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Review

Does fertility treatment increase the risk of uterine cancer? A meta-analysis

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ABSTRACT

An ongoing debate over the last two decades has focused on whether fertility treatment in women may lead to an increased risk of developing uterine cancer over a period of time. Uterine cancer (including mainly endometrial carcinoma and the less common uterine sarcoma) is the commonest reproductive tract cancer and the fourth commonest cancer in women in the UK. Our objective was to assess the association between fertility drugs used in the treatment of female infertility (both as an independent therapy and during in vitro fertilization cycles) and the development of uterine cancer.

A literature search was performed using Medline, Embase, Cochrane Library and Google Scholar databases for comparative studies until December 2014 to investigate a clinical significance of fertility treatment on the incidence of developing uterine cancer. General and MESH search headings, as well as the 'related articles' function were applied. All comparative studies of 'fertility treatment' versus 'non-fertility treatment' reporting the incidence of uterine cancer as an outcome were included. Uterine cancer incorporated the following terms: uterine cancer, uterine body tumours, uterine sarcomas and endometrial cancers. The primary outcome of interest was the uterine cancer incidence in all 'fertility treatment' versus 'non-fertility treatment' patient groups. Secondary outcomes of interest were: (a) uterine cancer incidence in 'IVF' versus 'non-IVF' patient groups; and (b) uterine cancer incidence according to type of fertility drug used. Odds ratio was the summary statistic. Random-effects modelling, graphical exploration and sensitivity analysis were used to evaluate the consistency of the calculated treatment effect.

We included six studies in our final analysis, which comprised 776,224 patients in total. Of these, 103,758 had undergone fertility treatment and 672,466 had not. There was 100% agreement between the two reviewers regarding the data extraction. All the studies contained groups that were comparable in age, although the criteria of reporting age varied. Taking all studies into account, the incidence of uterine cancer was 0.14% (150 of 103,758) in the fertility treatment group and 2.22% (14,918 of 672,466) in the non-fertility treatment group. Using the random-effect model to analyze uterine cancer incidence, this difference was not found to be of statistical significance: OR 0.78 (95% CI, 0.39–1.57). The degree of heterogeneity was high (I^2 = 68%).

The risk for the development of uterine and in particular endometrial cancer posed by infertility and an unopposed oestrogen state is widely recognized. The present analysis aimed to perceive whether standard fertility drugs were also a risk to future uterine cancer development. The treatment does increase the concentrations of unopposed oestrogen for a short periods of time but if successful leads to fertility. This meta-analysis points to a non-deleterious effect of fertility drugs towards the development of uterine cancer, a conclusion strongly supported by our sub-group analysis.

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Contents

Introduction

An ongoing debate over the last two decades has focused on whether the treatment of infertility in women may lead to cancer involving the uterus (uterine, endometrial or cervical cancer) over a period of time.

Currently 1 in 7 couples in the UK are affected by infertility [1]. This has resulted in an year on year increase in the use of fertility treatments [2]. These treatments may involve the use of 'stand-alone' medications, for example, anti-oestrogens such as clomiphene citrate (CC) and less frequently tamoxifen for ovulation induction. Fertility treatments may also be part of in vitro fertilization (IVF) cycles including the use of human menopausal gonadotropins (hMG), recombinant follicle-stimulating hormone (rFSH) and human chorionic gonadotropins (hCG).

Uterine cancer (including mainly endometrial carcinoma and the less common uterine sarcoma) is the commonest reproductive tract cancer and the fourth commonest cancer in women in the UK with 6834 new cases diagnosed in 2010 [3]. Risk factors for endometrial cancer can be split into two groups, endogenous such as a strong family history, increasing age (with 60 being the average age), polycystic ovarian syndrome (PCOS) and obesity; and exogenous, such as unopposed oestrogen and tamoxifen therapy and previous radiotherapy [4].

Fertility treatment often results in increased and unopposed supra-physiological levels of oestradiol. This exogenous risk factor may lead to endometrial hyperplasia, a premalignant condition that can predispose to atypical complex endometrial hyperplasia and therefore ultimately lead to endometrial cancer itself. The risk of uterine malignancy may also apply to simple fertility medications such as Tamoxifen as reported previously [5]. This is of a specific concern with regards to cases of anovulatory infertility, a large number of which are linked to PCOS [6]. While unexplained infertility has been associated with a later diagnosis of uterine cancer [7], patients with primary infertility secondary to anovulation seemed also to be particularly predisposed to developing uterine cancers. Brinton et al. reported a RR of 2.42 (95% CI: 1.0–5.8). However, in this study, only 5% of women were classified as PCOS [8]. Recently, Barry et al. published a meta-analysis which showed that women of all ages with PCOS are at an increased risk of endometrial cancer. The risk of ovarian and breast cancer however was not significantly increased overall. These results highlight the potential risk of gynaecological cancer morbidities associated with PCOS [9].

A review of the literature demonstrates that the effect of fertility treatment has been reported mainly with respect to ovarian and breast cancers, but not uterine cancer.

Objective

This meta-analysis of retrospective studies is aimed at assessing the association, if any, between fertility treatment used both as an independent therapy as well as during IVF cycles, and the development of uterine cancer following that treatment.

Materials and methods

The meta-analysis was done according to PRISMA guidelines. A literature search was performed using Medline, Embase, the Cochrane Library and Google Scholar databases for comparative studies until September 2014 to investigate a clinical significance of carrying out fertility treatment on the incidence of developing uterine cancer in the future. The following MESH search headings were used: fertility agents, infertility; female, infertility treatment, uterus, uterine, endometrial, sarcoma, cancer, neoplasm, uterine neoplasms, clomiphene citrate, hCG, hMG, tamoxifen and in vitro fertilization/IVF. Searches were also performed under the headings: clomiphene citrate, hMG, GnRH analogue and buserelin. The 'related articles' function was used to broaden the search and all citations identified were reviewed, irrespective of language. No studies comparing uterine cancer incidence and use of fertility treatment were found before 1998. Therefore, comparative articles, including this group, were found between 1998 and 2014.

Using these strategies, studies comparing infertility patient groups who did and did not undergo fertility treatment were identified, and data regarding the outcome of interest (uterine cancer) was extracted. The search strategy and included studies are shown in Fig. 1.

Data extraction

Two reviewers (Srdjan Saso and Louay Louis) independently extracted the data from each study. Quantitative data was extracted as follows: logistics (first author, year of publication,