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Incessant ovulation and ovarian cancer – a hypothesis re-visited

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Abstract

Ovarian cancer continues to be a silent killer. Most women have advanced disease at the time of diagnosis. Intensive efforts to develop effective screening strategies have not so far met with success. There is a need to re-visit the potential of prevention strategies. In 1971, the author submitted a hypothesis for a possible relationship between incessant ovulation and development of epithelial ovarian cancer. Subsequent research from different disciplines opened new frontiers to be explored for prevention in the general population and in high-risk groups, and for opportunistic interventions. The protective effect of oral contraceptive pills has been well documented. Widespread use of the pill in the past several decades is credited with a fall in the incidence of ovarian cancer in the general population, countering the effect of low parity. Removing the barriers against contraceptive access and satisfying the still unmet contraceptive need could expand the protective coverage. Enhanced understanding of the biological mechanisms involved in process of ovulation offers the promise of non-hormonal pharmacologic suppression of follicle rupture for women who have risk factors and do not need contraception. The evidence for a possible origin of epithelial cancer in the fimbria of the Fallopian tube presents an opportunity for preventive intervention, during hysterectomy, where salpingectomy alone may provide protection while one or both ovaries are conserved. Finally, the incessant ovulator egg-laying hen has demonstrated its potential as an experimental model for chemoprevention of epithelial ovarian cancer.

Key words: **Incessant ovulation, prevention, oral contraception, ovarian cancer.**

Introduction

Ovarian cancer is a silent killer. Most women have advanced disease at the time of diagnosis. Intensive efforts have been directed towards developing effective screening strategies. These efforts have not so far met with success (Moyer, 2012). Screening for ovarian cancer with the serum marker CA-125 and trans-vaginal ultrasound did not result in a decrease in ovarian cancer mortality, after a median follow-up of 12.4 years (National Cancer Institute, 2013a). There is a need to re-visit the potential of prevention strategies.

In 1971, the author submitted a hypothesis for a possible relationship between the repeated involvement of the ovarian surface in the process of ovulation and the frequency of the development of the common epithelial ovarian neoplasms (Fathalla, 1971). The hypothesis was based on epidemiological data of reproductive risk factors in ovarian cancer and on data from comparative oncology in animals with different ovulation patterns. In the human female, ovulatory cycles are almost continuous from menarche to the menopause. Social conditions of modern life not only render the majority of ovulations purposeless, but also allow relatively infrequent non-ovulatory physiological rest-periods of pregnancy and lactation. In other mammals, ovulations may be limited to a breeding season, and the reproductive potential is generally exercised to the full, allowing adequate physiological non-ovulatory rest-periods. Comparative ovarian oncology shows the rarity of epithelial tumours in these animals. An exception is the domestic fowl, with its frequent egg-laying, in which adenocarcinoma of the ovary is the commonest neoplasm. The plausibility of the hypothesis is supported by the unique nature of the ovulatory process as a hormone induced injury

involving processes of trauma and repair, with possibilities for DNA damage.

Subsequent research from different disciplines, briefly reviewed here, documented the protective effect of oral contraceptives, enhanced our understanding of the biological mechanism of the ovulation process including the possible pharmacologic production of luteinized unruptured follicles, brought evidence for a possible origin of epithelial cancer in the fimbria of the Fallopian tube, and demonstrated the usefulness of the egg laying hen as a model to study the pathogenesis and chemoprevention of ovarian cancer. These advances suggest new frontiers to be explored for prevention of ovarian cancer in the general population, for prevention in high-risk groups because of hereditary or reproductive factors and for opportunistic interventions.

Oral contraceptives (OCs) and ovarian cancer

The incessant ovulation hypothesis predicted in 1971 that suppression of ovulation by oral contraceptives will reduce ovarian cancer risk, a factor that should then be considered when the pros and cons of OCs are evaluated (Fathalla, 1971). The protective effect of OCs has been subsequently reported in several studies. A 2008 collaborative reanalysis of data from 45 epidemiological studies including 23 257 women with ovarian cancer and 87 303 controls from 21 countries confirmed this risk reduction and showed that the longer women had used oral contraceptives, the greater the reduction, and that the reduction persisted for more than 30 years after oral contraceptive use had ceased, but became somewhat attenuated over time (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008). More recently, a systematic review and meta-analysis of 24 case-control and cohort studies showed significant reduction in ovarian cancer incidence in ever-users compared with never-users and a significant duration-response relationship, with reduction in incidence of more than 50% among women using OCs for 10 or more years (Havrilesky et al., 2013). The review concluded that the observed association between OCs use and reduced ovarian cancer risk fulfills many of the classic criteria for causal inference in epidemiology, including strength of association, consistency across studies, temporality, a biological gradient, biological plausibility, and coherence.

The use of Depot Medroxyprogesterone Acetate (DMPA) was also found to be associated with a 39% reduction in the risk of epithelial ovarian cancer (Wilailak et al., 2012). A significant risk reduction (83%) was observed when the duration of DMPA use was more than 3 years. The protective effect of hormonal suppression of ovulation does not rule out a possible additional hormonal modifying effect, whether by suppressing gonadotrophin production or a direct effect of the hormonal drugs.

Reducing the risk of ovarian cancer in the general population

The prevalence of use of oral contraceptives can have an impact on the incidence of ovarian cancer. A report in 2008 estimated that oral contraceptives have already prevented some 200 000 ovarian cancers and 100 000 deaths from the disease, and that over the next few decades the number of cancers prevented will rise to at least 30 000 per year (Collaborative Group on Epidemiological Studies of Ovarian Cancer.

A study of the decline in ovarian cancer incidence and mortality among U.S. women age 35-59 years during the period 1970-1995, a period during which parity has declined while oral contraceptive use has increased, reported that although the decline in parity would be expected to increase ovarian cancer incidence, the increasing prevalence and duration of oral contraceptive use was probably responsible for the overall decline in incidence (Gnagy et al., 2000). In another study, the observed fall in incidence in Western Europe and a corresponding rise in Southern and Eastern Europe was explained to be partly attributable to increasingly widespread use of oral contraceptives in the former and to reduced fecundity in the latter (Bray et al., 2005).

According to a recent United Nations estimate, oral contraceptives are being used worldwide by 8.8 percent of women aged 15-49 married or in union, 18.4 percent in more developed regions, and 7.3 percent in less developed regions (United Nations Population Division, 2011). World users of oral contraceptives were thus estimated to be more than 100 million. Oral contraceptive use can be increased if women's contraceptive needs are met. According to the United Nations report, 11.2% of women aged 15-49 married or in union who were fecund but not using contraception at the time of the survey, reported not wanting any more children or wanted to delay the next child, (11.4% in less developed regions, 24.2% in least developed regions). This translates to a figure of 105,25,563 women worldwide. Easing of prescription requirements to allow over-the-counter access can be a move in the right direction (Grindlay et al., 2013).

Other beneficial and adverse side effects of OCs have to be taken into consideration when deciding on eligibility for use, and when women make informed contraceptive choices.

Ovarian stimulating drugs and ovarian cancer: A still debated clinical challenge

The increasing use of ovarian stimulating drugs in the past few decades to induce multiple ovulations in the treatment of infertility and in assisted reproduction raised concern about a possible long term effect on the development of epithelial ovarian cancer. Conflicting results have been reported in small studies (Gadducci et al., 2013). A recent Cochrane systemic review included a total of 182,972 women from 11 case-control studies and 14 cohort studies (Rizzuto et al., 2013). The review found no convincing evidence of an increase in the risk of invasive ovarian tumours with fertility drug treatment, but that there may be an increased risk of borderline ovarian tumours in subfertile women treated with IVF. Because of a high risk of bias in the studies analysed, the review called for more studies at low risk of bias. Confounding variables, in reference to the incessant ovulation hypothesis, include whether super-ovulation was followed by pregnancy, whether the infertile patients treated were regularly ovulating or were anovulatory, and whether other hormonal treatments, particularly progesterone, were administered in large doses after ovulation. While results so far are re-assuring, it is clinically wise to follow the recent guidance to limit the use of ovulation induction or ovarian stimulation agents to the lowest effective dose and duration of use. (NICE clinical guideline, 2013). Simplified protocols for infertility management are also to be encouraged (Ombelet, 2013).

The ovulation process

Ovulation is a unique process in that it constitutes a hormone-induced injury. Advances in molecular biology provided better understanding of the mechanisms involved in a complex process (Murdoch et al., 2010). The ovulatory surge of gonadotropin induces an inflammatory reaction which brings the actual rupture of the ovarian surface epithelium. The process is prostaglandin mediated. DNA-damaging reactive oxygen species are generated by inflammatory cells attracted to the vicinity of the ovulatory stigma. Potentially mutagenic lesions in DNA are normally countered by TP53 tumor suppressor-dependent cell-cycle arrest and base excision repair mechanisms. A link between incessant ovulation, inflammation and epithelial ovarian carcinogenesis is plausible (Fleming et al., 2006).

Advances in the understanding of the process of ovulation threw more light on the phenomenon of luteinized unruptured follicles (LUF), where the mature follicle does not rupture, the oocyte is not released and the process of luteinization and hormonal production proceeds as normal. Ovarian monitoring by ultrasound in women receiving ovarian stimulation drugs showed a higher frequency of LUF (Qublan et al., 2006). The LH surge induces the expression of the prostaglandin synthase 2 gene (PGS-3) that codes for an enzyme whose activity is essential for follicular rupture. If this enzyme were selectively inhibited, ovulation would be eliminated without blocking luteinization and synthesis of steroid hormones. Oral administration of the cyclooxygenase-2 (COX-2) inhibitor meloxicam was found to block the process of ovulation in nonhuman primates when administered to simulate emergency contraception (Hester et al., 2010). Pharmacologic production of luteinized unruptured follicles by prostaglandin synthetase inhibitors or other drugs to prevent ovulation and simulate a normal non-conception cycle with unaltered steroid patterns and levels and cycle length has been proposed as a promising lead for future contraception (Harrison and Rosenfield, 1996).

Interventions in patients at a high risk for developing ovarian cancer

Women with reproductive risk factors, women with a family history, and women who are BRCA1 and BRCA2 mutation carriers who need contraception can benefit from the protective effect of OCs if they conform to the eligibility criteria and make an informed choice. The same reproductive risk factors are associated with ovarian cancer risk in BRCA1 carriers to a similar relative extent as in the general population (Antoniou et al., 2009). Based on solid evidence, current use of estrogen/progestogen OCs is not associated with a long-term increased risk of breast cancer but may be associated with a short-term increased risk while a woman is taking OCs (National Cancer Institute, 2013 b). The risk of breast cancer declines with time since last use. Women with risk factors who have no need for contraception, either not being in sexual union or are infertile may benefit from periodic suppression of ovulation. A suggestion has been made that catholic nuns should have access to oral contraceptives (Britt and Short, 2012). Although non-hormonal pharmacologic suppression of ovulation, by prostaglandin synthetase inhibitors or other drugs to prevent rupture of the ovarian follicle, offers an attractive approach for contraception, its periodic use by women in high-risk groups who do not need contraception but need protection from ovarian cancer, may be more feasible. It will not require the level of effectiveness of OCs. It will not necessitate prolonged regular use. It will also be free from

hormonal adverse effects. A recent meta-analysis suggested that non-aspirin NSAIDs may be protective against ovarian cancer, but recommended that additional analyses, focusing on dose, duration, and frequency of NSAID use and accounting for ovarian cancer heterogeneity are necessary to further elucidate the association. (Murphy et al., 2012).

A Fallopian tube origin for epithelial ovarian cancer

Serous carcinomas of the ovary share many similarities and biochemical markers with the Fallopian tube epithelium. While this can be explained by the common embryonic origin of the ovarian surface epithelium and the Mullerian epithelium of the tube, it has recently raised the possibility that the fimbrial end of the Fallopian tube may be an alternative source or main source of ovarian serous carcinoma (Zheng and Fadare, 2012). A tubal fimbrial origin can also be explained by the incessant ovulation hypothesis. Ovulation has been shown to impact on both the ovarian surface epithelium and the tubal epithelial cells (King et al., 2011). An acute pro-inflammatory environment is created following ovulation at the surface of the ovary and within the distal fallopian tube. With the release of an oocyte with its adherent cumulus granulosa cells into the adjacent fallopian tube, both the ovarian surface and the tubal fimbria are bathed with follicular fluid containing inflammatory cytokines, reactive oxygen species, and steroids (Tone et al., 2012).

A tubal fimbrial origin of epithelial "ovarian" cancer, predisposed to by the repeated process of ovulation and ovum pick up, has implications for research and for cancer prevention. Routine careful examination of Fallopian tubes removed at the time of hysterectomy may offer clues to early stages of cancer and pre-cancer (Vang et al., 2012).

Tubal sterilization

Tubal sterilization has been reported to be associated with a reduced risk for ovarian cancer (Cibula et al., 2011). The use of perineal talc has been incriminated as a possible mechanism for ovarian cancer pathogenesis, which is prevented by tubal block. A prospective analysis of perineal talc use and the risk of ovarian cancer based on the Nurses' Health Study (a prospective study of 121 700 female registered nurses in the United States who were aged 30-55 years at enrollment in 1976), provided little support for any substantial association between perineal talc use and ovarian cancer risk overall; however, perineal talc use may modestly increase the risk of invasive serous ovarian cancer (Gertig et al., 2000).

An alternative explanation for a protective effect of tubal sterilization, taking into consideration a fimbrial origin of ovarian cancer and the role of ovulation, can be the disturbed process of ovum pick-up due to the distancing of the tubal fimbria from the site of ovulation after excision or cauterization of a part of the tube. Studies have suggested the importance of the proximity of the fimbrial ovarian relation as an important factor in ovum pick up and fertility (Roy et al., 2005).

Opportunistic intervention

When hysterectomy is performed on young women, removal of the ovaries will protect against the development of ovarian cancer, but it may have its negative effects. A report of over 24 years of follow-up, of 29,380 women participants of the Nurses' Health Study, concluded that compared with ovarian conservation, bilateral oophorectomy at the time of hysterectomy for benign disease was associated with a decreased risk of breast and ovarian cancer but an increased risk of all-cause mortality (Parker et al. 2009; 2013). In no analysis or age group was oophorectomy associated with increased survival. If the origin of cancer is mostly in the fimbrial end of the Fallopian tube, salpingectomy alone may be sufficient to reduce the risk of cancer and preserve ovarian function. While further research, in case control and longitudinal studies, is needed to verify the validity of this protective effect, salpingectomy can be recommended as a routine procedure if one or both ovaries are to be conserved at the time of hysterectomy.

Prophylactic oophorectomy is generally reserved for women who have a deleterious mutation in a BRCA1 or BRCA2 gene. Salpingectomy alone may offer an attractive alternative if ovarian conservation is desired (Kamran et al., 2013). A future pregnancy may still be possible by assisted reproduction. Further research is needed to validate this approach.

The hen as an experimental model

There are biological limitations for mammalian and primate animal models for ovarian epithelial cancer (Lu et al., 2009). The incessant ovulator egg-laying hen, on the other hand, presented a near ideal experimental model (Lee and Song, 2013). Clear advantages of the hen model include spontaneous tumor formation without the need for an exogenous carcinogen or genetic engineering. Approximately 83% of hens develop ovarian epithelial cancer after 3 to 4 years of continuous laying of eggs. Hens and women share an incessant ovulatory pattern,

involving repetitive epithelial injury and repair with associated inflammatory factors in a hormonal milieu. Genotoxic insults may target the ovarian surface epithelium or the fimbrial mucosa, both proposed sites of origin of epithelial ovarian cancer. The 2-year-old hen would have ovulated about the same number of times as a woman who has reached menopause. There are unique similarities in the characteristics and biomarkers of human and chicken ovarian cancers (Hakim et al., 2009). Recent research has shown that oral contraceptives decrease the prevalence of ovarian cancer in the hen, as it does in women (Trevinol et al., 2012). The incessant ovulator domestic hen offers a model for future studies on chemoprevention of epithelial ovarian cancer.

References

Antoniou AC, Rookus M, Andrieu N et al. Reproductive and hormonal factors, and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: Results from the international BRCA1/2 carrier cohort study. Cancer Epidemiol Biomarkers Prev. 2009;18:601-10.

Bray F, Loos AH, Tognazzo S et al. Ovarian cancer in Europe: Cross-sectional trends in incidence and mortality in 28 countries, 1953–2000. Int J Cancer. 2005;113:977-90. doi: 10.1002/ijc.20649.

Britt K, Short R. The plight of nuns: hazards of nulliparity. Lancet. 2012;379:2322- 3.

Cibula D, Widschwendter M, Ma´jek O et al. Tubal ligation and the risk of ovarian cancer: review and meta-analysis. Hum Reprod Update. 2011;17:55-67.

Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23 257 women with ovarian cancer and 87 303 controls. Lancet. 2008;371:303-14.

Fathalla MF. Incessant ovulation-a factor in ovarian neoplasia? Lancet. 1971; 2(7716):163.

Fleming JS, Clare R. Beaugie CR et al. Incessant ovulation, inflammation and epithelial ovarian carcinogenesis: Revisiting old hypotheses. Mol Cell Endocrinol. 2006;247:4-21.

Gadducci A, Guerrieri ME, Genazzani AR. Fertility drug use and risk of ovarian tumors: a debated clinical challenge. Gynecol Endocrinol. 2013;29:30-5. doi: 10.3109/09513590.2012.705382.

Gertig DM, Hunter DJ, Cramer DW et al.. Prospective study of talc use and ovarian cancer. J Natl Cancer Inst. 2000;92:249-52.

Gnagy S, Ming E1, Devesa S et al. Declining ovarian cancer rates in U.S. women in relation to parity and oral contraceptive use. Epidemiology. 2000;11:102-5.

Grindlay K, Burns B, Grossman D. Prescription requirements and over-the-counter access to oral contraceptives: a global review. Contraception. 2013;88:91-6.

Hakim AA, Catherine P. Barry CP et al. Ovarian adenocarcinomas in the laying hen and women share similar alterations in p53, ras, and HER-2/neu. Cancer Prev Res. 2009;2:114-21.

Harrison PF, Rosenfield A., Editors, Committee on Contraceptive Research and Development, Division of Health Sciences Policy, Institute of Medicine. Contraceptive research and development- Looking to the future. National Academy Press, Washington DC. 1996. p.134.

Havrilesky LJ, Moorman PG, Lowery WJ et al. Oral contraceptive pills as primary prevention for ovarian cancer: A systematic review and meta-analysis. Obstet Gynecol. 2013;122:139-47.

Hester KE, Harper MJK, Duffy DM. Oral administration of the cyclooxygenase-2 (COX-2) inhibitor meloxicam blocks ovulation in nonhuman primates when administered to simulate emergency contraception. Hum Reprod. 2010;25:360-7.

Kamran MW, Vaughan D, Crosby NA et al. Opportunistic and interventional salpingectomy in women at risk: a strategy for preventing pelvic serous cancer (PSC). Eur J Obstet Gynecol Reprod Biol. 2013;170:251-4. doi: 10.1016/j.ejogrb.2013.06.030.

King SM, Hilliard TS, Wu LY et al. The impact of ovulation on Fallopian tube epithelial cells: Evaluating three hypotheses connecting ovulation and serous ovarian Cancer. Endocrine-Related Cancer. 2011;18:627-42.

Lee J-Y, Song G. The Laying Hen: An Animal Model for Human Ovarian Cancer Reprod Dev Biol. 2013;37:41-9.

Lu KH, Yates MS, Mok SC. The Monkey, the Hen, and the Mouse: Models to Advance Ovarian Cancer Chemoprevention. Cancer Prev Res. 2009;2:773-5. doi: 10.1158/1940-6207.

Moyer VA, U.S. Preventive Services Task Force. Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med. 2012; 157:900-4.

Murdoch WJ, Murphy CJ, Van Kirk EA et al. Mechanisms and pathobiology of ovulation. Soc Reprod Fertil Suppl. 2010;67:189-201.

Murphy MA, Trabert B, Yang HP et al. Non-steroidal anti-inflammatory drug use and ovarian cancer risk: findings from the NIH-AARP Diet and Health Study and systematic review. Cancer Causes Control. 2012;23:1839-52.

National Cancer Institute (a): PDQ® Ovarian Cancer Screening. Bethesda, MD: National Cancer Institute. Date last modified 07/25/2013. Available at: http://cancer.gov/cancertopics/pdq/screening/ovarian/HealthProfessional. Accessed 16/09/2013.

National Cancer Institute (b): PDQ® Ovarian Cancer Prevention. Bethesda, MD: National Cancer Institute. Date last modified 23-07-2010. Available at: http://cancer.gov/cancertopics/pdq/prevention/ovarian/HealthProfessional. Accessed 26/09/2013

NICE (National Institute for Health and Care Guidance). Clinical guideline 156. : Assessment and treatment for people with fertility problems. Issued: February 2013. http://publications.nice.org.uk/fertility-cg156

Ombelet W. The Walking Egg Project: Universal access to infertility care –from dream to reality. FV&V in ObGyn. 2013;5:161-75.

Parker WH, Broder MS, Chang E et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. Obstet Gynecol. 2009; 113:1027-37. doi: 10.1097/AOG.0b013e3181a11c64.

Parker WH, Feskanisch, 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. doi: 10.1097/AOG.0b013e3182864350.

Qublan H, Amarin Z, Nawasreh M et al. Luteinized unruptured follicle syndrome: incidence and recurrence rate in infertile women with unexplained infertility undergoing intrauterine insemination. Hum Reprod. 2006;21:2110-3.

Rizzuto I, Behrens RF, Smith LA. Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility. Cochrane Database Syst Rev. 2013;8:CD008215. doi: 10.1002/14651858.

Roy KK, Hegde P, Banerjee K et al.. Fimbrio-ovarian relationship in unexplained infertility. Gynecol Obstet Invest. 2005;60:128-32.

Tone AA, Virtanen C, Shaw P et al. Prolonged postovulatory pro-inflammatory signaling in the Fallopian tube epithelium may be mediated through a BRCA1/DAB2 Axis. Clin Cancer Res. 2012;18:4334-44. doi: 10.1158/1078-0432.

Trevino1 LS, Buckles EL, Johnson PA. Oral contraceptives decrease the prevalence of ovarian cancer in the hen. Cancer Prev Res. 2012;5:343-9. doi: 10.1158/1940-6207.

United Nations Population Division | Department of Economic and Social Affairs. World contraceptive use 2011. www.un.org/esa/population/publications/contraceptive 2011/contraceptive2011.htm

Vang R, Shih IeM, Kurman RJ. Fallopian tube precursors of ovarian low- and high grade serous neoplasms. Histopathology. 2013;62:44-58. doi: 10.1111/his.12046.

Wilailak S, Vipupinyo C, Suraseranivong V et al. Depot medroxyprogesterone acetate and epithelial ovarian cancer: a multicentre case-control study. BJOG. 2012; 119: 672-7. doi: 10.1111/j.1471-0528.2012.03298.

Zheng W, Fadare O. Editorial Commentary: Fallopian tube as main source for ovarian and pelvic (non-endometrial) serous carcinomas. Int J Clin Exp Pathol. 2012;5: 182-6.