.

***Corresponding Author**

Dr Ranjit Manchanda
Consultant Gynaecological Oncologist
St Bartholomew's Hospital
7th Floor, Gloucester House
West Smithfield, London EC1A 7BE
Honorary Senior Lecturer
EGA Institute for Women's Health, University College London
Gynaecological Cancer Research Centre
First floor, Maple House
149 Tottenham Court Road
London W1T 7DN
Email- r.manchanda@ucl.ac.uk
Telephone- 02034472112

Key Words- ovarian cancer, opportunistic bilateral salpingectomy, high grade serous carcinoma, salpingectomy, risk reduction, fallopian tube

Acknowledgement:

We are grateful to the RCOG, the President of the BGCS, the President of the BSGE, and BSCCP as well as the members of their executive committees for their support of the survey. We thank members of the BGCS IT subcommittee for their support of our survey of UK clinicians.

This work is supported by researchers at the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

Disclosure

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests' statement

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

International Journal of Gynecological Cancer

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.

References

[1] Crum CP, Drapkin R, Miron A et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. *Curr Opin Obstet Gynecol*. 2007;**19**: 3-9.

[2] McAlpine JN, Hanley GE, Woo MM et al. Opportunistic salpingectomy: uptake, risks, and complications of a regional initiative for ovarian cancer prevention. *Am J Obstet Gynecol*. 2014;**210**: 471 e1-11.

[3] Committee opinion no. 620: salpingectomy for ovarian cancer prevention. *Obstet Gynecol*. 2015;**125**: 279-81.

[4] SGO. Salpingectomy for Ovarian Cancer Prevention. *SGO Clinical Practice Statement*: Society of Gynecologic Oncology 2013.

[5] Falconer H, Yin L, Gronberg H, Altman D. Ovarian cancer risk after salpingectomy: a nationwide population-based study. *J Natl Cancer Inst*. 2015;**107**.

[6] Madsen C, Baandrup L, Dehlendorff C, Kjaer SK. Tubal ligation and salpingectomy and the risk of epithelial ovarian cancer and borderline ovarian tumors: a nationwide case-control study. *Acta Obstet Gynecol Scand*. 2015;**94**: 86-94.

[7] Howitt BE, Hanamornroongruang S, Lin DI et al. Evidence for a Dualistic Model of High-grade Serous Carcinoma: BRCA Mutation Status, Histology, and Tubal Intraepithelial Carcinoma. *Am J Surg Pathol*. 2015.

[8] Cibula D, Widschwendter M, Majek O, Dusek L. Tubal ligation and the risk of ovarian cancer: review and meta-analysis. *Hum Reprod Update*. 2011;**17**: 55-67.

[9] Leonhardt K, Einenkel J, Sohr S et al. p53 signature and serous tubal in-situ carcinoma in cases of primary tubal and peritoneal carcinomas and serous borderline tumors of the ovary. *Int J Gynecol Pathol*. 2011;**30**: 417-24.

[10] Roh MH, Yassin Y, Miron A et al. High-grade fimbrial-ovarian carcinomas are unified by altered p53, PTEN and PAX2 expression. *Mod Pathol*. 2010;**23**: 1316-24.

[11] CRUK. Ovarian Cancer Key Stats. Cancer Research UK 2012:http://www.cancerresearchuk.org/cancer-info/cancerstats/keyfacts/ovarian-cancer/.

[12] Findley AD, Siedhoff MT, Hobbs KA et al. Short-term effects of salpingectomy during laparoscopic hysterectomy on ovarian reserve: a pilot randomized controlled trial. *Fertil Steril*. 2013;**100**: 1704-8.

[13] Barad DH, Weghofer A, Gleicher N. Utility of age-specific serum anti-Mullerian hormone concentrations. *Reproductive biomedicine online*. 2011;**22**: 284-91.

[14] Harlow SD, Gass M, Hall JE et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Menopause*. 2012;**19**: 387-95.

[15] Randolph JF, Jr., Zheng H, Sowers MR et al. Change in follicle-stimulating hormone and estradiol across the menopausal transition: effect of age at the final menstrual period. *J Clin Endocrinol Metab*. 2011;**96**: 746-54.

[16] Parker WH, Feskanich D, Broder MS et al. Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study. *Obstet Gynecol*. 2013;**121**: 709-16.

[17] Westhoff C, Davis A. Tubal sterilization: focus on the U.S. experience. *Fertil Steril*. 2000;**73**: 913-22.

[18] Kwon JS, McAlpine JN, Hanley GE et al. Costs and benefits of opportunistic salpingectomy as an ovarian cancer prevention strategy. *Obstet Gynecol*. 2015;**125**: 338-45.

[19] Tanner EJ, Long KC, Visvanathan K, Fader AN. Prophylactic salpingectomy in premenopausal women at low risk for ovarian cancer: risk-reducing or risky? *Fertil Steril*. 2013;**100**: 1530-1.

Copyright Transfer and Disclosure Form

Click here to download Copyright Transfer and Disclosure Form: RM_OBS paper_BMJ open_coi_form_v2.pdf

Copyright Transfer and Disclosure Form
Click here to download Copyright Transfer and Disclosure Form: coi_OBS_Chandrasekaran.pdf

Copyright Transfer and Disclosure Form
Click here to download Copyright Transfer and Disclosure Form: OBS paper_coi_disclosure-saridogan.pdf

Copyright Transfer and Disclosure Form
Click here to download Copyright Transfer and Disclosure Form: OBS paper_coi_disclosure_Burnell.pdf

Copyright Transfer and Disclosure Form

Click here to download Copyright Transfer and Disclosure Form: OBS paper_coi_disclosure_crawford.pdf

Copyright Transfer and Disclosure Form

Click here to download Copyright Transfer and Disclosure Form: OBS paper_coi_disclosure_brockbank.pdf

Copyright Transfer and Disclosure Form

Click here to download Copyright Transfer and Disclosure Form: OBS paper_CoI Discclosure_JK.pdf

Copyright Transfer and Disclosure Form

Click here to download Copyright Transfer and Disclosure Form: Jurkovic_OBS_paper_CoI_Discclosure.pdf

Copyright Transfer and Disclosure Form
Click here to download Copyright Transfer and Disclosure Form: OBS paper_coi_disclosure_Usha Menon.pdf