Acta Obstet Gynecol Scand 1997; 76: 89–95
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Acta Obstetricia et Gynecologica Scandinavica
ISSN 0001-6349

REVIEW ARTICLE

The impact of parity, infertility and treatment with fertility drugs on the risk of ovarian cancer

A survey

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Acta Obstet Gynecol Scand 1997; 76: 89–95. © Acta Obstet Gynecol Scand 1997

Key words: clomiphen citrate; epidemiology; fertility drugs; human choriogonadotropin; human menopausal gonadotropin; infertility; ovarian cancer; parity

Submitted 30 April, 1996
Accepted 19 August, 1996

The etiology of ovarian cancer is multifactorial. With our present knowledge, etiological factors are only found in a minority of cases. In the industrialized world, 10 new cases of ovarian cancer are developed per 100,000 women per year (1).

Women who experience one or more deliveries have a reduced risk of ovarian cancer compared with nulliparous women (2–7). There is a dose-response relationship so that the risk of ovarian cancer is diminished every time a woman gives birth. It is not finally established whether the increased risk of ovarian cancer among infertile women is due to the relative high proportion of nulliparous women among these women, or whether it is due to some kind of ovarian pathology, which may be responsible for the infertility as well as for the increased risk of ovarian cancer.

One of the difficulties in assessing the significance of infertility for ovarian cancer is the close connection between parity and fertility and between nulliparity and infertility (8). Furthermore, an epidemiological analysis of these problems has to face the fact that these 'spontaneous conditions' are influenced by, for example, the treatment with fertility drugs. As ovarian stimulation has increased dramatically through the last two decades (9) and, as ovarian cancer is still a serious disease, it is crucial to clarify the influence of these treatments on the risk of ovarian cancer.

The aim of this survey was to assess the influence of parity, infertility and treatment with fertility drugs on the risk of developing ovarian cancer. Several authors have, in reviews, summarized the multifactorial etiology of ovarian cancer (10, 11). This analysis was restricted to published scientific original data concerning specifically parity, infertility and medical infertility treatment.

Parity and fertility

Fourteen epidemiological studies concerning parity and infertility were found. While parity is well-defined, definitions of infertility vary between the studies from 'years of unprotected intercourse' over 'physician-diagnosed infertility'. Table I presents the results of the studies concerning the influence of nulliparity and infertility. A short presentation of each study is given below.

Joly et al. (6) found, in an American case control study covering the period 1957–1965, a 1.3 times increased risk of ovarian cancer among nulligravid women compared with women who had been

Abbreviations:
hMG: human menopausal gonadotropin; OR: odds ratio; RR: relative risk; DES: diethylstilbestrol; NS: not significant.

Table I. Parity, infertility, and ovarian cancer

First author (ref) Nationality. YP		Material Cases controls	Nulliparity % cases/% controls	Nulliparity OR[a]	Infertility % cases/% controls	Infertility OR[b]	Infertility OR[c]
Joly (6). USA	1974	399 1,153	20/13	1.3[d]*	22/16	1.5*	
McGowan (7). USA	1979	197 197	24/13	2.3[e]*	43/23	2.2**	2.0[NS]
Cramer (12). USA	1983	215 215	36/18	2.6**	20/18	1.2[NS]	
Hartge (14). USA	1989	296 343	30/25	1.3[f]*	44/28	1.0[NS]	2.2[NS]
Booth (16). UK	1989	235 451	28/19	1.7[f]*	14/8	1.9*	2.0[NS]
Whittemore (17). USA	1989	188 539	21/14	1.6*	33/29	1.0[NS]	1.8[NS]
Whittemore (18). USA	1992	3,000 10,000	24/14	2.1***	39/22	1.0[NS]	2.1[g NS]
Risch (19). Canada	1994	450 564	23/11	2.6**	17/11	0.7[NS]	1.5[NS]
Franceschi (26). Italy	1994	95 1,339	19/13	1.5[NS]	2/3	0.8[NS]	
Shushan (27). Israel	1996	200 408	17/5	3.8***	17/11	1.6[NS]	
Adami (21). Sweden	1994	3,486 19,980	28/20	1.7**			

Cohort studies		Cohort size	No. of cancers	Expected number	Relative risk[b]
Ron (13). Israel	1987	2,575	4	1.9	2.1[NS]
Brinton (15). USA	1989	2,335	11	8.6	1.3[NS]
Rossing (25). USA	1994	3,826	4	2.7	1.5[NS]
Venn (20). Australia	1995	10,358	6	3.6	1.7[NS]

YP=year of publication, *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, NS: not significant.
[a] Nulliparous versus parous unless otherwise specified.
[b] All infertile women; unadjusted for parity.
[c] Among nulliparous, or adjusted for parity.
[d] Nulligravidus versus women with one to two pregnancies.
[e] Nulliparous versus women with one to two births.
[f] Nulliparous versus women with two births.
[g] Nulligravidus instead of nulliparous.

pregnant once or twice. Infertility was significantly more frequent among 339 married cases (22.9%) than among 1,153 married controls (16.2%) corresponding to an odds ratio (OR) among infertile women of 1.5 ($p<0.05$) compared with married women without infertility.

McGowan et al. (7) conducted a case control study in USA including 197 women with ovarian cancer diagnosed 1974–77 and 197 healthy age matched controls. The crude OR among married nulliparous was 2.3 compared with women who had given birth once or twice. Significantly more cases (43%) than controls (23%) had difficulties in becoming pregnant (OR=2.2 (1.3–3.7)). Among ever-married, nulliparous women, those who had attempted to become pregnant, compared to those who had not, had a relative risk of ovarian cancer of 2.0 (NS).

In 1983 Cramer et al. (12) published the results of an American case control study including 215 patients with ovarian cancer diagnosed 1978–1981 and 215 population controls. They found an OR among nulliparous of 2.6 compared with parous women. Infertility implied an OR of 1.2 (NS) compared with women who had no difficulties in conceiving.

Ron et al. (13) observed four cases of ovarian cancer among 2,575 Israeli women treated for infertility during the period 1964–74 and followed for on average 12.3 years. The expected number of ovarian cancers according to the population statistics was 1.9, corresponding to a relative risk (RR) of 2.1. This risk was not adjusted for parity.

Hartge et al. (14) made a study in USA covering the period 1978–1991 including 296 cases and 343 hospital controls. A significant decreasing risk of ovarian cancer with increasing parity was demonstrated. Compared with women with two births, nulliparous had a 25% increased risk of ovarian cancer (trend $p=0.03$). The analysis of infertility was stratified in nulliparous and parous. Among parous women periods of infertility did not increase the risk of ovarian cancer whereas married nulliparous who had experienced infertility had an OR of 2.2 compared with married nulliparous without infertility.

In the same year, Brinton et al. (15) analysed retrospectively a cohorte of 2,335 American women evaluated for infertility during the period 1935–1964 and followed for on average 19 years. They found 11 cases of ovarian cancer corresponding to a RR of 1.3 (NS) among infertile compared with the general population.

In 1989, Booth et al. (16) published the results from a case control study in United Kingdom in-

cluding 235 cases of ovarian cancer diagnosed 1978–1983 and 451 controls. They found a 67% increased risk among nulliparous compared to women who had given birth twice. Thirty cases and 34 controls reported that they had problems in becoming pregnant (crude OR=1.9 (1.1–3.1)). Among nulliparous, 16 cases and 12 controls had never conceived, corresponding to a crude odds ratio among infertile nulliparous of 2.0 compared to nulliparous without difficulties in conceiving.

Also in 1989, Whittemore et al. (17) published a case control study from USA of 188 cases with epithelial ovarian cancer and 539 controls. Nulliparity implied a 64% increase in risk compared with parous women. The authors operated with three indices of infertility among ever-married women: Unsuccessful attempt to conceive; physician-diagnosed infertility; and doubts about ability to conceive. Nulliparous women with diagnosed infertility had a 1.8 fold increased risk of ovarian cancer compared with nulliparous without infertility. Among parous women, infertility did not influence the risk of ovarian cancer.

In 1992 Whittemore et al. (18) published a meta-analysis of 12 case control studies concerning risk factors of ovarian cancer. Compared with population controls, the risk of ovarian cancer decreased with increasing number of births corresponding to a risk reduction of 19% per birth. In total, nulliparity implied an OR of 2.1 compared with women who had given birth at least once. Based on data from three studies, ever-married, infertile, nulliparous women had a significantly 110% increased risk of ovarian cancer, compared to non-infertile, nulliparous women.

In a Canadian case control study, based on 450 patients with ovarian cancer (1989–1992) and 564 controls, Risch et al. (19) found an OR of ovarian cancer of 2.6 among nulliparous versus parous. Among parous women, infertility did not imply any increased risk of ovarian cancer (OR=0.52). Nulliparous, infertile women had a non significantly increased risk of ovarian cancer, OR=1.5 (0.6–4.1), compared with nulliparous without infertility. Two controls and no cases had been treated with clomiphene.

Finally, Venn et al. followed 10,358 Australian women referred for *in vitro* fertilization during the period 1978–92 for an average of 6.3 years (20). An observed number of six cases of ovarian cancer among these infertile women was slightly higher than the expected number calculated from population statistics; RR=1.7 (0.8–3.7).

Several other case-control studies include information about nulliparity with odds ratios of 1.6–1.9, but these do not contain applicable data of infertility (2–5, 21, 22). Among these, a recently published Swedish case control study by Adami et al. (21) included 3,486 women under 60 years of age with ovarian cancer and 19,980 age matched controls. Each birth was found to reduce the risk of ovarian cancer by 19% and nulliparous women had an OR of 1.7 compared to women with two full-term pregnancies.

Infertile women is a mixture of women who become pregnant and give birth and women who remain nulliparous. As birth reduces the risk of ovarian cancer it is crucial to stratify or control for parity in order to assess the impact of infertility in itself. Thus, it appears, that

* nulliparity in itself increases the risk of ovarian cancer about twice.
* infertility among women who later give birth, does not increase the risk of ovarian cancer, whereas
* infertility among women who remain nulliparous have a further 75% increased risk compared with nulliparous without infertility, and about a 3.5 times increased risk compared with parous women without infertility.

The conclusions are illustrated schematically in Fig. 1.

Infertility treatment

Three of 12 studies in the meta analysis of Whittemore et al. (4, 12, 14) were included in an analysis

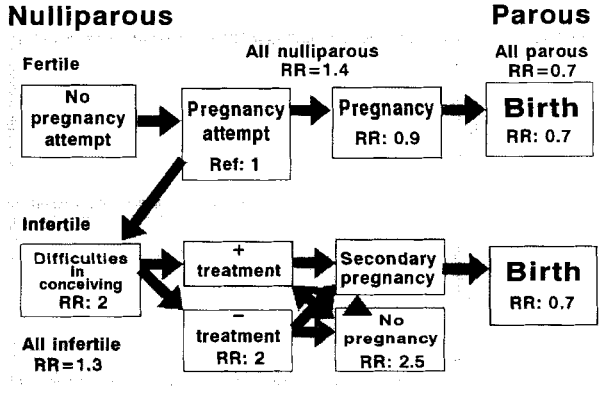

Fig. 1. Risk of ovarian cancer among different categories of patients according to parity, infertility and infertility treatment. The risk estimates indicated are a rough weighted average from the studies included in the review. The reference is nulliparous without infertility. Risk estimates are adjusted for age. For example: A woman decides to try to become pregnant for the first time. Her risk is from the beginning 1. If she succeeds in becoming pregnant and delivers, her relative risk decreases to 0.7. If she, on the other hand, has difficulties in conceiving her relative risk increases to 2.0. Independently of treatment with fertility drugs or not, her relative risk increases further to 2.5 if she remains nulliparous. If she, on the other hand, gives birth her risk decreases to the level for non-infertile; 0.7.

of the influence of medical treatment with 'fertility drugs'. Whittemore found that infertile women who had been treated with 'fertility drugs' had a 2.8 times increased risk of ovarian cancer compared with women without infertility ($p<0.01$). The risk was higher among those women who did not become pregnant (OR=27.0 (2.3–315.6)) than among women who conceived following the treatment (OR=1.4 (0.52–3.6)).

The study of Whittemore has been criticized for analytical problems (23). Furthermore, in 1995 Shapiro published a specified list of the drugs collectively called 'fertility drugs' in the meta analysis (24). Only one of 20 treated women with cancer and one of 11 treated controls had received clomiphene. For ten and four women respectively, the preparation was unspecified, and the remaining were treated with estrogen, diethylstilbestrol (DES), combinations of estrogen and progestogens, thyroid hormones of amphetamins. For all practical purposes this study, therefore, does not bring any useful information about the risk of ovarian cancer by use of drugs presently used for ovarian stimulation.

Rossing et al. (1994) published the results of a combined cohort and case control study including 3,837 women who were treated for infertility during the period 1974–85 (25). The women were followed for on average 11.3 years. During this period a total of 11 cases of ovarian cancer were observed. Four of these were truly invasive. Compared with an expected number of ovarian cancers in the normal population the relative risk of ovarian cancer including borderline tumors among infertile women was 2.5 (1.3–4.5) and of invasive cancer 1.5 (0.4–3.7) (Table I).

Rossing compared expositions among the 11 women with ovarian cancer with the same expositions among 135 women randomly selected from the cohort. The risk of ovarian cancer was not significantly increased among the women treated with 'fertility drugs' (primarily clomiphene): OR=2.3 (0.5–11.4) (Table II). On the other hand, treatment with clomiphene for more than 12 months increased the risk of ovarian cancer 7.2 fold (1.2–43.9). If additionally corrected for pregnancies at enrolment, the figure increased to 11.1. Stimulation with hCG did not imply any increased risk (RR=1.0 (0.2–4.3)).

Franceschi et al. (1994) published tentative results from an Italian case control study with the primary aim of assessing the influence of food and hormone replacement therapy for the development of ovarian cancer (26). The study had at the time of analysis included 195 cases and 1,339 controls. Crude OR of nulliparity was 1.5. Fewer cases (2.1%) than controls (2.5%) had suffered from infertility (OR=0.8), and fewer cases than controls had been treated with 'fertility drugs'; OR=0.7 (0.2–3.3). Among cases as well as among the controls, the frequency of infertility was remarkably small.

Table II. Infertility treatment and ovarian cancer. n=number of treated women, N=Total number of women

Case control First author (ref) Nationality, PDS		Cases n/N %	Controls n/N %	Infertility treatment Odds ratio 95% CI
Whittemore (18), USA	1956–86	20/622 3.2%	11/1,101 1.0%	2.8** (adjusted[a]) 1.3–6.1
Rossing (25), USA	1974–85	9/11 81.8%	87/135 64.4%	2.3[NS] (adjusted[b]) 0.5–11.4
Franceschi (26), Italy	1992–93	2/195 1.0%	15/1,339 1.1%	0.73[NS] (adjusted[c]) 0.16–3.30
Shushan (27), Israel	1990–93	24/200 12.0%	29/408 7.1%	1.31[NS] (adjusted[d]) 0.63–2.74
Cohort studies		Exposed/ cancers	Un-exposed/ cancers	Infertility treatment Relative risk
Venn (20), Australia	1978–92	5,564 3	4,794 3	1.45[NS] (adjusted[e]) 0.28–7.55

PDS=Period of data sampling. **$p\leq0.01$. NS: not significant.
[a] Adjusted for age, study, use of oral contraceptives.
[b] Adjusted for gravity and age at enrolment, and year of enrolment.
[c] Adjusted for age, education, use of oral contraceptives, number of pregnancies.
[d] Adjusted for age, parity, body mass index, region of birth, education, family history and interviewer.
[e] Compared with infertile women without ovarian stimulation, age adjusted.

In the cohort of infertile women followed by Venn et al. the observed number of ovarian cancers in the group of 5,564 treated women was three compared with three cases of ovarian cancer in the group of 4,794 women without ovarian stimulation (20). This observation corresponds to a relative risk of ovarian cancer among treated women of 1.45 compared with infertile women without ovarian stimulation and of 1.7 (0.6–5.3) when compared with the normal population. After adjustment for type of infertility, the relative risk of 1.7 was reduced to 1.5 (0.3–7.6). These figures were not corrected for parity.

Finally, Shushan et al. conducted a nationwide case-control study in Israel in 1990–93 including 200 cases of ovarian cancer (164 invasive, 36 borderline) and 408 geographically (but not age) matched controls (27). After adjustment for parity, age, body mass index, education and family history, women who had been treated with any kind of fertility drug had an OR of developing borderline ovarian cancer of 3.5 (1.2–10.1). The risk of

invasive cancer was not increased. Use of clomiphene alone did not increase the risk of borderline tumors, whereas women treated only with hMG had an adjusted odds ratio of 9.4 (1.7–52.1) and combined with clomiphene an odds ratio of 3.1 (1.0–9.7).

So far, data in all identified epidimiological studies agree on the following:

* Treatment with clomiphene for less than 12 months does not imply an increased risk of invasive or borderline ovarian cancer.
* Treatment with hCG does not increase the risk of ovarian cancer.
* Treatment with hMG does not increase the risk of invasive ovarian cancer.

One study has demonstrated an increased risk of ovarian cancer (including borderline tumors) after more than 12 months of clomiphene stimulation. One study has demonstrated an increased risk of borderline tumors after hMG stimulation, while three other studies did not demonstrate such an increased risk.

Except for an inconsistent increased risk of borderline tumors after hMG exposure, all available empiricism is consistent about the safety of medical infertility treatment for less than one year as far as the risk of ovarian cancer is concerned.

This supplementary conclusion is shown in Fig. 1, which attempts to give an integrated overall presentation of our present knowledge concerning the impact of parity, infertility and infertility treatment as regards the risk of ovarian cancer.

Discussion

The high consistency in the studies concerning the influence of nulliparity on the risk of ovarian cancer justifies the anticipation that nulliparity in itself implies a doubling of the risk of ovarian cancer. The risk seems to be higher among married women without children than among nulliparous in general. This may be explained by the circumstance that a smaller proportion of unmarried than married have attempted to become pregnant. Furthermore, women who have not attempted to become pregnant, do not know their ability to achieve pregnancy.

Infertility in itself implies a smaller risk than nulliparity. Those studies stratifying for parity, generally do not find any increased risk of ovarian cancer among temporary infertile women who later conceive. Among nulliparous, infertility may increase the risk of ovarian cancer by further 50–100%.

Although Rossing demonstrated an increased risk of ovarian tumors of 2.3 among stimulated women, this risk was not significant. Treatment with clomiphene alone for more than 12 months is an unusual regimen today. As neither Franceschi, Venn nor Shushan found any evidence of an increased risk of invasive ovarian cancer among women exposed for ovarian stimulation, we have so far no epidemiological evidence of an increased risk of invasive ovarian cancer among women undergoing prevalent ovarian stimulation. The risk of ovarian tumors was found to be increased after prolonged clomiphene stimulation in the study of Rossing, contrasting an increased risk after hMG but not after clomiphene treatment in the study of Shushan. These conflicting results may be influenced by different kinds of bias and confounding, e.g. duration of treatment. The risk of ovarian tumors associated with hMG and long-term clomiphene treatment respectively, could be consistent, if the duration of treatment with ovulation induction agents, rather than the specific drug *per se*, constituted the risk factor (28). The association between specific treatment regimens and ovarian cancer could also be influenced by the duration of infertility which has been found to be correlated to the risk of ovarian cancer (16, 17).

The proportion of borderline tumors to invasive neoplasms identified in the studies of Rossing (45%) and Shushan (22%) give evidence of selection bias. Since borderline tumors are often asymptomatic, some of the cases detected in these studies could be attributable to the more intensive screening of these infertile patients. Furthermore, there could be some confounding associated with the type of infertility. After stratification for type of infertility, odds ratios in the four cohorte studies shows conflicting results: Rossing found that ovulatory abnormalities implied the highest risk (RR=3.7), but the high risk associated with the long term use of clomiphene was found primarily among cases with other types of infertility (25). Ron found that male factor was associated with a significantly increased risk (RR=6.7) (13), whereas in the study of Venn, unexplained infertility implied the highest relative risk; RR=19.2 (2.2–165.0) (20). In the two latter studies none of the cases had ovulatory disturbances. Brinton found that women with hormonal disturbances had a relative risk of 1.6 and male factor infertility implied a relative risk of 2.0 (15). This confusing inconsistency may be a consequence of differences in treatment regimens for different subgroups of infertile women, patient selection and/or error of first order.

The risk of ovarian cancer is significantly increased among nulliparous women, especially if they are infertile. Therefore, any treatment estab-

lishing pregnancy and birth probably decreases the risk of ovarian cancer compared with the situation where no treatment is given and no pregnancy achieved. As the treatment with fertility drugs increases the chance of getting pregnant, it is in our opinion not correct to adjust the risk measures of fertility drugs for pregnancy or parity, unless this adjustment is done according to the status before treatment as realised in the study of Rossing et al. (25). Such an 'overcorrection' may be in effect in the study of Shushan et al. (27). Furthermore, no correction was made for infertility, possibly because it was found not to be significantly associated with ovarian cancers ($p=0.07$). Thus, the risk among users of fertility agents may be overestimated because these patients are at an increased risk due to their infertility.

Some of the differences between the studies may also be due to different reference groups.

The reference group, to which the drug-exposed women are compared, should preferentially be infertile women without medical treatment, with correction for or stratification according to parity and fertility type and other important confounders as e.g. previous use of oral contraceptives.

Conclusion

Nulliparity doubles the risk of ovarian cancer. Infertility followed by pregnancy and birth does not imply any increased risk of ovarian cancer, whereas infertility among nulliparous women may increase the risk by a further 50–100%.

For the time being there is no empirical evidence that the prevalent regimens of ovarian stimulation increase the risk of invasive ovarian cancer beyond the risk from the infertility and nulliparity among these women. The association to borderline tumors may be a consequence of surveillance bias and need further investigation.

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