Ovulation Induction and Ovarian Tumours: The Debate Continues

Pages with reference to book, From 353 To 356

Abstract

Objective: To critically review the published literature regarding the proposed association of ovarian stimulation and increased risk of ovarian tumors.
Design: A medline search (1966-1997) was done to identify case reports and epidemiological studies relevant to the issue in question. Review articles and critical reappraisals in the form of comments on studies done were also used.
Results: Various case reports, studies and review articles were identified as most relevant.
Conclusion: Despite a few studies showing an apparent association between ovulation induction and ovarian cancer, support for their results has not been forthcoming. From the available data a causal relationship is not substantiated. To settle this issue large prospective studies are needed. Meanwhile, close clinical surveillance of patients being treated with ovulation induction is required.

Introduction

Ovarian cancer represents the sixth most common female cancer and the fourth leading cause of death due to cancer in women. It is the most fatal gynaecological malignancy in the Western world as the 5 year survival is 40%[1,2]. European and North American countries represent areas with an incidence as high as 10-15 new cases of ovarian cancer per 100,000 women per year, while developing countries and Japan have rates of 2 -6.5 new cases per 100,000 women per year[2-4]. The three main types of ovarian cancers have different patterns of incidence by age. Germ cell tumors peak early in post-pubertal life, while epithelial and sex-chord stmmal tumors increase in incidence with increasing age. Ninety to ninety-five percent of ovarian tumors in women over the age of 35 years are of epithelial origin[4].
Clomiphene citrate (CC) was registered in 1967, human menopausal gonadotrophin(hMG)in 1969 andbromocriptine in 1978[5]. Inthe USAalone upto 1988, an estimated 1.9 million women aged 15-44 had taken fertility drugs[6]. This makes the possibility of a causal relationship between such agents and ovarian cancer extremely interesting.
The first case-report linking the use of fertility drugs with ovarian cancer came in 1982[7]. Since then, concern has been greatly increased due to studies that have found such an association[8,10].
Theoretical considerations
If any etiological role is to be postulated for fertility drugs then the epidemiological findings should fit coherently withanunderstanding of the natural histoiy of the disease.The etiology and mechanisms responsible for the development of ovarian neoplasms are still unclear. Current knowledge suggests that ovarian cancer like other solid malignant tumors, is induced many years prior to becoming clinically diagnosable. The proposed etiologies include that of ‘incessant ovulation’ ,the role of a hyper gonadotrophic state and that of malignant transformation of epithelial inclusion cysts[11-14]. Apart from this; infertility, envimnmental, hormonal and genetic factors are also thought to be involved in what is apparently a multi-factorial etiology of ovarian cancer[15]. Specific mutations responsible for the familial varieties of the disease have been discovered[16,17.]

She was a thin frail lady, with a diagnosis thai betrayed her constitution. She had Non-Hodgkin's Lyniphoma, with advanced disease admitted this time with what seemed as intestinal obstruction. They did not have too much hope forher from the start.
A conservative line of management was initiated, but her condition continued to deteriorate and it was reluctantly decided to do a laparotomy and explore for a cause of her condition. They found adhesive loops obstructing her intestines. Post-operatively, she did relatively well. Her ward course fmm thereon was an endless follow-up of blood counts, electrolytes and culture reports. I followed her up for almost two weeks, never ceasing to be amazed with her zest for life. In due course, she had managed to dictate her own management considerably, asking for opiate pain killers for what she described as excruciating pain in every part of the body. Over time I came to know her quite well. Until one day
We were in the operating theater for our usual procedures when we received an emergency call that she had crashed... Though she was intubated and resuscitated she passed away from what was assumed to be pulmonaty embolism or an acute myocardial event.
I stood there groping for some explanation. She had been perfectly well just two hours before on the rounds and yet Deep down inside I wanted to feel something for all that had happened, yet I could not manage to do so. It was as if somehow all my own emotions had been walled off from myself, consciously or unconsciously. It was not the first time that I had encountered a death on the wards and yet each time the same question resurfaces in the midst. Was this the real purpose of acclimatizing ourselves to everything around us, a process that starts right from the first day that you enter the hospital wards? The spectre of reality could never have been stranger. The paradoxes are enough to revulse any sane mind. Numbed emotions or that so called professional clinical detachment A few hours later, I passed by and there was a new patient on that bed.
Life goes on and so it must et the mind struggles for the elusive compromise.

Case Report

Forty-three cases have been reported from 1982 until 1997. Even though they give mainly clinical and not epiderniological- scientific data, an analysis is useful. For properevaluation cases are grouped into two main categories, epitheial and sex- chord stromal, as it seems that they represent different groups not only histogenetically but also etiologically.

Epithelial tumors

Thirty cases of this type have been reported until now. The following points need to be considered:

1. No information is given by most authors on familial history of the presented cases.
2. Different drugs were used during different periods, for different lengths of time and fOr different assisted reproduction techniques. This is important since:' firstly, each drug acts differently and secondly different assisted reproduction techniques act differently on ovarian surface epithelium.

2a. Clomiphene citrate acts directly on the hypothalamus and increases the pulse frequency of gonadotmphin-releasing hormone (GnRH). It effectively induces ovulation in 70-80% of the treated cycles[18,19]. Also, since it usually induces only mono- or -oligofolliculogenesis[18] , it is unlikely that the trauma incurred to the ovarian epithelium is greatly increased. Therefore, this does not fit in with the 'incessant ovulation' theoiy.

2b. Gonadotrophins were given inregimes ofone to five cycles in many cases and in most this occurred just before ovarian cancer diagnosis[20-22]. Also the duration of exposure, the physiological nature of the drug as well as the serum concentrations achieved are not consistent with the profile of a putative carcinogenic substance[23]. Additionally, several studies have demonstrated that epithelial ovarian

tumors do not possess gonadotrophin receptors[24].
3. Disorders of ovulation were the main cause of infertility in seven of the 30 patients (23.3%) and possible cause in another seven. As it will be discussed later on, anovulatoiy infertility per se bears an increased risk for ovarian cancer development.
4. The latent phase between the first ovarian stimulation cycle and ovarian cancer diagnosis varies widely between the reported cases. In 13 cases it was <2 years. This short latent period seems incompatible with cancer development due to ovulation induction.
5. Histological examination in 15 cases (50%) showed tumors of borderline malignancy. Ovarian tumors of borderline or low malignancy constitute 10-15% of the total[25,26]. Furthermore, an increased incidence of borderline tumors related to a history of infertility but not to nulliparity, suggests that the ovarian tumor in its early, pre-clinical development interferes with fertility in some manner, as is the case with sex-cord tumors[27].

Sex-cord stromal tumors A review of 13 cases of sex-cord stromal tumors in women who have undergone ovarian stimulation shows:

1. The latent phase.was very short in seven of the cases (1-6 cycles).
2. Existence of anoccultgmnulosacell tumoris possible in the twelve patients reported by Willmsen et aI(1993). This is indicated by the presence ofanovulatory fertility with cycle disorders prior to ovarian stimulation.
3. The above mentioned contention is also supported by the following evidence. Menstrual cycles were restored to normal in nine patients after removal of the affected ovary. Five of those patients later conceived spontaneously.

Epidemiological data While some have found no association between ovulation induction and ovarian cancer[28-30]. others have found a positive correlation[29-30], which have been the focus ofa lot of debate, particularly the series of three articles published by Whittemore et al, The Collaborative Ovarian Cancer Group (COCG)[9].

An early study involving 2,632 Israeli women failed to find any association betweenuse of fertility drugs and ovarian cancers[29]. A case-control study from China[30] reported an adjusted odds ratio for developing ovarian cancer of 2.1 (95% CI=20.2-22.7).

The COCG was a collaborative analysis of 12 case-control studies of ovarian cancer done between 1956 and 1986. The data-base were pooled and re-analyzed. The subjects numbered 2197 cases of ovarian cancer and 8893 controls. Detailed information on fertility was available in only three of those studies. This data consisted of 34 women with cancer and 23 without it. The results were as follows: the relative risk (RR) in women who had used fertility drugs was 2.8- itwas 4.0 for borderline tumors. The RR of ovarian cancer was increased in infertile women. In women with greater than 15 years' unprotected intercourse, the RR was 2.4. Women with an ovulatory disturbance had a relative risk of 2.1. Also pregnancy (full-term or not), oral contraceptives and lactation were associated with a decrease in epithelial ovarian cancer risk (invasive or borderline).

Support for the results and conclusions (regarding the use of fertility drugs) derived by Whittemore et al[9] has not been very forthcoming. The critics state, that to evaluate the plausibility of the findings it is necessary to have a list of cancer patients who took fertility drugs. The list should have information on the timing, age of patient, yearof diagnosis and other information like family history etc. The study is blamed for its (possible) failure to control for various confounding variables like parity, lactation, OCs and family history. It is also prone to various biases; diagnostic bias could account for thc strong association observed with borderline tumors in particular. Many non- responders in some of the studies could constitute a selection bias[5,23,31-33].

The database used in the study where infertility is analyzed, the average age of women is 53 years, with diagnosis being done between 1977 and 1981. If it is assumed that infertility treatment took place

between the ages of 30 and 40, then these women were treated between 1954 and 1967 on average. These results are not compatible with the use of new fertility drugs that were registered from 1967 onwards[5]. No information is provided in the study about the types of fertility drugs used, the doses and the length of treatment. This is important, as different drugs act differently. Then there is the question of validity of the original data used in the study. Pooling data from several studies with the same kind of bias can produce relative risk estimates that are statistically highly significant but nevertheless quite unconvincing of an underlying causal relation[23]. The incidence of all types of ovarian cancer has remained relatively constant over the last 30 years despite the widespread use of fertility drugs[34,35].
In the context of the incessant ovulation hypothesis, firstly, it is unlikely that the patients in the COCG studies ovulate "incessantly". The reason being that prior to 1970, fertility medications were mainly used for anovulatory infertility. So their risk even with addition of fertility medications, should be less than normo-ovulatory women. Secondly, the protection provided by various factors (pregnancy, OCs) should be proportional to the months of ovulation prevented. However, other authors have found the model based on ovulatory age to be unsatisfactory in that regard. For example, a single pregnancy and the lactation period that follows may be estimated to miss 3% of the ovulations, but a single pregnancy accounts for a 50% reduction in ovarian cancer incidence[36,39].
Another study[11] examined the risk of ovarian cancer in 3837 women evaluated for infertility between 1974 and 1985. The RR of developing any ovarian tumor was 2.5 times higher compared with general population. Stratifying for tumor type, the increased risk was more for tumors of low malignant potential than for the invasive type. The incidence ratio for the formerwas 3.3(95% CI= 1.1-7.8), while that forthe latterwas 1.5 (CI=0.4-3.7).
A couple of interesting observations were made concerning the use of CC. Comparing the infertile population who used CC with the general, the RR for patients who had _12 cycles was 10.9(95% CF 1.5-77.9), while for<12 cycles it was 0.8 (CI=0.1-5.7). If the relationship were truly causal one would expect a more consistent dose-dependent relationship. The second set of results concerned infertile gravid and infertile non-gravid CC users. The RR values for themwere 17.0 (95% CI= 1.22-242.8) and 10.8(CI=1 .5-77.9). This contradicts the well-established strong effect of parity on the risk of ovarian cancer. Additionally, the small number of ovarian tumors overall (n=11) and particularly for CC use of _12 cycles (n=5), limits the precision of risk estimates. A study done by Shushan et al - 1996[10] failed to confirm this set of results. It is entirely possible that those subjects receiving _12 cycles of CC may represent a subgroup of women with a particularly refractory infertility. There could be some underlying defect and this alone may predispose them to higher risk of ovarian neoplasms[40]. A well designed and executed study; it avoided many of the limitations of the previous studies. However, in the final analysis it is difficult to disregard the inconsistencies observed and they cast some doubt over the validity of the results of the study.
Another case-contml study, done in Israel10 found an increased risk in a subgroup of women withborderline tumors who had used hMG (adjusted OR=9.38,95% CI=1.66-52.08). The OR among women with borderline tumors was much higher than among women with invasive cancer.

Discussion

From the analysis of the data presented in the case-reports and studies many similarities have been found in both the results and limitations of the investigations. Thankfully, most of the studies found no increased risk for invasive cancer, however an association was observed with increased risk of borderline epithelial tumors[9-11] While a diagnostic bias cannot be ruled out, further investigations should analyze this association more carefully. Also, the rarity of cases reported;despite widespread use of CC and hMG make it unlikely that the therapy directly initiates neoplastic growth[23]. Most

commentators agree that there is a likelihood that follicular stimulation might activate certain types of pre-existing tumors inducing their earlier appearance. Bandera et al (1995) reported a case which supports that possibility.

It is a difficult task to resolve the question of causal relationbetween fertility drugs and ovanan cancer. Apart from our limited knowledge of the disease itself, its low prevalence and its association with infertility are major obstacles. Infertility has been established as an independent risk factor in addition to the effect of nulliparity in several studies. Harge et al (1989)[42] found the risk to be 2.8 times higher in married nulliparous with a history of infertility compared to non-married nulliparous women and Harlow et al (1988) [27] estimated this risk to be 6.0 for borderline tumors. It has been very difficult to adjust for the effect of infertility, because most women likely to be taking ovulation induction agents have some form of infertility. To reach the threshold of statistical significance very large studies are needed. de Mouzon[43] estimated that itis necessary to follow 20,000 exposed women and as many controls for 10 years, or 15,000 patients and as many controls for 15 years. Alternatively, a retrospective study in which 1100 cases are compared with 1100 well-matched controls could be done. This also requires a well designed database and detailed clinical information.

Apart from the skepticism regarding the technical shortcoming of the various studies undertaken so far, there are other reasons for the reluctance of many in the medical community to accept the results which show an association between fertility drugs and ovarian cancer.The issue is particularly sensitive for clinicians treating infertility; for them patient welfare, patient counselling and issues of potential liability and professional status are all of concern. It is no surprise that individuals affiliated with, sponsored by, or sympathetic to professional fertility societies would evaluate and if possible, discredit the findings of different studies- the COCG study in particular. Alice Whittemore defended the study in an article[44] ,stating that the group reported its findings because of “an obligation to alert the scientific community to the need to confirm or refute the association reported”. It was also stated that the reporting of an association is not equivalent to asserting a belief concerning the causality or lack of causality of the association.

Currently, two major projects involving cohorts of 12,000 and 10,000 women respectively45,46 are reported to be underway to further investigate this association.

Recommendations

If the above studies of ovarian cancer are to be translated into disease prevention, in view of relatively high risk for infertile women to develop ovarian carcinoma (and add to that the possible risk associated with fertility drugs), there is a need forcareful clinical evaluation withultrasound or other modem techniques before and during ovulation induction treatment.

Finally, probably the most important need is to put everything in perspective. Ovarian cancer is a rare disease. Assuming that a women lives up to the age of 85 years, her lifetime risk for ovarian malignancy is <1.5%. If the estimates of increased risk by the COCG were true, this risk is tripled to 4.5%. As many as 79% of women (in one study) were willing to accept an increase in their lifetime risk of ovarian cancer because of fertility treatment47. This risk if real must be compared with the 10% lifetime risk of breast cancer faced by all women and balanced against the physical and psychological benefits of pregnancy; which would greatly offset any increased risk associated with fertility treatment.

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