

## **Long term cancer risks in women after treatment with in vitro fertilization: do we have any answers yet?**

It has been 36 years since the first baby was born through in vitro fertilization [1] and in that time, many couples who would otherwise have been unable to conceive have benefitted. To date, around five million babies have been born worldwide through in vitro fertilization and related procedures (IVF) [2]. However, along with any medical procedure there are risks and many women are understandably concerned about the impact of IVF treatment on their long-term health. Hormone-related cancer risks are of particular concern. In this article we address studies that have examined the association between IVF treatment and the risk of cancers of the breast and ovary, borderline ovarian tumours, endometrial cancer and melanoma.

The ideal way to evaluate the safety of IVF treatment would be to conduct large randomised trials and follow women over a long period of time – perhaps 20 years or more or at least until they reach the average age at which cancer is diagnosed. However this is neither ethical nor practical. As an alternative, observational studies are an excellent research tool, provided their limitations are recognised. When reading observational studies, it is natural to assume that the reported risk measure represents the sole effect of the treatment of interest – in this case, of IVF. However this is not necessarily true. For example, studies that compare women undergoing IVF with the general population actually compare the effect of IVF combined with the effect of parity, age at first birth, infertility, socio-economic status and a host of other factors. These are factors that are associated with IVF treatment and are also risk factors for the disease under study. Their inclusion in the overall risk estimate has the potential to distort the estimate in one direction or the other. Comparisons between women having IVF and other infertility treatment may be preferable, as the two groups are more homogenous. Adjustment for known risk factors can further balance the two groups. Nevertheless one should always ask: do the two groups differ in ways other than IVF exposure that could contribute to the overall effect measure? Most studies follow women for only a short period of time – they can estimate the short-term but not long-term risk of disease. Often there are only a few cases identified. If the study population is small, follow-up is short and there are only a few cancer cases identified, then it is no surprise that no association between exposure and disease is observed. Not because an association does not exist, but rather because the study was incapable of detecting one - “absence of evidence is not evidence of absence” [3].

With these limitations in mind, what do we know about the association between IVF and the risk of breast cancer? A number of studies have compared women undergoing IVF with the general population. These studies [4-8] commonly followed women for only a short period of time (between 3.6 and 7.8 years), identified only a small number of breast cancer cases (between 5 and 87 cases), and were unable to adjust for important breast cancer risk factors. They generally did not find an association between IVF treatment and risk of breast cancer although one found a possible association [6]. In analyses restricted to women who had given birth, one study found a decreased risk of breast cancer associated with IVF treatment [9], another did not find an association between the two [10] while a third study found an increased risk [11]. Two other studies compared women having IVF with women having infertility treatment but not IVF [12, 13]. Neither study found an overall association between IVF treatment and breast cancer although the second study [13] which followed women for 16 years and identified 148 breast cancer cases in women who had undergone IVF treatment found an increased rate of breast cancer in women who commenced IVF treatment at

a young age. In a carefully designed meta-analysis, Sergentanis et al [14] combined the results of a number of these studies. They did not find any overall association between IVF and breast cancer, though their findings did suggest that parous women who had IVF may be at reduced risk of breast cancer while women commencing IVF before 30 years of age may be at increased risk. With all these conflicting results, we can only conclude that at the moment we do not know if IVF treatment is associated with an increased risk of breast cancer. We do, however, have some information about the indirect effects of IVF treatment. Women who have IVF deliver their first child at an average age of 32 years [13] compared with an average age of 28 years for women in the general population [15]. Later age at first birth is associated with an increased risk of breast cancer [13, 16]. By enabling late age at first birth, IVF treatment is indirectly contributing to an increase in a woman's risk of breast cancer.

Ovarian cancer is rare. The average age at diagnosis is 63 years [17]. These two characteristics combine to make it difficult to study: we need a large cohort and long follow-up in order to detect enough ovarian cancer cases to examine any potential associations. Studies to date have been based on only a small number of ovarian cancer cases. Four studies which compared women who had undergone IVF with the general population [4, 5, 7, 8] identified less than 10 ovarian cancer cases in women who had IVF and did not detect an association between IVF and ovarian cancer. Three larger studies compared women undergoing IVF with women seeking fertility treatment but not IVF [12, 18, 19]. They identified between 16 and 28 ovarian cancer cases and followed women for 8 to 17 years. Hazard ratios associated with IVF treatment were 1.58 (95% CI 0.75-3.29) [12], 1.36 (95% CI 0.71-2.62) [18] and 1.51 (95% CI 0.65-3.54) [19]. In a study restricted to parous women, Kallen et al [9] found an increased risk of ovarian cancer in IVF women compared with the general population. A meta-analysis [20] that included some of the studies described above (but not all – two of the larger studies [12, 18] were published after the meta-analysis was completed) found an increased risk associated with IVF treatment in comparisons with the general population but not when women seeking fertility treatment made up the comparison group. For a clearer answer, we will need larger studies, longer follow-up, detailed adjustment for confounding factors and ideally, a comparison between women having IVF and women undergoing other fertility treatment. In terms of an indirect effect of IVF treatment, we know that women who have given birth have around half the risk of ovarian cancer of women who remain childless [18, 21]. If we assume it is the process of pregnancy, birth and lactation that is associated with a decreased risk of ovarian cancer (rather than the underlying infertility that is associated with an increased risk) then for women who give birth after IVF, the overall effect of IVF treatment is to reduce their risk of ovarian cancer.

Like ovarian cancer, borderline ovarian tumours are rare. In fact, they are rarer than ovarian cancer, comprising only around 15% of all ovarian neoplasms [22]. Unlike ovarian cancer they are seldom fatal. Only three studies have examined the association between IVF treatment and borderline ovarian tumours [8, 19, 23]. One study [8] which observed only 4 cases among women treated with IVF did not find an association between IVF treatment and risk of borderline ovarian tumour. The two other studies were larger and both found an increased risk of borderline ovarian tumours in women who had undergone IVF treatment. The first [19] found a four-fold increase in risk; the second [23] found a 2.5-fold increase in risk. Despite these statistics, it is worth bearing in mind that twice or even four-times a small risk is still a small risk. While these findings contribute to our understanding of the aetiology of the disease, for most women they should not be a cause for concern.

A few studies have assessed the association of endometrial cancer with IVF treatment [4, 7, 8, 12]. The number of cancer cases in women treated with IVF in each of these studies was small (between 2 and 15). None of the studies found an association between IVF and endometrial cancer: either because none existed or because the studies were too small to detect an association. Larger studies with longer follow-up and adjustment for important confounders are needed before we can draw any conclusions.

Melanoma is not normally considered to be a hormone-related cancer although melanocytes are known to be hormonally responsive (consider, for example skin pigmentation often observed in pregnant women and women taking the oral contraceptive pill) and parity has been extensively studied in relation to melanoma risk [24]. Two studies have examined the association between IVF treatment and melanoma [8, 25]. The first [8] identified 12 cases of melanoma in women who had IVF and did not find an association between the two. The second, larger study [25], with 55 cases of melanoma in women who had undergone IVF treatment and an average of 17 years of follow-up found that women who had IVF and gave birth had a 3.6-fold increase in the risk of melanoma compared with women who had IVF but did not give birth. This increase in risk was not apparent among women who had non-IVF infertility treatment. This unexpected finding will need confirmation in future studies.

A further key consideration is the role of potential confounding factors. Parity and age at first birth are important risk factors and these have been included in some analyses [11-13, 18, 19, 23], while other studies have considered parous women separately from nulliparous women [9, 11, 18, 23, 25]. The cause of infertility may be important. For example, endometriosis is associated with an increased risk of ovarian cancer [18] and is more commonly diagnosed in women seeking fertility treatment. Women undergoing IVF are likely to be of higher socio-economic status [18] although this may vary from country to country depending on the cost of treatment. Socio-economic status is related to the risk of cancer. If socio-economic status confounds the association between IVF treatment and the risk of cancer then adjusting for socio-economic status could help to isolate the effect of IVF treatment. Another example that is more difficult to quantify is health-seeking behaviour. Women undergoing IVF may be more pro-active in seeking the health care they need and may therefore adopt life-long strategies that reduce their risk of cancer. Health-seeking behaviour may be an important confounding factor. If we are unable to take this into account, we risk underestimating the association between IVF treatment and cancer.

IVF has a relatively short history. Women who underwent treatment in its earliest days are only now approaching the average age at which cancer is diagnosed. Future studies with longer follow-up time will identify more cancer cases and this will allow for a more precise estimate of risk. With appropriate adjustment for confounding factors it should be possible to derive more accurate, unbiased estimates. At present, we do not have enough evidence to draw any firm conclusions about the potential association between IVF treatment and hormone-related cancers.

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