Epidemiologic Studies on The Association of Ovarian Cancer and Use of Long-Acting Progestogen-Based Contraceptives, Intrauterine Contraceptive Devices and Partner Vasectomy

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Summary

BACKGROUND

Oral contraceptives have been shown to be inversely associated with ovarian cancer. The interelation between use of other types of contraceptives and ovarian cancer have not been established. The objective of this narrative review was to examine epidemiologic studies of Intrauterine Contraceptive Devices (IUDs), long-acting progestogen-based contraceptives, partner vasectomy, and ovarian cancer.

METHODOLOGY

Relevant epidemiologic studies were identified through a search for the MEDLINE, EMBASE and CINAHL databases. All studies published in English on March, 2018 were included.

RESULTS

Of the 11 studies identified, two out of four reported statistically were significantly of lower risk for ovarian cancer associated with the use of Depot Medroxyprogesterone Acetate (DMPA). Whereas, two earlier studies observed statistically non-significant risk estimates greater than 1.00. Eight studies assessing the association between ever-use of IUDs and ovarian cancer had mixed findings. A pair of double studies assessing the interelation between partner vasectomy and ovarian cancer reported statistically non-significant risk estimates below 1.00.

CONCLUSION

Use of DMPA, levonorgestrel-releasing IUDs and partner vasectomy's association is of lower risk of ovarian cancer. The Association of Ovarian Cancer with use of IUDs only is not clear. However, copper- bearing IUDs possibly increase a risk. These findings are not definitive; more studies are needed to assess these associations more.

Key words: "Ovarian cancer, DMPA, Vasectomy, IUDs, Contraceptives".

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Introduction

Ovarian cancer continues to be a devastating disease despite advances in treatment. This is mainly because it is usually detected at an advanced stage (70% diagnosed at stage III) [1].

Reproductive factors had been shown to have a substantial influence on the risk of this disease. Of particular interest are contraceptives, as those, if causally associated with reduced risk, provide an

approach to prevention that was within an individual's control. In addition, because contraceptives are widely used, even a small variation in risk would have far reaching consequences for public health [2].

Oral Contraceptives (OCs) have been shown to be inversely associated with ovarian cancer ever-use of OCs was associated with a 30-40% lower risk than never-use. If considered causal as seems reasonable given both the consistency of the epidemiologic data and the plausibility of the likely mechanisms, then we can say that protection is greater with longer duration of use, with about 20% reduction in risk factor after 5 years of use, increasing to 50% or more after 15 years of use [3 - 7].

This protective effect declines with time since last use. A similar beneficial effect is seen in BRCA mutation carriers and in women with a family history of ovarian cancer, albeit from a higher baseline risk. Other factors known to be associated with a lower risk of ovarian cancer include parity, breastfeeding, and tubal ligation [5 - 8].

The association between use of other types of contraceptives and the risk of ovarian cancer has not been established. Because the mechanisms of action of OCs on ovarian cancer are not fully established, asking whether other approaches to contraceptives provide benefit is an important question. Here we present a narrative review of epidemiologic studies addressing the relationship between the risk of ovarian cancer and the use of intrauterine contraceptive devices (IUDs), long-acting progestogen-based contraceptives, and spousal/ partner vasectomy.

Materials and Methodology

Relevant epidemiologic studies were identified through a research of the MEDLINE, EMBASE and CINAHL database using the key words ('ovarian cancer'/'ovarian tumour') and ('injectable contraceptive agent'/ 'medroxyprogesterone acetate' /'contraceptive implant') and ('intrauterine contraceptive device'/ intrauterine contracept*') 'vasectomy' and 'cancer risk'.

All original studies published in English on 20th March, 2018 were included. Additional papers were found by checking reference lists. No eligibility criteria was used based on quality of individual studies. Alternatively, study quality was assessed, with relevant comments included in the text and *Tables* next. pg.

A total of 11 articles were identified. Of which:

1. Four studies assessed the association of ovarian cancer and use of Depot Medroxy Progesterone Acetate (DMPA).
2. Eight reported on the association with the use of IUDs.
3. Two examined the association with partner vasectomy (some studies investigated more than one type of contraceptive).

RESULTS

Progestogen-Based, Long-Acting Contraceptives

Whether there was an association between progestogen-based, long-acting contraceptives and the risk of ovarian cancer, which DMPA has been most studied, no establishement had been made. Study summary assessing the relationship between use of DMPA, and the risk of ovarian cancer is presented in ***Table 1. next page.***

In a study in Shanghai involving 229 women with ovarian cancer and a similar number of controls, there was no statistically significant association between DMPA and ovarian cancer: compared to never-use, ever-use of DMPA associated with an odds ratio (OR) of 2.8 (95% confidence interval [CI]: 0.9, 8.5). There was no relationship between duration of DMPA use and the risk of ovarian cancer.

However, only a small number (24 cases and 6 controls) of participants had used DMPA. In addition, in this study, contrary to what is otherwise well established, an inverse association between OCs and ovarian cancer was not found (OR = 1.8; 95% CI: 0.8, 4.1, confined to short duration users [<1 year]) [9].

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives, conducted in Mexico and Thailand, found no association between DMPA use and ovarian cancer. There was also no relationship between ovarian cancer and patterns of use of DMPA (duration of use; time since first use). Ever-use of DMPA was associated with a relative risk (RR) of 1.07 (95% CI: 0.6,

Table 1: *Summary of Epidemiologic Studies Assessing the Association of DMPA and the Risk of Ovarian Cancer.*

Author (Year)	Study Period	Study Design and Area	Study population	Results		Adjusted for	Comments
				Ever Vs Never use	*Patterns of Use*		
Wilailak et al.[6] (2012)	2006 to 2008	Hospital-based case-control study (12 Hospitals across Thailand)	Cases: 330; 20 -70 years old; with EOC Controls: 982 age matched patients 59 cases and 252 controls had ever-used DMPA.	OR=0.61 (95% CI: 0.44, 0.85; P=0.002)	Use for >3 years: OR=0.17 (95% CI: 0.07, 0.39; P<0.001)	Breastfeeding, combined OCs, parity, family history of gynaecological cancer	The largest case-control study assessing the association between DMPA use and ovarian cancer
Urban et al. [3] (2012)	1995 to 2006	Hospital-based case-control study (Johannesburg, South Africa)	Cases: 182; 18 -79 years old; with ovarian cancer Controls: 1,492 women with cancer types that are not associated with hormonal contraceptives 24 cases and 390 controls had ever-used DMPA.	OR=0.35 (95% CI: 0.17, 0.71; P = 0.004)	Use for ≥ 5 years: OR=0.07 (95% CI: 0.01, 0.49; P = 0.008)	Age, year of diagnosis, education, smoking, alcohol, parity, age at first birth, & number of sexual partners	High prevalence of use of injectable contraceptives (26%). Low power to assess associations by type of contraceptive used. OCs assumed to be combined OCs, and Injectables to be progesterone-only preparations
Stanford & Thomas. (1991) [10] (The WHO Collaborative Study of Neoplasia and Steroid Contraceptives)	1979 to 1988	Hospital-based case-control study (Mexico & Thailand)	Cases: 224; born after 1925; with EOC. Controls: 1,781; matched on age, hospital and year of interview 9.8% of cases and 12.9% of controls had ever-used DMPA.	RR=1.07 (95% CI: 0.6, 1.8).	Use for ≥ 5 years: RR=1.09 (95% CI: 0.4, 3.2) Age in years at diagnosis: ≥ 40, RR=1.35 (95% CI: 0.7, 2.6); > 40, RR=0.82 (95% CI: 0.3, 1.9)	Parity and oral contraceptive use.	Low power to detect association between ovarian cancer and DMPA.Included tumours of borderline malignancy
Shu et al. [9] (1989)	1984 to 1986	Population-based case-control study (Shanghai China)	Cases: 229; 18 to 70 years old; with ovarian cancer. Controls: 229; matched on age 6 cases and 24 controls had ever-used DMPA	OR= 2.8; (95% CI: 0.9, 8.5)	No relationship with duration of use	Education, parity, ovarian cyst, and age at menarche	No association with ever-use of OCs (OR=1.8; 95% CI= 0.8, 4.1). Low statistical power.

CI: confidence interval; DMPA: depot medroxyprogesterone acetate; EOC: epithelial ovarian cancer; OCs: oral contraceptives; OR: odds ratio; RR: relative risk.

1.8). Although there was a difference in the direction of association between histologically borderline and malignant tumours among histological subtypes, the differences were not statistically significant.

However, the study had low statistical power to detect an interelation between DMPA use and epithelial ovarian cancer. (23% chance of detecting a 25% risk reduction of Epithelial Pvarian Cancer(EOC), at a statistical significance level of 0.05, in ever-users of DMPA, and much lower power to detect an association with duration of use) [10].

Two recent, large studies have found DMPA to be inversely associated with ovarian cancer, with evidence of a dose-response relationship with longer duration of use.

In a large hospital-based case-control study involving South African black women, compared to never-use of hormonal contraceptives, ever-use of injectable contraceptives was found to be inversely associated with the risk of ovarian cancer (OR = 0.35; 95% CI: 0.17, 0.71). Exclusive use of injectable contraceptives for ≥5 years was also associated with a statistically significant lower risk (OR = 0.07; 95% CI: 0.01, 0.49);

However, it was noted that the association with long duration use was based only on one case. In addition, in this study, injectable contraceptives were assumed to be progesterone-only preparations, but use of combined injectable contraceptives in this group of women cannot be ruled out [3].

A more recent hospital-based case-control study carried out in Thailand found a statistically significant lower risk in ever-users compared to never-users of DMPA (OR = 0.61; 95% CI: 0.44, 0.85). An inverse trend in risk was observed with longer duration of use, with a statistically significant lower risk being observed after more than 3 years of use (OR = 0.17; 95% CI: 0.07, 0.39). So far, this is the largest case-control study done to assess the association between DMPA use and risk of ovarian cancer [6].

Intrauterine Contraceptive Devices (IUDs)

Studies have produced conflicting results regarding the use of IUDs and ovarian cancer. A summary of studies assessing the relationship between use of IUDs, and the risk of ovarian cancer is presented in ***Table 2 next page.***

In the Shanghai, case-control study, compared to never-use, ever-use of an IUD was linked with a possibly lower risk of ovarian cancer (OR = 0.5; 95% CI: 0.2, 1.1), but the study had low statistical power [9].

A prospective cohort study (the Shanghai Women's Health Study [SWHS]), reported no association between risk of ovarian cancer and use of IUDs (hazard ratio [HR] = 1.03; 95% CI: 0.62, 1.73, for ever-use compared to never-use).

Overall, no conection was found between use of any contraceptive method and ovarian cancer including oral contraceptive use and tubal ligation, (HR = 1.10; 95% CI: 0.66, 1.82 and HR = 1.17; 95% CI: 0.62, 2.20, respectively). This study had a small number of cases and the sample size and power were probably inadequate to assess the association between intrauterine contraceptive use and ovarian cancer (power and sample size calculations were not provided). In addition, information was not available on the type of IUDs or OCs used [11].

After a longer follow up (mean follow-up of 12.6 years), compared to never-use, ever-use of IUDs was not associated with a statistically significant lower risk of ovarian cancer (HR=0.79; 95% CI: 0.55, 1.13). However, relative to never use, use for >20 years was inversely associated with ovarian cancer (HR=0.62; 95% CI: 0.40, 0.97). A dose-duration response was also observed (P-trend = 0.04).

There was no difference in risk between serous and non-serous tumours. No association was observed between use of oral contraceptives or tubal ligation and ovarian cancer (HR = 1.02; 95% CI: 0.69, 1.51 and HR = 0.96; 95% CI: 0.60, 1.56, respectively) [12].

A hospital-based case-control study in Vietnam reported a statistically significant lower risk of ovarian cancer in ever-users of IUDs (OR=0.5; 95% CI: 0.4, 0.8). In this study, the relationship between risk and duration of use was not described, and type of IUDs used was not specified. More so, use of OCs was not associated with ovarian cancer (OR=0.8; 95% CI: 0.4, 1.6) [13].

Ness et al. also observed a statistically significant lower risk of ovarian cancer with IUD use (OR = 0.75; 95% CI: 0.59, 0.95). In this study, IUDs were inversely

Table 2: *Summary of Epidemiologic Studies Assessing the Association of Use of IUDs and the Risk of Ovarian Cancer.*

Author (Year)	Study Period	Study Design and Area	Study population	Results		Adjusted for	Comments
				Ever Vs Never use	Patterns of Use		
Soini et al. [14] (2016)	1994 to 2013.Mean follow-up: 11.5 years	Population-based prospective cohort study (Finland)	93, 843 women; 30-49 years old in 1994-200777 diagnosed with invasive and 55 with borderline ovarian tumours during follow up.	Invasive: SIR=0.59 (95% CI: 0.47, 0.73) Borderline: SIR=0.76 (95% CI: 0.57, 0.99)	Years of use: Invasive: SIRs 0.63 for <5 years; 0.55 for 5-9.99 years; 0.59 for ≥ 10 years. Borderline: SIRs 0.84 for <5 years; 0.58 for 5-9.99 years; 0.92 for ≥ 10 years.	Not done	Findings relate to use of LNG-IUS Lack of information on possible confounders. Risk of selection bias: participants were on LNG-IUS for the treatment of menorrhagia.
Huang et al [12] (2015) (Shanghai Women's Health Study [SWHS])	1997 to 2011 Mean follow-up: 12.6 years	Population-based prospective cohort study (Shanghai, China)	70, 259 women; 40-70 years old at recruitment 174 diagnosed with ovarian cancer during follow up.91 cases had ever-used IUDs.	HR=0.79 (95% CI: 0.55, 1.13)	Years of use:<20 HR =0.93 (95% CI: 0.63, 1.37); ≥20 HR=0.62 (95% CI: 0.40, 0.97)	Age, education, use of other contraceptives, ovulatory years, irregular cycles, family history of cancer, BMI, & exercise.	Lack of information on type of IUD used No association with ever-use of OCs (HR=1.02; 95% CI: 0.69, 1.51).
Soini et al. [15] (2014)	1994 to 2009.	Population-based prospective cohort study (Finland)	93, 843 women; 30-49 years old in 1994-200759 diagnosed with invasive and 40 with borderline ovarian tumours during follow up	Invasive: SIR=0.60 (95% CI: 0.45, 0.76) Borderline: SIR=0.76 (95% CI: 0.54, 1.03)	Invasive: SIRs 0.60 for ≥1 LNG-IUS purchase; 0.51 for ≥2 LNG-IUS purchase. Borderline: SIRs 0.76 for ≥1 LNG-IUS purchase; 0.71 for ≥2 LNG-IUS purchase.	Not done	Findings relate to use of LNG-IUS Lack of information on possible confounders. Risk of selection bias: participants were on LNG-IUS for the treatment of menorrhagia.
Le et al. [13] (2012)	2001 to 2006	Hospital-based case-control study (12 provinces of Northern Vietnam)	Cases: 262; born 1947-1966; with ovarian cancer.Controls: 755; matched on age.	138 cases and 539 controls had ever-used IUDs.	OR=0.5 (95% CI: 0.4, 0.8)	Not reported.	Age, education, parity, age at menarche, OC use, BMI, and menopausal status.

BMI: *Body Mass Index,* ***CI:*** *Confidence Interval,* **EOC:** *Epithelial Ovarian Cancer,* **HR:** *Hazard Ratio,* **LNG-IUS:** *Levonorgestrel Releasing Intrauterine System,***OCS:** *Oral Contraceptives;* **OR:** *Odds Ratio,* **PMH:** *Post-Menopausal Hormone,* **RR:** *Relative Risk;* **SIR:** *Standardised Incidence Ratio.*

Table 2: *(cont. on page 12)*

associated with ovarian cancer among those with short duration of use (OR = 0.53; 95% CI: 0.39, 0.72 for use for ≤4 years), but there was a statistically non-significant positive association with prolonged use (OR = 1.11; 95% CI: 0.63, 1.96 and OR = 1.40; 95% CI: 0.82, 2.39, for use for 5-9 years and ≥10 years respectively).

It is instructive to note that only a small number of participants (n = 14) had used the progestin-containing IUD, which may not have the same association as the copper-bearing IUDs. In this population-based case-control study, all the contraceptive methods assessed were found to be inversely associated with ovarian cancer [4].

In contrast, the US Nurses' Health Study reported a significant higher risk of ovarian cancer for ever-users of IUDs compared with never-users (RR = 1.76, 95% CI: 1.08, 2.85), with the association being stronger for serous and *endometrioid* histological subtypes: RR = 2.17 and RR = 2.40 respectively (95% confidence intervals for these relative risks were not provided).

In this study, the relationship between risk and duration of use was not reported. In addition, the IUDs used by participants in this study were mainly the copper-bearing type and may not reflect the association (if present) with the newer *levonorgestrel*-releasing IUDs (LNG-IUS) [5].

An inverse association specifically between use of LNG-IUS and ovarian cancer has been reported. In a large cohort study in Finland that involved 93,843 women (1,083,126 women-years), use of LNG-IUS for the treatment of menorrhagia was associated with a lower risk of both invasive and borderline ovarian cancer (standardised incidence ratio [SIR] = 0.59; 95% CI: 0.47, 0.73 and SIR = 0.76; 95% CI: 0.57, 0.99, respectively).

Among invasive tumours, the inverse association was strongest for *Mucinous Carcinoma* (SIR = 0.49; 95% CI: 0.24, 0.87) and weakest for *Serous Carcinoma* (SIR = 0.75; 95% CI: 0.55, 0.99), although differences in risk between histologic types were not statistically significant [14].

A lower risk for ovarian cancer (SIR = 0.60; 95% CI: 0.45, 0.76 for invasive and SIR = 0.76; 95% CI: 0.54, 1.03 for borderline tumours) was reported after a shorter follow-up in the same study (855, 324 women years) [15].

However, these risk estimates were not adjusted for possible confounders including parity, and use of OCs. Use of LNG-IUS by the reference population or history of *Oophorectomy* could not be ruled out.

Furthermore, the findings of this study may not be generalizable because participants were on treatment for *menorrhagia* therefore, their risk for ovarian cancer may differ from that of the general population.

(cont. from pg 10)**- Table 2:** *Summary of Epidemiologic Studies Assessing the Association of Use of IUDs and the Risk of Ovarian Cancer.*

Author (Year)	Study Period	Study Design and Area	Study population	Results		Adjusted for :	Comments
				Ever Vs Never use	Patterns of Use		
Ness et al. [4] (2011)	2003 to 2008	Population-based case-control study (Western Pennsylvania, Eastern Ohio, & Western New York State)	Cases: 902; ≥ 25 years old; with primary epithelial ovarian, fallopian tube, or peritoneal cancer Controls: 1,800 frequency matched by age & telephone exchange 12 cases and 17 controls had ever-used IUDs.	OR=0.75 (95% CI : 0.59, 0.95)	Duration of use: ORs 0.53 for ≤4 years; 1.11 for 5−9 years; 1.40 for ≥10 years	Age, parity, race, infertility, family history of ovarian cancer, and use of other contraceptives	Borderline tumours included Histological slides reviewed by study pathologist.Use of any type of contraceptive was inversely associated with ovarian cancer.
Dorjgochoo et al. (2009) [11](Shanghai Women's Health Study [SWHS])	1996 to 2006 Median follow-up: 7.5 years	Population-based prospective cohort study (Shanghai, China)	66, 661 women; 40-70 years old at recruitment 94 diagnosed with ovarian cancer during follow up.47 women with ovarian cancer had ever-used IUDs.	HR=1.03 (95% CI: 0.62, 1.73)	Years of use: <14 HR =1.13 (95% CI: 0.64, 2.02); ≥14 HR=0.93 (95% CI: 0.51, 1.70) Age-1st use: <30 HR= 1.23 (95% CI: 0.68, 2.24); ≥30 HR=0.90 (95% CI: 0.51, 1.62)	Education, age at menarche, parity, BMI, menopausal status, regular exercise, family history of cancer, & smoking.	Histological slides reviewed by study pathologist. Low statistical power Lack of information on specific type of contraceptive used
Tworoger et al. (2007) [5] (US Nurses' Health Study)	1976 to 2004 (28 Years Follow up)	Prospective cohort study(USA)	107,900 US married, female registered nurses; 30-55 years old. 612 diagnosed with invasive EOC during follow up 18 women with ovarian cancer had ever-used IUDs.	RR=1.76 (95% CI: 1.08, 2.85)	Not reported	Age, current BMI, BMI at 18 years, parity, PMH use, smoking, duration of OC use, and age at menarche & menopause	The longest prospective cohort study of incident ovarian cancer, published to date.Repeated measure of variables of interest Histology reports reviewed by study pathologist. Included borderline tumours.
Shu et al. [9] (1989)	1984 to 1986	Population-based case-control study (Shanghai China)	Cases: 229; 18 to 70 years old; with ovarian cancer. Controls: 229; matched on age 3 cases and 3 controls had ever-used IUDs.	OR= 0.5 (95% CI: 0.2, 1.1)	Not reported	Education, parity, ovarian cyst, and age at menarche	No association with ever-use of OCs (OR=1.8; 95% CI: 0.8, 4.1). Low statistical power.

BMI: *Body Mass Index,* ***CI:*** *Confidence Interval,* **EOC:** *Epithelial Ovarian Cancer,* **HR:** *Hazard Ratio,* **LNG-IUS:** *Levonorgestrel Releasing Intrauterine System,***OCS:** *Oral Contraceptives;* **OR:** *Odds Ratio,* **PMH:** *Post-Menopausal Hormone,* **RR:** *Relative Risk;* **SIR:** *Standardised Incidence Ratio.*

Vasectomy

There have been only two studies of the association between partner vasectomy and ovarian cancer. The US Nurses' Health Study, a prospective cohort study, found no association between spousal vasectomy and ovarian cancer (RR = 0.87; 95% CI: 0.63, 1.19) [5], whereas a population-based case-control study found an inverse association of borderline statistical significance with vasectomy (OR = 0.7; 95% CI: 0.61, 0.99) [4]. A summary of these studies is presented in ***Table 3.***

Table 3. *Summary of Epidemiologic Studies Assessing the Association of Partner Vasectomy and the Risk of Ovarian Cancer.*

Author (Year)	Study Period	Study Design and Area	Study population	Results		Adjusted for :	Comments
				Ever Vs Never use	Patterns of Use		
Ness et al. [4] (2011)	2003 to 2008	Population-based case-cont(Western Pennsylvania, Eastern Ohio, & Western New York State)	Cases: 902; ≥ 25 years old; with primary epithelial ovarian, fallopian tube, or peritoneal cancer. Controls: 1,800 frequency matched by age & telephone exchange 14 cases and 17 controls had ever had a vasectomised partner.	OR = 0.77 (95% CI: 0.61, 0.99)	Not reported	Age, parity, race, infertility, family history of ovarian cancer, and use of other contraceptives	Borderline tumours included Histological slides reviewed by study pathologist. Use of any type of contraceptive was inversely associated with ovarian cancer.
Tworoger et al. (2007) [5] (US Nurses' Health Study)	1976 to 2004 (28 Years Follow up)	Prospective cohort study (USA)	107,900 US married, female registered nurses; 30-55 years old. 612 diagnosed with invasive EOC during follow up 46 women with ovarian cancer had ever had a vasectomised partner.	RR=0.87 (95% CI: 0.63, 1.19)	Not reported	Age, current BMI, BMI at 18 years, parity, PMH use, smoking, duration of OC use, and age at menarche & menopause	The longest prospective cohort study of incident ovarian cancer, published to date. Repeated measure of variables of interest Histology reports reviewed by study pathologist. Included tumours of borderline malignancy

BMI: *Body Mass Index,* ***CI:*** *Confidence Interval,* ***EOC:*** *Epithelial Ovarian Cancer,* ***OCs:*** *Oral Contraceptives, Or: Odds Ratio,* ***PMH:*** *Post-Menopausal Hormone, RR: Relative Risk.*

Discussion

In contrast to the inverse associations found recently, large studies on DMPA use and ovarian cancer, findings of the earlier studies on the same risk are surprising. This is because the biologic effects of DMPA could be expected to be protective. Inspide of , the low number of participants in these studies and the fact that DMPA had been used only for a short time made it hard to have strong confidence in the results of these studies [6].

Several hypotheses to explain the inverse association between OCs and ovarian cancer that had been suggested include:

(i) Inhibition of ovulation
(ii) Suppression of *endogenous gonadotropin*
(iii) Androgen and oestrogen production
(iv) Increased levels of circulatory *progesterone*

Long-acting *progesterone*-based contraceptives exert effects similar to those suggested to be responsible for the protective effect of OCs. Most importantly, these contraceptives inhibit ovulation. Use of DMPA also leads to a decrease in *plasma oestrogen* to levels similar to that found in the early to mid-follicular period (100pg/ml) [16,17, 18, 19].

Lower levels, similar to post-menopausal levels (*100pmol)*, had been reported in users experiencing *amenorrhoea*. Although DMPA inhibits endogenous progesterone production use of DMPA results in high levels of plasma progesterone (1ng/ml) for the 3 months following injection DMPA inhibited the mid-cycle LH surge but, overall, did not affect *gonadotropin* levels

From the above, the overall effect should be a reduced risk of ovarian cancer if, indeed OCs confer protection through these proposed biologic mechanisms.[3, 17].

On the other hand, it had been suggested that DMPA might not have had the same effect as the progestin components of OCs because they did not belong to the same class of progestins. Most of the progestins in combined OCs were *19-nortestosterone* derivatives, whereas DMPA was a progesterone derivative [18].

It had also been suggested that DMPA might have an androgenic effect, which could thus, increase the risk of ovarian cancer [20].

Differences in associations between long-term and short-term use of IUDs were reported. The higher risk with longer duration of use had been attributed to the fact that IUDs require replacement every 5 to 10 years, thus, longer use means more replacements. That can increase the risk of upper-genital-tract infections.

In contrast, the lower risk associated with short-term use may be explained by the spermicidal effect of IUDs, thus reducing local inflammation, or use of the newer *levonorgesterel*-releasing IUDs (LNG-IUS), which might have been associated with lower risks of ovarian cancer.

Use of IUDs was thought to increase the risk of infection and inflammation in the peritoneal cavity, which might lead to a higher risk of ovarian cancer [4, 5]. Chronic inflammation, including sub-clinical inflammation, had been shown to increase the risk of cancer in affected organs [21-23].

Consistent with the inflammatory hypothesis in ovarian *carcinogenesis* was the observed lower risk with prolonged use of low-dose aspirin, and other non-steroidal anti-inflammatory agents [19, 24]. Exposure to inflammatory factors such as asbestos and talc had been linked to ovarian cancer although available evidence was inconclusive. The inflammatory hypothesis was also supported by the higher risk of ovarian cancer in women with *endometriosis* [19, 25, 26].

Pending further evidence and considering the hypotheses of ovarian *carcinogenesis,* whereas *levonorgestrel* - releasing IUDs (LNG - IUS) were associated with lower risk as were other long-acting progestogen - based contraceptives, copper - bearing IUDs (Cu - IUDs), that cause inflammatory reaction, were less likely to be protective and could increase risks.

The relationship between spousal / partner vasectomy and the risk of ovarian cancer was the least studied. Available evidence pointed towards no association or an inverse association. How and why vasectomy might modify the risk of ovarian cancer have not been determined. From the proposed theories of the pathogenesis of ovarian cancer, the following biological mechanisms were worthy of consideration.

The constituents of semen, might have the potential to cause inflammation, partly gain access to the upper genital tract via facilitation by *spermatozoa*. *Spermatozoa* have the ability to bind most of the seminal

constituents. Infectious agents from the lower genital tract are thought to be responsible for upper genital tract infection [28].

Spermatozoa have been proposed as one of the factors that facilitate the ascent of bacteria from the lower to the upper genital tract [29]. Following deposition of *spermatozoa* into the female genital tract, other than the single *spermatozoa* that fertilizes the ovum, all undergo degeneration [30].

Therefore, in the absence of *spermatozoa,* a lower risk of infection and inflammation could be predicted and, thus, lowering risk of ovarian cancer. Vasectomy results in the reduction of seminal plasma content of *dihydrotestosterone* and *Testosterone* In addition, the absence of spermatozoa, which usually bind hormones in semen - including *Testosterone*, follicle stimulating hormone (FSH), luteinizing hormone (LH), and oestrogen - could lower the risk because of the lower levels of these hormones in the upper genital tract [27, 31].

A reduction in seminal constituents of prostatic origin following vasectomy was demonstrated. That include; the *polyamines (spermine* and *spermidine*). Oxidation products of *polyamines* could have a similar effect on risk of ovarian cancer as they did in cervical cancer. It had been suggested that, the presence of *diamine* oxidase and *polyamine* oxidase in cervical mucus, *spermine, spermidine*, and *putrescine* in the semen of male partners could contribute to the progression from HPV infection to cervical cancer [27, 32, 33, 34].

The *polyamines spermine* / *spermidine,* and the *diamine, putrescine* were oxidised by *polyamine* oxidase and *diamine* oxidase in the female genital tract (cervical mucus). Their oxidative products include oxygen radicals and hydrogen peroxide, acrolein, and reactive aldehydes which are genotoxic and may also have immunosuppressive effects [34].

When assessing the association between vasectomy and the risk of ovarian cancer, selection bias and the possibility of uncontrolled confounding were both issues. That was because vasectomy - a permanent contraceptive method - was usually done at an older age after the completion of childbearing. Higher parity, use of OCs, and other factors might be (or might have been) more prevalent in women whose partners underwent vasectomy.

It has been suggested that the inverse association with ovarian cancer observed with use of contraceptives in general could be explained by the fact that, infertile women tend not to use contraceptives and were at a higher risk of ovarian cancer. In this case, the higher risk in non-users could be confounded by infertility. Alternatively, it could be that contraceptives had a relationship with ovarian *carcinogenesis* that was yet to be exploited [4].

The reviewed studies had several limitations. First, in the case-control studies, there was the risk of misclassification of controls as they were not tested for the presence of asymptomatic ovarian cancer. However, ovarian cancer was not common and, therefore, the prevalence of undiagnosed ovarian cancer in controls would be expected to be quite low.

Second, in most of those studies, histology was not reviewed by a single pathologist and that poses the risk of inter-pathologist variation. There was also the possibility of recall bias, especially in relation to duration in use of specific contraceptives. As women often use more than one type of contraceptives, it was also difficult to disaggregate possible differences associated with the use of different contraceptives.

Third, the use of hospital - based controls had a high potential for biasness. Although, possibly less likelihood of recall bias given that access to health care could be more likely associated with specific forms of contraceptives. In addition, these were all observational studies, so there was potential for uncontrolled confounding by unidentified or unmeasured confounding factors. Furthermore, most of the studies had insufficient numbers of participants and did not report associations with long-term use.

Conclusion

In conclusion, the association of ovarian cancer with use of contraceptives other than oral contraceptives still merits attention. For the fact that, the evidence it will provide to women about choices of contraceptive method they might make and the light it will cast on ovarian cancer aetiology and prevention.

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