Incessant ovulation and ovarian cancer
A swan song
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The Swan song is based on a popular belief that the swan, when it approaches the end of life, makes a musical song. The relation of incessant ovulation to ovarian cancer has been a subject that interested me for a long time. Considering age, this is probably the last time I talk about it. This is why I labeled the talk as a swan song.
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.
On World Cancer Day this year, the International Agency for Research on Cancer issues a press release, highlighting that the global battle against cancer will not be won by treatment alone, and that effective prevention strategies are urgently needed to prevent cancer crisis.

Because ovarian cancer is a silent killer, prevention strategies are particularly important. There is a need to re-visit the potential of prevention strategies. The incessant ovulation hypothesis presents such opportunities for prevention.

In 1971, I 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).
This is a copy of the Lancet communication of 1971. I do not expect you to read it on the screen. But I am showing it to make two points that may be of help to our younger colleagues. As you can see, the paper is only one page, and it has been the most cited paper of all my publications. Brevity is a virtue in scientific communication. A paper is not judged by its length but by its message. The second point is to direct attention to the phrasing of the title: Incessant ovulation: A factor in ovarian neoplasia? While the lay press tries to attract readers by putting exciting exaggerated headlines, scientific communication should be different. In this title, incessant ovulation is proposed as a factor, not the factor or the cause, and it is put as a question not a statement.

The hypothesis was based on epidemiological data about 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.
My aim in revisiting the incessant ovulation hypothesis with you today is to share with you some recent data on the potential implications of the hypothesis for ovarian cancer prevention, in the light of both current knowledge and future promising research.

I propose to discuss the potential implications under the above four main headings. Let us start with prevention in the general population.
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). At the time,
there were no epidemiologic studies about the topic. But many studies followed, and I want to share with you some results from large studies.

A 2008 collaborative re-analysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls from 21 countries confirmed this risk reduction, showed that the longer that 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).
Oral contraceptives (OCs) and ovarian cancer

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.

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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.
OCs and reducing the risk of ovarian cancer in the general population

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. Ovarian cancer and oral contraceptives, 2008)

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).
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OCs prevalence

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 one hundred million (out of 1,178, 863 000 women). 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 more than 100 million women worldwide. Easing of prescription requirements to allow over-the-counter access can be a move in the right direction (Grindlay et al, 2013).
Should we increase OCs use to maximize its impact on prevention of ovarian cancer worldwide? The answer has to be qualified. 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. What we should do is to fulfill the contraceptive unmet need. If this overall need is met, may more women who are medically eligible will make an informed choice to us OCs to avoid an unwanted pregnancy and benefit secondarily from the cancer protective effect.

Contraceptive unmet need

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.

Meeting the contraceptive unmet need will increase OCs use and can decrease ovarian cancer incidence in the general population.

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

- 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.

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

Most of the studies have not confirmed a link between these drugs and invasive ovarian cancers, although some studies have suggested that the risk of borderline ovarian tumors may be increased. More large well-designed studies are still needed to further clarify the effects on cancer risk of these drugs and will allow more in-depth subgroup analysis based on both patient and disease characteristics.


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.

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

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.

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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).

We move next to prevention in high risk groups

These high risk groups fall in different categories.
Incessant ovulation and ovarian cancer
Implications for cancer prevention

High risk groups:
- Women with reproductive risk factors.
- Women with a family history and women who are BRCA1 and BRCA2 mutation carriers.

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).

- Women who need contraception
- Women who do not need contraception

Let us start with women in high risk groups who need contraception. 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). The concern about a long term increase risk of breast cancer is not based on solid evidence.
Prevention in patients at a high risk for developing ovarian cancer

Women with risk factors who need contraception can benefit from the protective effect of OCs if they conform to the eligibility criteria and make an informed choice.

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). The risk of breast cancer declines with time since last use.

But what about women with high risk factors who do not need contraception? 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.
Incessant ovulation and ovarian cancer
Implications for cancer prevention

High risk groups:
- Women with reproductive risk factors.
- Women with a family history; women who are BRCA1 and BRCA2 mutation carriers.
- Women who need contraception
- Women who do not need contraception

In a recent paper to the Lancet, a proposal was made that catholic nuns should have access to OCs use.

Oral contraceptives for nuns??

Today, the world’s 94 790 nuns still pay a terrible price for their chastity because they have a greatly increased risk of cancer: a hazards of their nulliparity. Nulliparous women have a higher number of ovulatory menstrual cycles than do parous women because of the absence of pregnancy and lactation, and an increased number of cycles affects cancer risk.

If the Catholic Church could make the oral contraceptive pill freely available to all its nuns, it would reduce the risk of cancer, and give nuns’ plight the recognition it deserves.


It is true that women at high risk of ovarian cancer, who do not need contraception, may benefit from periodic suppression of ovulation. But using the pill for this purpose is an
“over-kill”. OCs are powerful hormonal drugs and their prolonged use is justified by their contraceptive beneficial effect. Can scientific research help? Mother nature says yes.

**Prevention in patients at a high risk for developing ovarian cancer**

For women with risk factors who have no need for contraception, either not being in sexual union or are infertile and who may benefit from periodic suppression of ovulation

A research question:

Can we suppress only the process of follicular rupture without inhibition of follicular growth and without suppression of the development of corpus luteum?

Luteinized unruptured follicles in ovary are known to occur in mammals and women.

Van de Lagemaat R et al. Reproduction 2011;142:893-96
Red circle indicates the retained oocyte. Cumulus expansion and oocyte maturation seemed to have been completed; however, the final follicle rupture did not take place.

**Prevention in patients at a high risk for developing ovarian cancer**

For women with risk factors who have no need for contraception, either not being in sexual union or are infertile and who may benefit from periodic suppression of ovulation

A research question:
- Can only the ovulation process be suppressed without inhibition of follicular growth and development of corpus luteum?
- Can the process of follicular rupture be suppressed with pharmacologic non-hormonal agents?

The answer of recent advances in molecular biology is yes. We now have a much better understanding of the process underlying follicular rupture.
This picture is from a rare video shown on the television channel BBC.

The human egg has been caught, in close, emerging from the ovary. It does not give the picture of a simple peaceful traumatic puncture of the ovarian surface epithelium.

**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 ovulation process

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 and reconciled 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 (US Institute of Medicine Report, 1996).
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**Prevention in patients at a high risk for developing ovarian cancer**

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 periodic use by women in high risk groups who do not need contraception but need protection from ovarian cancer. 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. But further research is needed.

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.
Prevention in patients at a high risk for developing ovarian cancer

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).

Incessant ovulation and ovarian cancer
Implications for cancer prevention

- Prevention in the general population
- Prevention in high risk groups
- Opportunistic interventions
- New research frontiers
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.

Can the incessant ovulation hypothesis suggest an alternative to oophorectomy for ovarian cancer prevention? Yes, there is the promise of prophylactic salpingectomy.
Incessant ovulation and ovarian cancer
Implications for cancer prevention

The promise of prophylactic salpingectomy as an opportunistic intervention and an alternative to oophorectomy

A Fallopian tube origin for epithelial ovarian cancer

Serous carcinomas of the ovary share many similarities and biochemical markers with the Fallopian tube epithelium.
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).

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. The impact of the ovulation process on the tube should not be surprising in view of the close relationship of the tubal fimbria to the ovary at the time of ovulation.
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).
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).

**Opportunistic intervention**

If the origin of serous cancer is mostly in the fimbrial end of the Fallopian tube, salpingectomy alone may be sufficient to reduce the risk of serous 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.**

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.

**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).

**Incessant ovulation and ovarian cancer**

**Implications for cancer prevention**

- Prevention in the general population
- Prevention in high risk groups
- Opportunistic interventions
- New research frontiers

The hen as an experimental model
Our hero for future research on the prevention of ovarian cancer is the incessant ovulating egg laying hen.

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 (Hakim et al., 2009).

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of the hen model include spontaneous tumor formation without the need for an exogenous carcinogen or genetic engineering.

The hen as an experimental model

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).

The incessant ovulator egg laying hen presents a near ideal experimental model to develop new chemoprevention strategies.

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Incessant ovulation and ovarian cancer
Implications for cancer prevention

“Take home” messages:

■ Meeting the contraceptive unmet need will increase OCs use and can decrease ovarian cancer incidence in the general population.
■ It is advisable to limit the use of ovulation induction or ovarian stimulation agents to the lowest effective dose and duration of use.

Incessant ovulation and ovarian cancer
Implications for cancer prevention

“Take home” messages (cont.):

■ Women with risk factors who need contraception can benefit from the protective effect of OCs if they conform to the eligibility criteria and make an informed choice.
■ Women with risk factors who have no need for contraception, may benefit from periodic suppression of ovulation with the promise of pharmacologic non-hormonal suppression of ovulation.
Incessant ovulation and ovarian cancer
Implications for cancer prevention

“Take home” messages (cont.):
■ Salpingectomy can be recommended as a routine procedure if one or both ovaries are to be conserved at the time of hysterectomy.
■ The incessant ovulator egg laying hen presents a near ideal experimental model to develop new chemoprevention strategies.

A final thought about incessant ovulation, the changing woman and the challenge to the Ob/Gyn profession

Let me conclude with a final thought about incessant ovulation, the changing woman and the challenge to our profession. Women have incessant ovulation because they have changed socially but not biologically.

From the hunter gatherer to the modern woman

The modern woman in the post-industrial society has to cope with her new life while burdened with a reproductive system that has evolved to serve well the survival and reproductive success in her life in a hunter-gatherer society.
From the hunter gatherer to the modern woman

A woman in a hunter-gatherer society will get her first pregnancy soon after puberty, will lactate for three or four years, then will have other successive pregnancies and breastfeeding periods. During her reproductive life span, she will probably have no more than 50 ovulations, spaced by prolonged physiological anovulatory rest periods.

Incessant ovulation is only one of the challenges which the changing woman continues to present to our noble profession. Where are women going, and where are they taking us in the future has been a topic of science fiction, about women in a brave new world.

Quo vadis Ms Homo sapiens?
The changing woman
A continuing challenge to the Ob Gyn profession

- Reproduction: A function of women, not the function of women
- The breast: from maternal to sexual
- Divorce of sex from reproduction:
  - Sex without reproduction
  - Reproduction without sex
- The vagina: from a birth canal to a pleasure canal

Women in a Brave New World

Women in a Brave New World
The end of viviparity

"Mustapha Mond leaned forward, shook a finger at them. ‘Just try to realize it’, he said, and his voice sent a strange thrill quivering along their diaphragms, ‘Try to realize what it was like to have a viviparous mother’

Aldous Huxley. Brave new world, 1977

Not only will fertilization take place in vitro, but embryonic and foetal development will also take place in vitro in special incubators or hatcheries. There will be an end to pregnancy and delivery.
Will that mean the end for the noble profession of obstetrics?
Probably not.

Women in a Brave New World
The end of viviparity
But not the end of obstetricians

“Dr Wells advised me to have a
Pregnancy substitute.”

“But, my dear, you’re only nineteen. The first pregnancy substitute isn’t compulsory till twenty-one.”

‘I know, dear. ..Dr Wells told me that brunettes with wide pelvises, like me, ought to have their first Pregnancy Substitute at seventeen.’


In this passage of the novel, obstetrician will be till in business and in demand to administer “pregnancy substitutes”. The clever Dr Wells twists the rules to do more business by informing his client how she needs the substitute earlier.
So, women may continue to change. But our profession will continue to be around, will adapt, and will continue to do good business.
References


Hester KE, Harper MJ, Duffy DM. Oral administration of the cyclooxygenase-2 (COX-


Roy KK, Hegde P, Banerjee K, et al.. Fimbrio-ovarian relationship in unexplained

An open access article based on the lecture: