Infertility treatment and the risk of cancer

BACKGROUND A possible correlation between hormonal stimulation during treatment of infertility and the risk of cancer of the breast, the ovaries, the cervix or the uterus has been investigated in a number of epidemiological studies. The purpose of this article is to review the relevant literature and summarise the findings.

KNOWLEDGE BASE This review article is based on literature searches in the databases MEDLINE, Cochrane and EMBASE.

RESULTS No studies showed a specific general correlation between hormonal ovulatory stimulation used as pre-treatment to assisted fertilisation and an increased risk of cancer of the breast, the ovaries, the cervix or the uterus. Most studies detected no increased risk. Some studies, however, showed an increased risk of cancer among certain sub-groups, such as women who have received repeated treatment with clomiphene citrate.

INTERPRETATION On the basis of the studies reviewed, the conclusions are ambiguous. It is therefore necessary to monitor the long-term effects of infertility treatment on women's health. Further good -quality large-scale population studies are necessary, with longer follow-up periods and better adjustment for confounding factors.

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MAIN MESSAGE

There is no clear correlation between the use of ovulation-stimulating drugs for assisted fertilisation and an increased risk of cancer of the breast, the ovaries, the cervix or the uterus.

Infertility may in itself be correlated with an elevated risk of certain forms of cancer.

Further good-quality epidemiological studies are required.

Population studies show a prevalence of infertility of approximately 9 %, and a little more than half of infertile couples will seek examination and treatment (1). Assisted fertilisation in the form of intrauterine insemination (IUI) or in-vitro fertilisation (IVF) is often used in the treatment of infertile couples. In the Western world, 2.3 % of all live births have been conceived with the aid of assisted fertilisation (2). In the case of in-vitro fertilisation, a combination of hormones is commonly used, such as gonadotropin-releasing hormone (GnRH) agonist or antagonist, gonadotropins and progesterone, as well as clomiphene citrate (CC). The latter is often used as a hormonal stimulant in the initial phase of examination and treatment, and in the case of intrauterine insemination. There is evidence that treatment with female sex hormones during the menopause is associated with an elevated risk of several forms of cancer, for example in the breast and in the endometrium (3), possibly due to increased cell growth. An increased number of ovulations, follicular aspirations, inflammations and repair mechanisms may play a role in ovarian cancer (4).

A possible correlation between infertility, treatment of infertility with ovulatory stimulants and the occurrence of cancer, especially in the breast, the ovaries, the uterus or the cervix, has been subject to numerous epidemiological studies. The purpose of this review article is to summarise the findings reported by the literature on the correlation between treatment of infertility and the risk of cancer.

Knowledge base

The article is based on a literature search in MEDLINE, Cochrane and EMBASE, completed on 1 September 2011. The following search terms were used: «fertilization in vitro», «intracytoplasmic sperm injection», «assisted reproductive techniques», «ovulation induction», «superovulation», «chorionic gonadotropin», «follicle stimulating hormone», «luteinizing hormone», «progesterone», «chlomiphene», «neoplasms», «ovary», «uterus», «endometrium», «cervix uteri», «myometrium», «breast», «mammary glands», «trophoblastic neoplasms», «choriocarcinoma», «placental site trophoblastic tumor», «hydatiform mole». The search was restricted to «systematic reviews» and «observational studies». A total of 1 128 articles were identified. Human studies published in English were included.

The abstracts of the articles were read by AKO and NBO, and articles describing cancer and pre-stages of cancer related to follicle-stimulating and/or ovulation-stimulating treatment of infertility were included. Case histories were excluded. The articles were read in full by RS, AKO and NBO. We also included certain articles published after the completion of the search until submission of the manuscript.

The risk of breast cancer

According to figures from the Cancer Registry of Norway for the period 2005–2009, the cumulative risk of breast cancer among Norwegian women was 8 % (5). Table 1 shows data and conclusions from publications that describe the risk of breast cancer after inferti-

Table 1: Studies that have investigated the risk of breast cancer after infertility treatment

First author (ref.)	Year	Number of participants	Hormone treatment	Cases of breast cancer	Risk (95 % CI)
Cohort studies					
Lerner-Geva (11)	2012	2 431	CC, CC + hMG, hMG	153	SIR =1.2 (0.98–1.4)
Yli-Kuha (13)	2012	9 175	Not specified	50	OR = 0.85 (0.57–1.30)
Källeén (14)	2011	24 058	Not specified	112	OR = 0.76 (0.62–0.94)[1]
Calderon-Margalit (6)	2009	15 030	CC, hMG, unknown	32	HR = 1.42 (0.99–2.05)
Orgeas (20)	2009	1 135	CC, Gon	54	SIR = 1.90 (1.08–3.35)[1]
Silva (21)	2009	7 355	CC, Gon	102	SIR = 1.26 (1.03–1.53)[1]
Jensen (17)	2007	54 362	CC, hMG, GnRH-analogue, Gon, Prog	331	RR = 3.36 (1.3–8.6)[1]
Lerner-Geva (19)	2006	5 788	CC hMG, CC + hMG	131	SIR = 1.4 (1.0–1.8) SIR = 1.1 (0.9–1.4)
Terry (15)	2006	116 671	CC, hMG	1 357	OR = 0.60 (0.42–0.85)[1]
Brinton (16)	2004	12 193	CC CC ≥ 20 years' follow-up Gon	108 31	RR = 1.02 (0.8–1.3) RR = 1.60 (1.0–2.5)[1] RR = 1.07 (0.7–1.6)
Gauthier (9)	2004	92 555	CC, hMG, hCG	133	RR = 0.95 (0.82–1.11)
Lerner-Geva (10)	2003	1 082	Not specified	5	SIR = 0.82 (0.22–2.10)
Dor (7)	2002	5 026	CC, hMG, FSH, LH, GnRH-analogue	11	SIR = 0.69 (0.46–1.66)
Doyle (8)	2002	4 188	CC, hMG, hCG, GnRH-analogue	43	RR = 0.95 (0.47–1.92)
Venn (22)	1999	29 700	CC, hMG, GnRH-analogue, GH	87	RR = 0.96 (0.74–1.13)
Rossing (12)	1996	3 837	CC hCG	15 4	RR = 0.5 (0.2–1.2) RR = 0.5 (0.2–1.8)
Case-control study					
Katz (18)	2008	7 162	CC, hMG, Prog	41	RR = 1.24 (1.03–1.48)[1]

SIR = standard incidence rate, OR = odds ratio, HR = hazard ratio, RR = relative risk
CC = clomiphene citrate, hMG = human menopausal gonadotropin, GnRH = gonadotropin-releasing hormone, Gon = gonadotropin, Prog = progesterone, GH = growth hormone
[1] Significantly altered risk

lity treatment. Several reports conclude that there is no elevated risk of breast cancer after infertility treatment (6–13). Some studies conclude with a reduced risk of breast cancer after treatment for infertility (14, 15). However, there are more studies that report an elevated risk of breast cancer after treatment for infertility (16–22), especially following repeated treatment with clomiphene citrate (16, 19, 20), progesterone (17) and when nulliparous women were treated with gonadotropin (17), during the first year after IVF treatment (22), or when the woman was 30 years or older at the time of the first IVF treatment (18).

A meta-analysis published in 2010 (23) concluded that there was no correlation between breast cancer and hormonal stimulation with the aid of clomiphene citrate, gonadotropins, and gonadotropin-releasing hormones. The authors pointed out, however, that the studies included in the meta-analysis were heterogeneous, and that the follow-up after hormonal stimulation had been of a short duration.

The risk of ovarian cancer

The lifetime risk of ovarian cancer in women is 1.2 % (5). A number of studies have investigated the correlation between ovarian cancer and infertility treatment (Table 2). Most studies report no elevated risk of ovarian cancer in women who have been treated for infertility (6–8, 11, 13, 21, 22, 24–30). Some studies, however, report an elevated risk of ovarian cancer (10, 14, 31), an elevated risk of borderline tumours (30, 31) and an elevated risk after long-term use of clomiphene

Table 2: Studies that have investigated the risk of ovarian cancer after infertility treatment

First author (ref)	Year	No. of participants	Hormone treatment	Cases of illness	Risk (95 % CI)
Cohort studies					
Lerner-Geva (11)	2012	2 431	CC, hMG, CC + hMG	Ovarian cancer 18	SIR = 1.0 (0.6–1.6)
Yli-Kuha (13)	2012	9 175	Not specified	Ovarian cancer 9 Borderline tumour 4	OR = 1.68 (0.31–9.27) OR = 2.57 (0.69–9.63)
Van Leeuwen (30)	2011	25 152	CC, hMG, FSH, hCG, GnRH, Prog	Ovarian cancer 30 Borderline tumour 31	SIR = 1.35 (0.91–1.92) SIR = 1.93 (1.31–2.73)[1]
Källén (14)	2011	24 058	Not specified	Ovarian cancer 26	OR = 2.09 (1.39–3.12)[1]
Calderon-Margalit (6)	2009	15 030	CC, hMG, unknown	Ovarian cancer 1	HR = 0.61 (0.08–4.42)
Jensen (26)	2009	54 362	hMG, FSH CC hCG GnRH analogue	Ovarian cancer 26 Ovarian cancer 58 Ovarian cancer 49 Ovarian cancer 15	RR = 0.83 (0.5–1.37) RR = 1.14 (0.79–1.64) RR = 0.89 (0.62–1.29) RR = 0.80 (0.42–1.51)
Sanner (31)	2009	2 768	Gon CC, Gon	Ovarian cancer 9 Borderline tumour 7	SIR = 5.89 (1.91–13.75)[1] SIR = 3.61 (1.45–7.44)[1]
Silva (21)	2009	7 355	CC, Gon	Ovarian cancer 12	SIR = 1.10 (0.57–1.93)
Brinton (24)	2004	12 193	CC, Gon	Ovarian cancer 15 Borderline tumour 5	RR = 0.82 (0.4–1.5) RR = 1.09 (0.4–2.8)
Lerner-Geva (10)	2003	1 082	Not specified	Ovarian cancer 3	SIR = 5.0 (1.02–14.6)[1]
Dor (7)	2002	5 026	CC, hMG, FSH, LH	Ovarian cancer 1	SIR = 0.57 (0.01–3.20)
Doyle (8)	2002	4 188	CC, hMG, hCG, GnRH analogue	Ovarian cancer 4	RR = 0.59 (0.12–3.00)
Venn (22)	1999	29 700	CC, hMG, GnRH analogue, GH	Ovarian cancer 7	SIR = 0.88 (0.42–1.84)
Rossing (32)	1994	3 837	CC 1–11 cycles CC ≥ 12 cycles hCG	Ovarian cancer /borderline tumour 3 Ovarian cancer/borderline tumour 5 Ovarian cancer/ borderline tumour 3	RR = 0.8 (0.1–5.7) RR = 11.1 (1.5–82.3)[1] RR = 1 (0.2–4.3)
Case-control studies					
Cusido (25)	2007	299	CC, Gon	Ovarian cancer 42	Not significant
Rossing (28)	2004	2 015	CC, hMG, FSH	Ovarian cancer 378	OR = 1.0 (0.4–3.0)
Mosgaard (27)	1998	1 952	CC, hCG, hMG	Ovarian cancer 231	OR = 1.5 (0.51–4.39) nulliparous OR = 1.46 (0.56–3.81) multiparous
Shushan (33)	1996	608	CC, hMG	Ovarian cancer 200	OR = 9.38 (1.66–52.08)[1]
Franceschi (29)	1994	1 534	CC, Gon	Ovarian cancer 195	OR = 0.7 (0.2–3.3)

SIR = standard incidence rate, OR = odds ratio, HR = hazard ratio, RR = relative risk
CC = clomiphene citrate, hMG = human menopausal gonadotropin, GnRH = gonadotropin-releasing hormone, Gon = gonadotropin, Prog = progesterone, GH = growth hormone, FSH = follicle-stimulating hormone, hCG = human choriogonadotropin, LH = luteinising hormone
[1] Significantly altered risk

citrate (32) or use of human menopausal gonadotropin (hMG) (33).

The risk of uterine and cervical cancer

Figures from the Cancer Registry of Norway show a cumulative risk of cancer of the uterus and the cervix of 2.1 % and 0.9 % respectively (5). Tables 3 and 4 show data and conclusions from publications that describe the risk of uterine and cervical cancer after treatment for infertility. Six studies (6, 11, 21, 22, 34, 35) reported a significantly elevated risk of uterine cancer. The elevated risk was associated with the use of clomiphene citrate (6, 21, 34), a temporarily elevated risk during the first year after the treatment (22) and a long period (30 years) of follow-up (11). Several other articles concluded that infertility treatment is not associated with a risk of uterine cancer (7, 8, 13, 14, 35). Källén and collaborators and Yli-Kuha and collaborators, having reviewed 24 058 and 9 175 women respectively who had undergone treatment for infertility, found a reduced risk of cervical cancer when compared to other women (13, 14). Other reports (6–8, 10, 36) concluded that infertility treatment did not lead to an elevated risk of cervical cancer.

Table 3: Cohort studies that have investigated the risk of uterine cancer after infertility treatment

First author (ref)	Year	No. of participants	Hormone treatment	Cases of uterine cancer	Risk (95 % CI)
Lerner-Geva (11)	2012	2 431	CC + hMG, CC, hMG	30	SIR = 1.7 (1.1–2.4)[1]
Yli-Kuha (13)	2012	9 175	Not specified	4	OR = 2.0 (0.37–10.9)
Källén (14)	2011	24 058	Not specified	6	Not stated
Calderon-Margalit (6)	2009	15 030	CC, hMG, unknown	5	HR = 3.32 (1.31–8.42)[1]
Silva (21)	2009	7 355	CC + Gon CC Gon	18	SIR = 2.51 (1.01–5.16)[1] SIR = 2.23 (1.07–4.11)[1] SIR = 1.93 (0.05–10.75)
Jensen (35)	2009	54 362	CC, hCG Gon GnRH analogue	84	RR = 1.36 (0.83–2.23) RR = 2.21 (1.08–4.50)[1] RR = 1.09 (0.47–2.52)
Althuis (34)	2005	8 431	CC	19	SIR = 2.14 (1.3–3.3)[1]
Dor (7)	2002	5 026	CC, hMG, FSH, LH, GnRH analogue	2	SIR = 2.25 (0.25–8.11)
Doyle (8)	2002	4 188	CC, hMG, hCG, GnRH analogue	3	RR = 0.72 (0.06–8.62)
Venn (22)	1999	29 700	CC, hMG, GnRH analogue, GH	5	SIR = 1.09 (0.45–2.61) SIR = 4.96 (1.24–19.8) (1 year after treatment)[1]

SIR = standard incidence rate, OR = odds ratio, HR = hazard ratio, RR = relative risk
CC = clomiphene citrate, hMG = human menopausal gonadotropin, GnRH = gonadotropin-releasing hormone, Gon = Gonadotropin, Prog = Progesterone, GH = growth hormone, FSH = follicle-stimulating hormone, LH = luteinising hormone
[1] Significantly altered risk

Table 4: Cohort studies that have investigated the risk of cervical cancer after infertility treatment

First author (ref)	Year	No. of participants	Hormone treatment	Cases of cervical cancer	Risk (95 % CI)
Yli-Kuha (13)	2012	9 175	Not specified	34	OR = 0.51 (0.30–0.85)[1]
Källén (14)	2011	24 058	Not specified	164	OR = 0.61 (0.52–0.71)[1]
Calderon-Margalit (6)	2009	15 030	CC, hMG, unknown	2	HR = 1.68 (0.40–7.04)
Althuis (36)	2005	8 422	CC Gon	7 2	RR = 1.61 (0.5–4.7) RR = 1.39 (0.3–6.4)
Lerner-Geva (10)	2003	1 082	Not specified	3	SIR = 4.61 (0.93–13.49)
Dor (7)	2002	5 026	CC, hMG, FSH, LH, GnRH analogue	1	SIR = 0.58 (0.01–3.22)
Doyle (8)	2002	4 188	CC, hMG, hCG, GnRH analogue	3	Cannot be estimated

SIR = standard incidence rate, OR = odds ratio, HR = hazard ratio, RR = relative risk
CC = clomiphene citrate, hMG = human menopausal gonadotropin, GnRH = gonadotropin-releasing hormone, Gon = gonadotropin, LH = luteinising hormone, FSH = follicle-stimulating hormone
[1] Significantly altered risk

Discussion

This literature review has not determined any clear correlation between hormonal infertility treatment used in the context of assisted fertilisation and an elevated risk of cancer of the breast, the uterus or the cervix. Since many of the women who have undergone hormonal infertility treatment are still relatively young, many years will pass until they reach the age where the incidence of cancer is at its highest. A general feature of the studies included was a low number of cancer cases. Several studies showed a trend towards an elevated risk following infertility treatment. Despite the large cohorts, the number of women who developed cancer was too low to achieve significant results. This demonstrates the need for larger studies and meta-analyses that can provide more precise results. It is also worth bearing in mind that epidemiological studies cannot provide any specific conclusions regarding the cause of the development of cancer. Other factors associated with both infertility and cancer, such as overweight (37, 38), may also play a role. Infertility in general, as well as causes of infertility, such as endometriosis (39, 40), ovulatory disorders, polycystic ovary syndrome (37, 41) and tubal factors (42, 43) may also have an effect

on the risk of developing cancer in the breast, the ovaries or the uterus.

The hormonal treatment exposes the women to supraphysiological concentrations of exogenous hormones, causing an increase in the concentrations of oestrogen and progesterone that may possibly contribute to an elevated risk of breast cancer. Most of the studies we reviewed in Table 1 showed that there was no elevated risk of breast cancer associated with infertility treatment, although one of the studies, (a case-control study) (18), concluded that women who underwent IVF treatment after the age of 30 were diagnosed with cancer at an earlier time (average age 43.9) than women in the general population, who in this study were aged 60 on average at the time of diagnosis. One study indicated that IVF treatment protects women against breast cancer (14). On the other hand, some of the studies reviewed show an elevated risk of breast cancer, especially following treatment with clomiphene citrate and 20 years of follow-up (16), gonadotropin (21) and progesterone (17). Again, however, the results are unconvincing and the evidence is not clear.

Treatment with clomiphene citrate and gonadotropins in the context of assisted fertilisation stimulates follicle maturation and induces ovulation. The ovulation may in itself be part of mechanisms associated with ovarian-cancer aetiology (44, 45). The hypothesis of incessant ovulation (45) postulates that frequent ovulation causes damage to and repair of the surface epithelium of the ovary and increases the likelihood of DNA mutations and may generate a predisposition for malign transformation (4). This may explain why multiparous women have a risk of ovarian cancer which is 30–70 % lower than in nulliparous women (46–48).

In their study, Källén and collaborators (14) describe the risk of cancer in women who have given birth after IVF treatment. Their control group consisted of women who had given birth with no IVF treatment. They detected an elevated risk of cancer, especially ovarian cancer, in the IVF women both before and after pregnancy/delivery. However, the cancer risk was somewhat reduced after delivery. A possible explanation could be that pathologies of the ovaries may be the cause of the infertility as well as the elevated risk of ovarian cancer. Jensen and collaborators draw the same conclusion in their studies of a cohort of 54 362 women (26, 49). A study from the Netherlands published in 2011 (30) and a study from Sweden published in 2009 (31) assessed the risk of borderline ovarian tumours and invasive ovarian cancer, and reported a possible elevated risk of borderline tumours of the ovaries and also a possible elevated risk of invasive ovarian cancer after treatment with gonadotropin (31). It is important to underscore that borderline ovarian tumour is essentially a benign disease with a low likelihood of malignancy. We have nevertheless chosen to include this finding in Table 2, since it will be important to the women concerned. The conventional treatment for this condition includes bilateral oophorectomy and hormone replacement.

Despite the large cohorts of women who receive in-vitro fertilisation, only a small number of women develop cancer, and the studies are based on small numbers. This calls for continued monitoring of the long-term effects of hormonal stimulation in the context of infertility treatment with regard to the risk of development of invasive ovarian cancer and borderline tumours.

After 30 years of follow-up, Lerner-Geva and collaborators detected a significant increase in the incidence of endometrial cancer in women who had been treated with clomiphene citrate and hMG (11). One study describes a temporarily elevated risk of uterine cancer during the first year after a completed ovulation induction, especially among women suffering from unexplained infertility (22). Several studies concluded that infertility treatment with clomiphene citrate, hMG, gonadotropin and gonadotropin-releasing hormone analogues may give rise to an elevated risk of uterine cancer (6, 11, 21, 34, 35), while others failed to detect any elevated risk (7, 8, 13, 14). There was no expected elevated risk of cervical cancer after treatment of infertility with the aid of exogenous hormones. This was also the conclusion in all the studies reviewed (Table 4). However, a reduced risk of cervical cancer was reported by two studies (13, 14). A possible explanation could be that women who undergo treatment of infertility have more frequent gynaecological examinations, and are thus treated for cell atypia in the cervix at an earlier stage (13).

Conclusion

Treatment with follicle-stimulating drugs does not appear to increase the risk of cancer in general, although infertility may in itself constitute a risk factor for development of cancer. This means that interpretation of epidemiological studies of cancer risk following infertility treatment of infertility is a demanding task. It appears that certain subgroups of infertile women may be more exposed to an elevated cancer risk as a result of infertility treatment. The risk of cancer also depends on whether the woman in question has achieved pregnancy and given birth as a result of the treatment. There may be grounds for caution with regard to long-term use of clomiphene citrate, especially if there is no anovulation.

Clarification of predictive factors is crucial to identify any women who should be provided with extra follow-up after the completion of infertility treatment. Our review shows that continued monitoring of the long-term effects of hormonal treatment on the health of the women concerned is required.

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