

## Assessment of Reproductive and Gynecological Risk Factors in Ovarian Cancer Development

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(Ann Coll Med Mosul 2025; 47 (1):47-52).

Received: 24<sup>th</sup> Jan. 2025; Accepted: 22<sup>th</sup> Feb. 2025.

### ABSTRACT

**Background:** Ovarian cancer (OC) is the most deadly gynecological cancer in women. It is usually presented with non-specific symptoms leading to late diagnosis.

**Aim:** To investigate some reproductive and gynecological risk factors for OC in Nineveh governorate in an attempt to participate in the prevention strategy.

**Methods:** The current study has been conducted in Mosul city, Northern Iraq. It is a case-control study that has included 100 women diagnosed histopathologically with OC (cases) and 200 women with no ovarian problems by ultrasonographical examination (control). Using Minitab version 20 software statistical program, descriptive and analytic statistics have been done.

**Results:** This study reveals that there is a highly significant risk of OC with nulliparity (OR= 4.72, P-value<0.001), the history of hysterectomy (OR=6.32, P-value=0.018), the past history of period of infertility (OR= 3.27, P-value< 0.001), and the women who used medications for induction of ovulation for more than or equal to six months (OR=2.25, P-value=0.031). While highly significant protective effects against OC have been shown in the parous women as (OR=0.16, 0.19, 0.26), (P-value<0.001, <0.001, 0.001) for women with parity (1-2), (3-4), ( $\geq 5$ ) respectively and the usage of any type of oral contraceptive pills (OCP) as (OR=0.32, P-value <0.001).

**Conclusion:** This study explores some important risk factors for OC development in Nineveh governorate like nulliparity, hysterectomy, and the history of periods of infertility.

**Keywords:** Hysterectomy, Infertility, Nulliparity, OCP, Ovarian cancer.

### تقييم عوامل الخطورة التناسلية والنسائية المسببة لسرطان المبيض

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### الخلاصة

**الخلفية:** سرطان المبيض هو أكثر أنواع السرطانات النسائية فتكاً لدى النساء. وعادة ما يظهر بأعراض غير محددة تؤدي إلى التشخيص المتأخر.

**الأهداف:** دراسة بعض عوامل الخطر التناسلية والنسائية لسرطان المبيض في محافظة نينوى في محاولة للمشاركة في استراتيجية الوقاية.

**الأشخاص والطرق:** أجريت الدراسة الحالية في مدينة الموصل (مركز محافظة نينوى)، شمال العراق. وهي دراسة الحالة والشاهد شملت ١٠٠ امرأة تم تشخيصهن نسيجياً بسرطان المبيض (حالات) و ٢٠٠ امرأة لا يعانين من أي مشاكل في المبيض عن طريق الفحص بالموجات فوق الصوتية (مجموعة ضابطة). وباستخدام برنامج الإحصائي الإصدار ٢٠، تم إجراء إحصاءات وصفية وتحليلية. Minitab.

**النتائج:** تكشف هذه الدراسة عن وجود خطر كبير للغاية للإصابة بسرطان المبيض مع النساء اللاتي ليس لهن ولادات سابقة (OR = 4.72, P-value < 0.001), تاريخ مرضي لاستئصال الرحم (OR = 6.32, P-value = 0.018), تاريخ سابق لفترة عقم (OR = 3.27, P-value < 0.001), والنساء اللاتي استخدمن أدوية لتحفيز التبويض لفترة أكثر من أو تساوي ستة أشهر (OR = 2.25, P-value = 0.031). في حين تم إظهار تأثيرات وقائية عالية الأهمية ضد سرطان المبيض لدى النساء اللاتي لديهن ولادات سابقة كون (OR = 0.16, 0.19, 0.26), (P-value, 0.001, 0.001, 0.001) للنساء اللاتي لديهن ولادات ( $\geq 5$ ), (3-4), (1-2) على التوالي, واستخدام أي نوع من حيوب منع الحمل الفموية (OCP) كون (P-value < 0.001, OR = 0.32).

**الاستنتاج:** تستكشف هذه الدراسة بعض عوامل الخطر المهمة لتطور سرطان المبيض في محافظة نينوى مثل عدم الولادة، واستئصال الرحم، وتاريخ مرضي لفترة عقم.

**الكلمات المفتاحية:** استئصال الرحم، عقم، سرطان المبيض، حبوب منع الحمل الفموية.

## INTRODUCTION

Ovarian cancer is the most deadly cancer among other types of gynecological cancers all over the world<sup>1</sup>. It needs an appropriate management plan with a good approach to assessment, diagnosis, and treatment<sup>1</sup>, due to the non-specific symptoms at presentation leading to advanced-stage diagnosis<sup>2</sup>.

There are three types of ovarian cancer originating from three distinct ovarian cells, the first originates from the ovarian surface epithelium and represents the most common type of OC(95%) and has a heterogeneous nature which is known as epithelial ovarian cancer (EOC), the second type originates from the germ cells which is known as germ cell tumor, and the third type originates from the stromal cells which is known as a sex-cord-stromal tumor, the last two types form about 5% of all types of OC<sup>1</sup>.

There is an anticipated increase in the mortality rate of OC in the future. So, the identification of the most common risk factors of OC could help in formulating preventive measures<sup>3</sup>. Increased parity decreases the risk of all histological subtypes of EOC in women in premenopausal and postmenopausal age<sup>4</sup>. This is explained by a theory called "incessant ovulation" which suggests that continuous ovulatory cycles without any interruption periods like pregnancy or lactation lead to a destruction of the epithelial layer of the ovary and leads to an increased risk of OC<sup>5</sup>.

The most significant protective effect of the usage of OCP has been observed in many studies. Several studies revealed that this protective effect increases with longer duration of use of OCP<sup>6,7</sup>. The study of the relationship between infertility treatment and OC is difficult because both nulliparity itself and infertility act as risk factors for OC development. This relationship remains controversial. Some studies have revealed a potential relation<sup>8</sup>, while others have found no association<sup>9</sup>.

The study aims to investigate the reproductive and gynecological risk factors for OC in Nineveh governorate.

## SUBJECTS AND METHODS

The current case-control study has been conducted from November 2023 till November 2024 at three governmental hospitals / Nineveh Health Directorate in Mosul City after getting three administrative agreements, the first from the College of Medicine/ University of Mosul (No 9141; Date 2/10/2023), the second from Nineveh Health Directorate(No 42231; Date 12/10/2023), for the collection of data at the Oncology and Nuclear Medicine Hospital and Al-Salam Teaching Hospital for collection of cases and controls and the third from Nineveh Health Directorate issued (No13988, Date7/4/2024) after opening of new Oncology Department in Ibn\_Sinna General Teaching Hospital.

The three hospitals were, namely, The Oncology and Nuclear Medicine Hospital, the Oncology Department of Ibn\_Sinna General Teaching Hospital, which are regarded as the main hospitals that receive all oncological cases from all Nineveh Governorate, and Al-Salam Teaching Hospital.

The participants of 100 women with histopathological diagnosis of OC as cases and 200 women who have no ovarian abnormality approved by ultrasound as control, after gaining their verbal consent to participate in the study, with the exclusion of any women resident outside Nineveh Governorate or any case with secondary ovarian tumor.

By direct interview and using the predefined structured questionnaire which has been checked for its validity and reliability, the data has been collected. Descriptive and analytic statistics have been done by using Minitab version 20 software.

## RESULTS

Table 1 reveals that nulliparous women show 4.72 risks for developing OC, this risk is statistically very highly significant( P-value<0.001), while the parous women have shown a highly significant protective effect against OC as(OR=0.16, 0.19, 0.26),(P-value<0,001, <0.001, 0.001) for women with parity (1-2), (3-4), ( $\geq 5$ ) respectively, in comparison to nulliparous women.

Table 1: The association between parity and the occurrence of OC in the study population.

Parity		Cases		Controls		OR	95% CI (OR)	P- Value*
		No.	(%)	No.	(%)			
Parous	1-2	12	13.8	42	22.0	0.16	0.06-0.43	<0.001
	3-4	20	23.0	59	30.9	0.19	0.08-0.48	<0.001
	≥ 5	37	42.5	80	41.9	0.26	0.11-0.61	0.001
Nulliparous		18	20.7	10	5.2	4.72	2.08-10.73	<0.001
Total		87	100.0	191	100.0			

\* Chi-square test was used.

Table 2 shows that the history of hysterectomy shows a highly significant risk effect for developing OC (OR=6.32, P-value=0.018). The women who have a past history of period of infertility in their lives (regardless of its duration or if they had been treated or not for infertility), exert a very highly significant risk for OC development (OR= 3.27, P-value< 0.001) in comparison to those who do not have a history of infertility. The women who used medications for induction of ovulation for more than or equal to six months have a significantly increased risk of OC development, with an (OR=2.25, P-value=0.031) in comparison to those who have not used these medications.

Table 2: The association between gynecological history and the occurrence of OC in the study population.

Variables		Cases (n=87)		Controls (n=191)		OR	95% CI (OR)	P- Value*
		No.	(%)	No.	(%)			
History of abortion	Present	32	36.8	87	45.5	0.70	0.41-1.17	0.171
	Absent	55	63.2	104	54.5			
History of ectopic Pregnancy	Present	3	3.4	4	2.1	1.67	0.37-7.63	0.681**
	Absent	84	96.6	187	97.9			
History of hysterectomy	Present	6	6.0	2	1.0	6.32	1.25-31.90	0.018**
	Absent	94	94.0	198	99.0			
History of infertility	Present	26	29.9	22	11.5	3.27	1.73-6.20	<0.001
	Absent	61	70.1	169	88.5			
Usage of medications for induction of ovulation	≥ 6months	17	17.0	15	7.5	2.25	1.06-4.76	0.031
	< 6months	10	10.0	40	20.0	0.50	0.24-1.05	0.063
	Absent***	73	73.0	145	72.5	-----	-----	Ref.
Age at first pregnancy	10 -	26	36.6	83	45.6	0.71	0.40-1.27	0.246
	20 -	38	53.5	86	47.3	-----	-----	Ref.
	30 – 40	9	9.9	13	7.1	1.57	0.62-3.98	0.342
Age at menarche	10	0	0.0	2	1.0	0.00	-----	1.000**
	11-13	64	64.0	138	69.0	-----	-----	Ref.
	≥ 14	36	36.0	60	30.0	1.29	0.78-2.15	0.320
Age at menopause	< 50	15	29.4	11	27.5	1.10	0.44-2.75	0.841
	≥ 50	36	70.6	29	72.5			

\* Chi-square test is used. \*\* Fisher exact test is used.

Table 3 reveals that the usage of any type of OCP for any duration shows a very highly significant protective effect against OC development (OR=0.32, P-value <0.001). Similarly, the use of IUCD has a protective effect, however it is not significant.

Table 3: The association between methods of contraception and the occurrence of OC in the study population.

Contraception Method		Cases (OC) (n=87)		Controls (No OC) (n=191)		OR	95% CI (OR)	P- Value*
		No.	(%)	No.	(%)			
OCP***	Yes	19	21.8	89	46.6	0.32	0.18-0.57	<0.001
	No	68	78.2	102	53.4			
Tubal ligation	Yes	2	2.3	4	2.1	1.10	0.20-6.12	0.999**
	No	85	97.7	187	97.9			
IUCD	Yes	13	14.9	40	20.9	0.66	0.33-1.32	0.238
	No	74	85.1	151	79.1			

\* Chi-square test is used. \*\* Fisher exact test is used. \*\*\*any type for any duration

## DISCUSSION

Statistically speaking, between one-third to two-fifths of the total number of cases of cancer can be prevented by eliminating or reducing risk factors<sup>3</sup>. So, efforts should be exerted to find out the risk factors behind the increasing trends of OC cases in Nineveh governorate as registered by The Oncology and Nuclear Medicine Hospital in Mosul.

The result of the current study shows about five folds odds significant increase in the risk of developing OC in nulliparous women (OR= 4.72, P-value<0.001) in comparison to parous women is consistent with Shukur, R. et al.(2019)<sup>10</sup> a study in Baghdad city which stated that nulliparity increase the risk of OC. On the other hand, the parous women showed a highly significant protective effect against OC and this result agrees with a case-control study which stated that childbirths decrease the risk of all histologic subtypes of EOC in women in both premenopausal and postmenopausal age<sup>4</sup>.

According to the Million Women Study which is done by Gaitskell, K. et al.(2018)<sup>11</sup>, parous women had an estimated(26%) lower risk of OC than nulliparous women, and each additional birth was associated with an overall(6%) reduction in OC rise. Moreover, as shown in a result of another study parous women have shown a 30–60%lower risk than nulliparous women for developing OC<sup>12</sup>.

Concerning the history of hysterectomy, this study has revealed that the hysterectomised females show a high risk and significant effect of developing OC,(OR = 6.32, P-value=0.018), This may be due to decreased parity or even nulliparity as a consequence of hysterectomy. This result is inconsistent with the result of a total of 18 case-control studies included in the meta-analysis and done by Huo, X. et al.,(2019)<sup>13</sup> which has revealed that no relationship is there between hysterectomy and OC. According to another systematic review and meta-analysis study that agrees with the

current result and done by Jordan et al., (2013)<sup>14</sup> which revealed that the risk of OC increases after hysterectomy over time.

The history of infertility in the current study regardless of its duration or if it is treated or not shows about a 3fold significant increase in risk for developing OC(OR=3.27), (P-value <0.001) this result is consistent with a study done by Jiang, Y. T. et al.(2020)<sup>15</sup> including evidence from nine prospective cohort studies and revealing that infertility is a risk factor for developing OC.

The women who used ovulation induction medications for more than six months in the current study have shown more than double the risk of developing OC compared to those who did not use these medications.

The result of this study confirms many other studies' results like the systematic review and meta-analysis study conducted by Yu, L. et al.(2023)<sup>16</sup> revealing that nulliparous women who were treated with ovulation induction treatment showed a higher risk for developing OC. Similarly, the result of a cohort study done by Reigstad, M. M. et al.(2017)<sup>17</sup> has shown that the use of clomiphene citrate for ovulation induction increases the risk of OC development.

The usage of any type for any duration of OCP shows a protective effect against developing OC. (OR=0.32), (P-value <0.001) and this protective effect is compatible with the result of Shukur R.Z., et al.(2019)<sup>(10)</sup> study which has revealed that the use of OCP is considered a protective factor against the development of OC since (58.0 %) of OC cases were not using contraceptive pills. Similarly, a study conducted by Al-Kurdy et al.,( 2024 )<sup>18</sup> in Al Diwaniyah province suggested that hormonal contraceptives may reduce the risk of OC. The strengths of the current study are the limited research about OC in Nineveh governorate, cost and time efficiency since it is a retrospective study, and feasibility for hypothesis generation about the associations between OC and various

risk factors which can encourage further research and inform clinical practice and public health planning.

The limitations of the current study have appeared in Nineveh population specificity since the current study results may not be generalizable to all populations, the effect of confounding factors can't be ruled out, and failure to establish causality since it is a retrospective study.

## CONCLUSIONS

The current study has concluded that nulliparity, history of the presence of a period of infertility (regardless of its duration or if it is treated or not for infertility) during life, history of hysterectomy, and the usage of medications for induction of ovulation show highly significant risk effect for developing OC.

On the other hand, the usage of any type of OCP for any duration and the parous women have a significant protective effect against OC development.

Drawing the attention of healthcare providers to distinguish the risky women and encouraging more health educational programs about OC is fundamental. Implementing and supporting further longitudinal research to deeply investigate and confirm the risky effect of the risk factors is recommended.

## Acknowledgments

The authors express sincere gratitude to the head of the Department of Family and Community Medicine for their unlimited support and encouragement. A lot of thanks are also extended to Nineveh Health Directorate for offering facilities and to all the participants who enhanced the success of this study.

## Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

## Research Highlights

1. Nulliparity, history of presence of period of infertility, past history of hysterectomy, and the usage of medications for induction of ovulation show highly significant risk effect for developing OC.
2. The usage of any type of OCP for any duration and the parous women have a significant protective effect against OC development.

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