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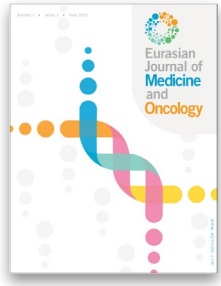

Systematic Review

Is Pregnancy Characteristic Associated with Ovarian Cancer? A Review of the Available Evidence

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Abstract

Numerous epidemiological studies examining the etiology of ovarian cancer and the role of pregnancy related factors in ovarian cancer has been one of the topics of interest to many researchers. Various articles have only mentioned the link between some risk factors and ovarian cancer, but no study has addressed the various dimensions of this issue to this day. Therefore, due to the important position of ovarian cancer among gynecological cancers, this study was conducted to investigate the pregnancy-related risk factors for ovarian cancer.

To determine the relationship between pregnancy characteristic and ovarian cancer, a comprehensive search was carried out in English databases such as; Medline, Web of Science Core Collection, and Scopus using keywords; pregnancy, ovarian cancer (or 'carcinoma of the ovary' or 'ovarian neoplasm' or 'ovarian tumor'), risk factor, pregnancy characteristic terms and a combination of these terms. Full-text, English language, and original articles were included in this study.

In total, 35 articles were entered into the study. The relationship between pregnancy related factors and ovarian cancer were studied. Although there was a weak association between some factors such as preterm birth and the risk of ovarian cancer, only the strong protective effect of parity was seen in the articles.

The results of this study did not show that pregnancy related factors increase the risk of ovarian cancer. In summary, the findings are inadequate regarding some risk factors such as gender of fetus, multiple pregnancy, placental and fetal weight, parity, miscarriage, preeclampsia, and gestational diabetes, and raised questions for future research.

Keywords: Ovarian cancer, pregnancy, risk factor

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Ovarian cancer is the seventh most common cancer among women. According to GLOBOCAN, in 2020, 313,959 cases of ovarian cancer were identified, which with increasing trend, attracted the attention of many researchers.[1] In addition to the high prevalence, ovarian cancer is often diagnosed in advanced stages and its 5-year survival rate varies from 35% to 57% in different regions, which makes it one of the deadliest cancers.[2] In the absence of protective factors against this cancer, the lifetime risk of ovarian cancer is approximately 2.7%.[3] The underlying mechanisms of ovarian cancer are unknown. Numerous epidemiological studies examining the etiology of ovarian cancer have suggested a number of risk factors, including demographic, hormonal, genetic, and lifestyle factors.

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[4] Among these risk factors, the role of pregnancy-related factors in ovarian cancer has been one of the topics of interest to many researchers.[5-8] Numerous hypotheses have been proposed in this regard, one of the most well-known of which is the incessant ovulation hypothesis, which suggests that ovulation increases the risk of mutation and eventually, the ovarian cancer.[7] However, this and other similar hypotheses continue to discuss the role of pregnancy in changing the risk associated with ovarian cancer. During pregnancy, the level of placental hormones increases significantly compared to before pregnancy, and some of these hormones are involved in increasing the incidence of gynecological cancers. Therefore, researchers have linked reduced ovulation cycles,[8] lower circulating gonadotropins,[9] reduced inflammation[10] and changes in circulating steroid hormones[11] to the changes in the risk of pregnancy-related ovarian cancer. Various articles have only mentioned the link between some risk factors and ovarian cancer, but no study has addressed the various dimensions of this issue to this day. Therefore, due to the important position of ovarian cancer among gynecological cancers, this study was conducted to investigate the pregnancy-related risk factors for ovarian cancer.

Materials and Methods

Search Strategy

To investigate the relationship between different features of pregnancy and ovarian cancer, a comprehensive search was conducted in three English databases of Medline, Web of Science Core Collection (Indexes: SCI-EXPANDED, SSCI, A & HCI Timespan) and Scopus, using keywords such as pregnancy, ovarian cancer (or 'carcinoma of the ovary' or 'ovarian neoplasm' or 'ovarian tumor'), risk factor, pregnancy characteristic terms and a combination of these terms. The articles published until 20th April 2020, were considered. All keywords were checked with PubMed Medical Subject Heading (MeSH). Then, in order to avoid the loss of relevant articles, a manual search was also performed in valid journals, followed by the references of full-text articles and related systematic reviews. All retrieved articles were transferred to a database on Endnote X7. To reduce errors during the review process, the PRISMA statement and the guide recommended by Moher et al.[12] were used.

Study Inclusion Criteria

The criteria for entering the study included; full-text observational studies, English language articles, use of the above mentioned keywords in the title or abstract of the article, and articles that investigated the link between one of the characteristics of pregnancy and ovarian cancer.

Exclusion Criteria

Case reports, case series, letter to the editor, systematic reviews and studies conducted on other factors or outcomes were excluded.

Study Selection

Two researchers (ZM, HS) independently and carefully reviewed the retrieved articles and any disagreement between them was resolved by other researchers and the final decision was made based on inclusion criteria. At first, the articles were evaluated by reviewing their titles and abstracts. In the next step, the full text of the selected articles was reviewed and the findings were extracted. At the end, the references of selected articles were reviewed to make the search more comprehensive and to retrieve articles that could not be found in the original search.

Data Extraction

The main features of selected articles are shown in Table 1. The risk scales used in this study included the Incidence Rate Ratio (IRR), Rate Ratio (RR), Hazard Ratio (HR), and Odds Ratio (OR).

Results

Characteristics of Selected Studies

Figure 1 is a PRISMA flow diagram that shows the search results. Using the search strategy, 178 articles were found

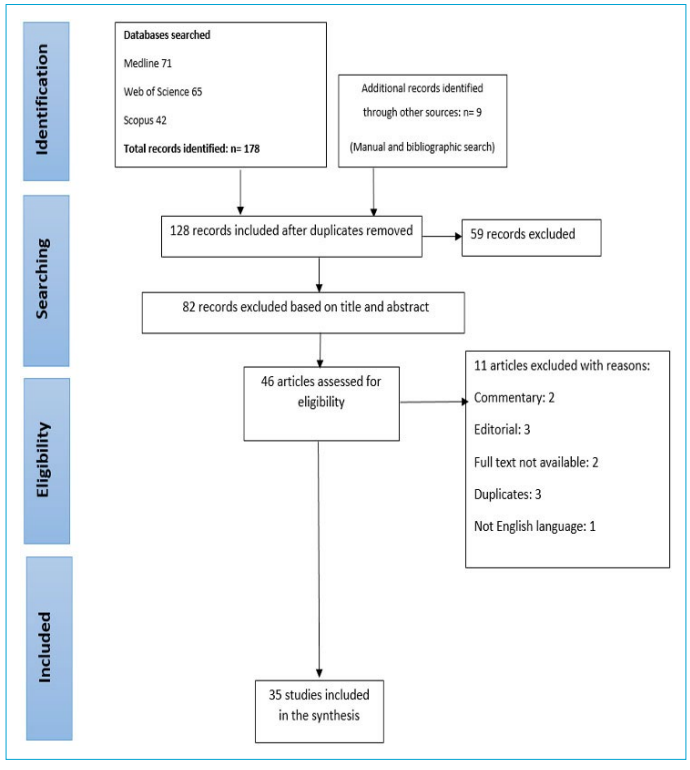

Figure 1. Flowchart of the included eligible studies in review.

and entered the study. The 9 articles were retrieved manually and in this step, 187 articles were selected for the review. Duplicate articles were removed by Endnote software. After reviewing the title and abstract, 82 articles were not related to the purpose of this study and did not meet the study criteria, so they were removed from the review. Also, 11 articles were deleted for scientific reasons (Commentary: 2, Editorial: 3, Full text not available: 2, Duplicates: 3, Not English language: 1). Finally 35 articles selected for the review. An attempt was made to identify and include all articles related to each of the risk factors associated with pregnancy.

Description of the Studies

In general, 35 studies published from 1992 to 2020 were selected for the analysis. From the total of 35 studies, 17, 16 and 2 studies had been done by cohort, case-control and nested case- control methods, respectively (Table 1).

Risk factors

Fetal Sex

During pregnancy, sex of the fetus changes the hormones of mother in different ways.[46] Concentrations of estradiol, alpha-fetoprotein[47, 48] and human chorionic gonadotropin[49] are lower in the mother of male fetus. Male sex is associated with a reduced risk of breast cancer and other hormone-related cancers.[7] In this regard, several studies have examined the relationship between fetal sex and the risk of ovarian cancer. The results of a study showed that, women whose children were all males had a lower risk of ovarian cancer compared to those who only had female children (OR: 0.80 [0.58, 1.10]), and this protection was more in women who had both male and female children (OR: 0.58 [0.43, 0.79]).[26] In the study of Baik et al., the risk of ovarian cancer decreased with increasing male fetus and increased with increasing female fetus. According to the results of this study, compared to women who had a daughter, multivariate odds ratio (95% CI) of invasive ovarian epithelial cancer was 0.92 (0.87-0.98) in women who had a son, 0.87 (0.80-0.94) in those who had two sons, and 0.82 (0.73-0.94) in those who had three sons or more.[17] A study in USA found that giving birth to a male newborn was associated with an 8% reduction in the risk of ovarian epithelial cancer. The results of this study showed that male gender of all children reduces the risk by 11% and increasing the number of male children has a greater protective effect (adjusted-OR: 0.92, 0.91, 0.84, for 1, 2, and 3+ boys compared to all girls).[23] However, the results of a case-control study showed that women who only had male children had a slightly higher risk of ovarian cancer than those who had only girls (OR: 1.22 [0.94, 1.60]). According to the findings of this study, women who had a son had a 2-fold increase in the risk of ovarian mucosal cancer (OR: 2.19 [1.15, 4.17]) and there was a relationship between higher risk factor and higher number of male infants (Ptrend: 0.003).[29] In a cohort study of 1208.001 parous women, there was no association between child sex and the risk of ovarian epithelial cancer. However, there was a significant increase in the risk of endometrioid tumor in women with female child compared to women with male child (IRR: 1.35 [1.03–1.76]). The adverse effect of female child was more pronounced in women who had at least three children (IRR values of 1.34, 1.28 and 1.61 in women with one, two and ≥ three children, respectively).[15]

Pre-term and Post-term

The results of a case-control study showed that among all parous women, there was a 50% increased risk of ovarian cancer in women who had one preterm delivery (OR: 1.48 [1.02,2.15]) compared to women who had only full-term deliveries. Among women with two deliveries, those who had their deliveries between 16 months and less than 18 months were twice as likely to have ovarian cancer (OR: 2.00 [1.00, 3.99]).[29] The Cnattingius study showed a (≥42) increased risk of ovarian epithelial cancer (HR: 1.48 [1.00-2.19]) in women who had post-term pregnancies compared to women with full-term pregnancies (40-41).[22] A cohort study of 1174,352 Swedish women who gave birth between 1973 and 2001 showed that, women with moderate (35-36 weeks) or severe preterm pregnancies (35 weeks or less) had an increased risk of ovarian epithelial cancer (RR: 1.4 [1.0-2.0] and RR 2.3 [1.3-3.8], respectively) compared to those with full-term pregnancies (40 weeks or more).[34] In the Sieh's study, women who gave birth before 37 weeks of gestation had a higher risk of non-epithelial ovarian tumors (HR: 1.86 [1.03–3.37]; p : 0.04). According to the findings of this study, preterm delivery is associated with an increased risk of sex-cord stromal tumors (HR: 4.39 [2.12–9.10]; p<0.001).[37] Skold et al., in a population-based case-control study conducted in Denmark, Finland, Norway, and Sweden between 1976 and 2013, found that preterm delivery was associated with an increased risk of ovarian cancer, and this risk increased with decreasing gestational age [Pregnancy length (last pregnancy) ≤30 versus 39-41 weeks, (OR 1.33 [1.06-1.67]), adjusted for number of births].[38]

Multiple Pregnancies

Multiple pregnancies may increase the risk of ovarian cancer by changing the mother's hormones and increasing levels of estrogen and progesterone. However, the findings

Table 1. Characteristics of included studies

Reference	Country	Design	Period	Study population	Mean age at entry	Mean follow up	Adjusting factor	Effect size	Main finding
Adami/ 1994[13]	Sweden	Case- control		Case: 3486 Control: 19980			Exact age at diagnosis or enrolment	OR	Decreased the risk for each 5-year increment in age at first childbirth by about 10%.
Albreksten/ 1997 [14]	Norway	Cohort		1145076	Range: 20-56	16.4	Age, birth cohort and parity	IRR	No association between high age childbirths and stromal tumors.
Albreksten/ 2007[15]	Norway	Cohort		1208001	Range: 20-74	22.9	Age, birth-cohort, number of births, and maternal age at first and most recent birth.	IRR	No significant association between twin births and risk of ovarian cancer. Non- significantly higher risk between twin girls than singleton births
Baik/ 2008[16]	Sweden	Nested case-control	1961-2001	Case: 5341 Control: 29047	Case: 52.7 Control: 52.2		Age, number of pregnancies, age at first childbirth, education level, and area of residence, gender of the 1st and 2nd infants	RR	No association between birth spacing and ovarian cancer risk.
Baik/ 2007[17]	Sweden	Nested case-control	1961-2001	Case: 7407 Control: 37658			Age at diagnosis and age at first childbirth, parity, educational level, and area of residence	OR	lowered maternal risk of invasive epithelial ovarian cancer in case of male offspring
Bodelon/ 2013[18]	USA	Cohort	1992-2006	125473	Range: 50-74	10.55	BMI at study entry, duration of use of OC, duration of use of HT, first degree family history of breast and/or ovarian cancer.	HR	Reduced risk of ovarian cancer by parity
Braem/ 2012[19]	European countries	Cohort	1992-2010	274442	Mean: 50.4-53.5	11.5	Parity (number of full term pregnancies) and oral contraceptive use (duration of use), body mass index, menopausal status, educational level and age at menarche	HR	Increased risk of epithelial ovarian cancer in multiple miscarriages
Calderon-Margalit/ 2009 [20]	US	Cohort		37927		33.5	Parity	HR	Increased risk of ovarian cancer by preeclampsia
Chen/ 1996 [21]	USA	Case- control	1986-1988	Case: 322 Control: 426	Case: 54 Control: 48		Age, OC use, and number of births	RR	No association between spontaneous abortion and ovarian cancer risk.
Cnattingius/ 2008 [22]	Sweden	Cohort	1982-1989	395171	31	13.7-18.3	Age, birth year of first child, child's gender, highest attained parity, and maternal age at first birth, and mutually adjusted for placental	HR	Increased risk of ovarian cancer by hormone exposure such as placental weight (pregnancy weight and gestational age hormone levels increase with placental weight)

Table 1. CONT.

Reference	Country	Design	Period	Study population	Mean age at entry	Mean follow up	Adjusting factor	Effect size	Main finding
Fu/ 2020 [23]	USA	Case- control	2003-2008	Case: 902 Control: 1802	Case: 57.37 Control: 60.20		Age, race, education level, duration of oral contraception use, and number of full-term births	OR	Altered risk of ovarian cancer by fetal sex
Fuchs/ 2017 [24]	Israel	Cohort	1988-2013	104715		12	Parity, maternal age, and fertility, treatments and a history of GDM	OR	Increased risk of ovarian cancer in patients with a history of GDM
Gaitskell/ 2018 [6]	UK	Cohort	1996-2001	1144762	56.1	14.6 (16.7 million person- years)	Age, region, socioeconomic status, tubal ligation, family history of breast cancer, hysterectomy, BMI, smoking, and use of contraceptive or menopausal hormones	RR	Reduced risk of ovarian cancer by parity
Gierach/ 2005 [25]	USA	Case- control	1994-1998	Case: 739 Control: 1313	Case (Range): 20-69 Control: ≤65		Age, number of livebirths/stillbirths, duration of oral contraceptive use, race, ever having had a tubal ligation, family history of ovarian cancer, and educational level	OR	No association between spontaneous or induced abortion and ovarian cancer risk.
Gierach/ 2006 [26]	USA	Case- control	May 94-July 98	Case: 511 Control: 1136	Case (Range): 20-69 Control: ≤65		Age, race, education, oral contraceptives, breast feeding, tubal ligation, and ovarian cancer family history.		Decreased risk of ovarian cancer risk by bearing both male and female offspring compared to having all girls.
Han/ 2018 [27]	Korea	Cohort	2002-2015	102900		10	Age, BMI, smoking status and fasting blood glucose (FBG) level	HR	No association between GDM and ovarian cancer risk.
Ji/ 2007 [28]	Sweden	Cohort		30409		28	Age, age at first childbirth, twin birth, and the number of pregnancies	RR	No associations between twin births and ovarian cancer risk.
Jordan/ 2009 [29]	Australia	Case-control	2002-2005	Case: 1203 Control: 1286	Case: 59.4 Control: 57.4		Age, duration of hormonal contraceptive use, level of education, smoking, status, and BMI	OR	Altered risk of ovarian cancer by hormonal milieu of a pregnancy
McGuire/ 2016 [30]	US	Cohort	1993-1996	310290	Range: 50-79		Parity HRs are adjusted for birth year and OC use, and OC HRs are adjusted for birth year and parity	HR	Decreased risk of ovarian cancer by parity.
Modan/ 2001 [31]	Israel	Case- control	1994-1999	Case: 840 Control: 751	<40-≥70		Ethnic background and age	OR	Decreased risk of ovarian cancer among carriers of a BRCA1or BRCA2 mutation with each birth.
Mogren/ 2009 [32]	Sweden	Cohort		40951	Range: 24-68	The follow-up started from the date of first	Maternal age at first birth, parity, oral contraceptives, estrogen replacement therapy, and age	RR	Increased risk of ovarian cancer by increasing maternal age at first birth Decreased risk of ovarian cancer by multiparity

Table 1. CONT.

Reference	Country	Design	Period	Study population	Mean age at entry	Mean follow up	Adjusting factor	Effect size	Main finding
						birth and ended at the diagnosis of cancer, date of death, or losing date of the study (31 December 1996)	at menopause		
Moorman/ 2008 [33]	US	Case- control	1000-2006	Case: 896 Control: 967	Range: 20-74		Age , race, family history of breast or ovarian cancer, age at menarche, tubal ligation, infertility, body mass index, number of full-term pregnancies, and age at last pregnancy	OR	Decreased risk of premenopausal ovarian cancer by parity. Decreased risk of ovarian cancer by later age at pregnancy
Mucci/ 2007 [34]	Sweden	Cohort		1174352	28.8	10.3	Age at birth, birth year, parity, infant sex, and maternal education, birth weight and gestational age	RR	Altered risk of ovarian cancer by hormonal milieu of a pregnancy.
Negri/ 1992 [35]	Italy	Case- control	1983-1991	Case: 953 Control: 2500	Case: 54 Control: 52		Age	RR	Increased risk of ovarian cancer by interrupted pregnancy per se and not predisposition to spontaneous abortion.
Peng/ 2019 [36]	Taiwan	Cohort	2000-2013	1466596	GDM group: 31.61 Non GDM group: 28.83	6.84	Age and comorbidities.	HR	No association between ovarian cancer and GDM.
Sieh/ 2014 [37]	USA	Cohort		1536057	19.1	31.6 million person- years	Gestational age at birth, fetal growth, birth order, maternal age at birth, maternal education, Family history of ovarian and breast cancer, and parity, live births	HR	Increased risk of sex cord-stromal tumors with preterm birth
Skold/ 2018 [38]	Multi country	Case- control	1976-2013	10957 Control: 107864	52		Number of births, pregnancy length, age at first or last birth, smoking, and parity	OR	Decreased risk of ovarian cancer by high parity, full-term pregnancies and pregnancies at older ages.
Soegaard/ 2007 [39]	Denmark	Case- control	1995-1999	Case- 554 Control: 1564			Age, pregnancy and duration of oral contraceptive use	OR	Decreased overall risk of ovarian cancer with ever being pregnant, increasing and older age at first and last pregnancy.
Tavani/ 1993 [40]	Italy	Case-control	1983-1992	Case: 194 Control: 710	Range: <25-44		Age	RR	Decreased risk of ovarian cancer by abortion. No significant association between parity and ovarian cancer risk.

Table 1. CONT

Reference	Country	Design	Period	Study population	Mean age at entry	Mean follow up	Adjusting factor	Effect size	Main finding
									Increased risk of ovarian cancer by having first or last birth when older than 30 years compared to those delivering under age 25. increased risk of ovarian cancer by decreasing time since last birth
Titus/ 2001 [41]	Lebanon	Case- control	1992-1997	Case: 563 Control: 523	Range: 20-74		Age, state, and the number of full term singleton live births	OR	Decreased risk of ovarian cancer by higher parity, increased age at first or last birth, and time since last birth No association between early pregnancy losses, abortions, and stillbirths and ovarian cancer risk Decreased risk of ovarian cancer by preterm, term, and twin births.
Tung/ 2003 [42]	USA	Case- control	1993-1999	Case: 558 Control: 607	Control: 55.8 Case: Mucinous: 52.6 Serous: 57.6 Endometrioid: 53.6 Clear cell: 57.4		Study site, OC use, pregnancy status, tubal ligation, age, race, and education	OR	Decreased risk of ovarian cancer by factors suppressing ovulation, including pregnancy.
Vachon/ 2001 [5] among	US	Cohort	1986-1997	31377	Range: 56-81	13	Hysterectomy, physical activity, waist-to-hip ratio, and parity	RR	Increased risk of ovarian cancer by nulliparity. (Nulliparity may be more strongly associated with an increased risk of ovarian cancer women with a family history of breast or ovarian cancer, compared with women who do not have a family history of those cancers)
Whiteman/ 2003 [43]	Australia	Case- control		Case: 791 Control: 853	Range: 18-79		Parity, older age at first and last births, and shorter time since last birth	OR	Decreased ovarian cancer risk by pregnancy at older ages
Wu/ 2017 [44]	USA	Case- control		Case: 1225 Control: 1833	Range: <45-65+		Family history of ovarian cancer, history of endometriosis, talc use, tubal ligation, infertility, number of incomplete pregnancies, age at menarche, BMI, education, SES, age duration of menopausal hormone, and duration of OC use at ages <35 yrs and 35+ yrs and type of menopause, type and	RR	Decreased risk of ovarian cancer by parity
Yang/	Taiwan	Cohort	from the time	1292462		27402995.5	Parity	RR	Decreased risk of ovarian cancer by parity

Table 1. CONT.

Reference	Country	Design	Period	Study population	Mean age at entry	Mean follow up	Adjusting factor	Effect size	Main finding
2007 [45]			of their first childbirth to December 31, 2003			person-years			

OR: Odds Ratio, IRR, IRR: Incidence Rate Ratio, RR: Rate Ratio, HR: Hazard Ratio, BMI: Body Mass Index, HT: Hormone Therapy, SES: Socio- Economic Status, OC: Oral Contraceptive, GDM: Gestational Diabetes Mellitus.

of studies reported different results. In one case-control study, there was no association between multiple pregnancies and the risk of ovarian cancer.[29] The results of another multicenter case-control study also confirmed the findings of this study. [38] The results of a cohort study showed no significant association between multiple pregnancies and the risk of ovarian epithelial cancer, but in women with female twins there was a slight increase in the risk of ovarian cancer compared to women with singleton pregnancy, whereas in women with female twins or mix twins, the risk was slightly lower.[15] In the study of Ji et al., the relative risk of ovarian cancer after giving birth to twins was 0.95 (0.79–1.15).[28]

Placental and Fetal Weight

In the Cnattingius' study, the relationship between placental weight and the risk of ovarian cancer was investigated and the results showed that, women with more placental weight (700 g) had increased risk of ovarian epithelial cancer (HR: 1.47 [1.14-1.90]) compared to women with less placental weight (500-699 g).[22] In the study of Skold et al., there was no association between fetal weight and risk of ovarian cancer.[38] In the Mucci's study, low birth weight was associated with a reduced risk of ovarian cancer in the mother (RR: 0.7 [0.4-1.0]).[34]

Time of Delivery

The protective effect of older age on first delivery has been confirmed in several studies.[33] WU et al, in a study stated that a five years gap between each delivery reduces the risk of ovarian cancer by 13% ([5%-21%], p=0.003). The first delivery after the age of 35 is associated with a 47% reduction in the risk of ovarian cancer compared to the first delivery before the age of 25.[44] Another study in Australia found that older age at first and last delivery is associated with a significant reduction in the risk of ovarian cancer.[45] Another study by Albreksten et al., showed that the risk of germ cell tumors increases with age in the first and last delivery.[14] In their study, Baik et al., concluded that the relative risk of invasive ovarian epithelial cancer is 1.0 [0.98–1.01] for each year increase in the intervals of deliveries.[16] The results of a multicenter case-control study with 10957 cases and 107864 controls showed that older age at first and last delivery is associated with a reduced risk of ovarian cancer [first birth: 30-39 versus <25 years: adjusted OR 0.76 [0.70- 0.83]; last birth 30-39 versus <25 years: adjusted OR 0.76 [0.71-0.82]. [38] A study conducted in 1994 found that for every 5 years increase in first delivery, a 10% reduction in ovarian cancer is observed (odds ratios 0.89 [0.84-0.94] epithelial cancer, 0.92 [0.77-1.10] stromal cancer, 0.92 [0.65-1.32] germ-cell cancer, 0.93 [0.80-1.09] borderline tumors).[13] The results of a case-control study in Italy showed that the highest risk of ovarian cancer is seen in people who experience their first or last delivery over the age of 30 (RR 2.0 and 2.4, respectively), compared to those who give birth under the age 25.[40] Mogren also stated that, the risk of ovarian cancer increases with increasing maternal age in the first delivery.[32]

Parity

In a study in USA, the relative risk of ovarian cancer was reduced by 31% when experiencing a singleton delivery compared to nulliparity.[44] Another study by Albreksten et al. (1997) found no relationship between full-term pregnancy and the risk of germ cell tumors.[14] The results of a case-control study showed that increased parity has a protective effect against all types of ovarian cancer (≥4 births versus 1; OR 0.63 [0.59-0.68]) and this effect is more prominent in clear-cell tumors (OR 0.30, [0.21-0.44]).[38] McGuire et al., in a study showed that, the risk of epithelial ovarian cancer in women under 75 years of age decreases with increasing parity. In this study, the risk of ovarian epithelial cancer was reduced by 12% in women under the age of 65 for each full-term pregnancy, and this reduction was 8% in 65-74 years old women.[30] The results of a prospective cohort study showed that among women with no history of ovarian and breast cancer among their first-degree relatives, nulliparity is associated with an increased risk of ovarian cancer (RR: 1.4 [0.9 –2.4]).[5] The results of a case-control study showed that in women with and without BRCA1 and BRCA2 mutations, delivery had a protective effect on the risk of ovarian cancer, and this effect increased with increasing delivery [≥5 births;

OR 0.47[0.32-0.69]).[31] In the study of Adami et al., increased parity was associated with a reduced relative risk of all types of invasive ovarian cancer (odds ratio for each additional birth 0.81 [0.77-0.85]), epithelial cancer (0.81 [0.77-0.86]), stromal cancer 0.84 [0.72-0.98]), and germ-cell cancer (0.71 [0.48-1.05]).[13] Although the protective effect of parity has not been confirmed by Tavani,[40] it has been confirmed by other studies.[6, 18, 32, 33, 39, 40, 42]

Recurrent Miscarriage

In a cohort study, which began in 1992 in 10 European countries, 1.035 people were diagnosed with ovarian cancer over an average of 11.5 years. In this study, which measured the relationship between miscarriage and risk of ovarian cancer, no significant relationship was found between miscarriage and the risk of ovarian cancer compared to people without a history of miscarriage. However, according to the findings of this study, women with a history of 4 or more miscarriages had a significantly higher risk of ovarian cancer (HR 4 vs. 0: 1.74 [1.20–2.70]). The results of this study showed that induced recurrent miscarriage was not associated with an increased risk of ovarian epithelial cancer (HR 4 vs. 0: 1.46 [0.68–3.14]).[19] Another study conducted in 1992 in Italy found a significant and inverse relationship between the number of miscarriages and the risk of ovarian cancer. The results of this study indicated the relative risk of 0.9 in one miscarriage [0.7-1.1] and 0.8 in two miscarriages [0.6-1.0].[35] This result has been confirmed in the case study of Tavani et al.[40] In the study of Gierach et al., there was no relationship between miscarriage (spontaneous and induced) and ovarian cancer in nulliparous or multiparous women (for nulliparous women, OR: 1.12, and for multiparous women, OR : 0.95 [0.76, 1.18]).[25] Chen et al., in their study of women who had given birth at least once, showed that miscarriage was not correlated to increased risk of ovarian cancer (RR : 1.1, [0.8-1.6]).[21] The results of a case-control study also did not show an association between miscarriage and risk of ovarian cancer.[41]

Preeclampsia

The main feature of preeclampsia is its antiangiogenic status, which is essential in suppressing tumor growth. Therefore, some studies have examined the role of preeclampsia in reducing the risk of cancer. However, studies that examined the relationship between preeclampsia and the risk of ovarian cancer have reported different results. The results of a cohort study showed that preeclampsia was associated with a twofold increase in the risk of ovarian cancer (HR, 2.59; [1.35-4.94]).[20] In a case study by Skold et al., there was no association between preeclampsia and the risk of ovarian cancer.[38]

Gestational Diabetes (GDM)

The results of a cohort study showed that, the risk of ovarian cancer increased in women with GDM (OR 2 [1.03–4.04], p=0.037).[24] The results of a retrospective cohort study showed that GDM was associated with an increased risk of ovarian cancer, although this increase was not statistically significant (HR 1.23, [0.901–1.673], p=0.193).[27] However, a cohort study in Taiwan showed no association between gestational diabetes and the risk of ovarian cancer (adjusted HR 0.903, [0.649-1.256], p=0.5438).[36]

Discussion

The pathogenesis and progression of ovarian cancer is still debated by many researchers. Various hypotheses have been proposed to explain the etiology of ovarian cancer, the most controversial of which is the effect of hormones on the occurrence of cancer. This study provided evidence on correlation between hormonal changes and pregnancy-related factors with risk of ovarian cancer. Based on data from the last 29 years regarding the relationship between different aspects and characteristics of pregnancy and the risk of maternal ovarian cancer, it can be argued that preterm delivery and increasing maternal age in the first delivery increase the risk of ovarian cancer. However, the findings are inadequate regarding some risk factors such as gender, multiple pregnancy, placental and fetal weight, parity, miscarriage, preeclampsia, and gestational diabetes, and raised questions for future research.

Pregnancy is one of the main protective factors against ovarian cancer. Although the mechanism of this protection is not well understood, it can lead to anovulation, decreased gonadotropin secretion, and significant increases in estrogen and progesterone levels. Each of these factors, in addition to pregnancy-related problems and ultimately pregnancy outcome (term delivery, preterm delivery, multiple births), may explain the relationship between hormone-related cancers such as ovarian cancer and pregnancy-related factors.[50] A better understanding of the biology that governs this relationship can play a vital role in protecting high risk women against ovarian cancer. Among all pregnancy-related factors, parity is significantly and inversely associated with the risk of ovarian cancer. Parity plays a protective role against ovarian cancer as it reduces ovulation cycles and increases progesterone levels.[51]

In addition to the role of parity in protecting against ovarian cancer, the association between various risk factors such as obesity, smoking, and the use of oral contraceptives also changes with parity. Accordingly, some studies have suggested that although the high BMI increases the risk of ovarian cancer in nulliparous women, it does not change

the risk of cancer in multiparous women.[52] In a similar study, use of contraceptive pills reduced the risk of ovarian cancer only in multiparous women.[53]

Fetal sex also plays a significant role in the occurrence of hormonal changes during pregnancy. Lower estradiol and hCG levels and higher progesterone levels in male fetus may explain the findings of some articles regarding the different risk of ovarian cancer in different fetal sexes.[54] According to the findings of this study, the relationship between fetal sex and increased risk of ovarian cancer was insignificant and required further studies to confirm or rule out this relationship.

There are hypotheses that state insulin resistance and hyperinsulinemia can increase the risk of some cancers. By binding to the insulin-like growth factor-I receptor, insulin exerts its mutagenic effect, leading to an increased risk of cancer.[55] In addition, hyperglycemia can increase the activity of immune system and tumor growth by increasing oxidative stress and the production of inflammatory cytokines.[56, 57] Obesity, on the other hand, is a risk factor for ovarian cancer as well as gestational diabetes, and therefore as a confounding factor, undermines some associations between gestational diabetes and ovarian cancer. Although the link between gestational diabetes and cancer is theoretically possible, this study by reviewing the previous studies ruled out the link between diabetes and the occurrence of ovarian cancer.

Progesterone has a protective role against ovarian cancer.[58] Therefore, it may be argued that any factor associated with a decrease in progesterone may increase the risk of ovarian cancer. According to the results of studies, some miscarriage cases, especially recurrent miscarriage, are associated with luteal phase defects and therefore a decrease in progesterone levels, which can act as one of the possible mechanisms of ovarian cancer.[11] Thus, miscarriage and induced abortion may have different effects on the risk of ovarian cancer, and therefore determining the relationship between miscarriage and cancer risk requires further investigation, including the type of miscarriage/abortion, the level of circulating hormones, and the cause of miscarriage/abortion. Findings from previous studies have shown conflicting results in regard to the association between miscarriage/abortion and risk of ovarian cancer.

An in-depth review of previous studies in this regard has led to the following suggestions: The fact that different factors have different effects on different histological types of ovarian cancer is due to the different origin of each type of ovarian cancer. High-grade and low-grade serous carcinomas originate from the fallopian tube epithelium, endometrioid and clear cell carcinomas originate from the endometriosis region, and mucinous tumors originate from transitional epithelial nests. Therefore, clarifying the effect of each of the pregnancy-related risk factors on different types of ovarian cancer histology seems necessary in future studies. In addition, hormonal changes are one of the most important underlying factors in the occurrence of various types of ovarian cancer. For example, increased concentrations of testosterone (adjusted OR 2.16; 95% CI 1.25–3.74), androstenedione (adjusted OR 2.16; 95% CI 1.20–3.87) and 17-hydroxy progesterone (adjusted OR 2.62; 95% CI 1.27–5.38) is associated with increased sex-cord stromal histologic type;[59] However, an increase in 17-hydroxy progesterone is associated with a 1.3 fold increase in the risk of ovarian epithelial cancer.[60] Considering that some pregnancy hormones are determined to measure trisomy during pregnancy, the association between hormones, their increasing time and the type of ovarian cancer can be considered in the future.

Although the use of multiple studies is one of the strengths of this study, the small sample size in some studies, short follow-up time and lack of control of confounding factors in some cases prevented us from obtaining stronger results in this area. Most women experience pregnancy at a young age, and longer follow-up times may yield different results. Therefore, the relationship between pregnancy, its various aspects and the occurrence of ovarian cancer is still a question that needs to be answered by studies with higher sample size and longer follow-up time.

Disclosures

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