Scientific evidence in support of AB 1317

AB1317 requires advertisements seeking oocyte donors to include a warning that there are potential risks associated with human egg donation, that the long-term risks have not been determined, and to advise consultation with a reproductive care specialist prior to entering into a donor contract.

THE 2007 IOM REPORT FINDINGS

Both the statements that there are potential risks, and that long-term risks associated with egg donation have not been determined are supported by the **2007 Institute of Medicine Report entitled *Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research*.**[1] This report contains the following statements:

"One of the most serious concerns about ovarian stimulation is that it may increase the chances that a woman will suffer certain types of cancer later in her life…In particular, … there are three types of cancer that would seem to have a plausible biological link to the hormone regimens used in ovarian stimulation: breast, ovarian, and endometrial cancers….There are several reasons to be concerned that the hormones used in assisted reproduction might make these three cancers more likely. First all three of them seem to be affected by hormones" [p.22].

After reviewing conflicting findings and from various studies on ovarian cancer and downplaying the likelihood of cancer, the report goes on to state, "At this time, however, the state of knowledge is not conclusive, and clarification of the exact relationship between ovarian cancer and treatment with fertility drugs will require additional long-term follow-up studies." (p, 25)

Later the report continues, "One study in particular focused just on women who had taken clomiphene and looked at the rates of various cancers. It found that as time elapsed since the treatment, there did seem to be an increase in risk for breast, ovarian, and endometrial cancers, with the highest risks for the endometrial cancers. This is of particular concern, Dr. Ness [Chair of Section on Cancer Risk] said, because it raises the possibility that many studies have missed the increased cancer risk because they haven't followed their subjects for enough years." (p 26.)

In summarizing, the report states, "One of the most striking facts about in vitro fertilization (IVF), Dr. Guidice [Committee Chair]commented, is just how little is known for sure about the long term health outcomes for the women…" Although more than a million IVF cycles have been performed in the United States over the

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[1] Guidice, L. et al., 2007. *Assessing the Medical Risks of Human Oocyte donation for Stem Cell Reseach: Workshop Report*. Institute of Medicine and National Research Council. Published by The National Academies Press, Washington, DC.

past 20 years…there are no registries that track the health of the people who have taken part. …the studies vary quite a lot in terms of study design, the number of subjects, and outcome, so it is impossible to draw a consistent picture from them." (p. 51)

In addition to cancer, some scientists have expressed concern regarding the long-term effects of egg harvesting on young women's fertility. As the IOM report states: "We don't really have data to tell us, if these individuals who donated their eggs were followed, how their fertility would compare with a matched control group." (p. 53)

STUDIES THAT SHOW INCREASES IN CANCER AMONG WOMEN WHO HAVE UNDERGONE OVARIAN HYPERSTIMULATION

OVARIAN CANCER

The earliest evidence of a link between ovulation-stimulating drugs and ovarian cancer was derived from a meta-analysis of 12 case-control studies of ovarian cancer conducted by Whittemore et al. 1992[2]. In this study nulligravid [never pregnant] women, experienced a 27-fold increase in risk associated with drug usage, however, this risk was based on small numbers.

In 1994 Rossing et al[3], found that clomiphene use was associated with an estimated 2 to 3 fold increased risk of ovarian cancers.

In a 2007 article[4], National Cancer Institute epidemiologist Dr. Louise Brinton points out that although some more recent studies have been more reassuring, women who were exposed to these drugs "are just beginning to enter the ovarian cancer age range. Furthermore, less information is available on gonadotrophins than clomiphene, given that the latter was the drug of choice in earlier time periods. Thus, additional follow-up data are needed to fully evaluate effects of both exposures"[p. 40].

The most optimistic recent study on ovarian cancer concludes by acknowledging, "only a small proportion of the women in the cohorts were followed up for a

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[2] Whittemore, AS, *et al*. "Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cencer Group. *American Journal of Epidemiology* 1992: 136:1184-203.

[3] Rossing, MA, *et al*. "Ovarian tumors in a cohort of infertile women. *New England Journal of Medicine.* 1994; 331:771-6.

[4] Brinton, L. "Long-term effects of ovulation-stimulating drugs on cancer risk." *Reproductive BioMedicine Online*:www.rbmonline.com/Article/2808 on web 16 May2007.

sufficient time. Longer follow-up is needed to assess the effect of latency on risk of ovarian cancer after exposure to fertility drugs.[5]

BREAST CANCER

In a 2006 study of 5788 women attending an Israeli clinic, investigators found a significantly elevated risk of breast cancer related to clomiphene exposure.[6]

An Australian study[7] found an approximately two-fold increased risk of breast cancer within 1 year of treatment.

ENDOMETRIAL CANCER

According to Dr. Louise Brinton, Chief of the Hormonal and Reproductive Epidemiology Branch of the National Cancer Institute "The two largest cohort studies both raise some concern regarding effects of ovulation-stimulating agents on the endometrium." An Israeli study found a two-fold increase in risk.[8] A US study found increases in risk among subjects with higher dosages of exposure or longer follow-up periods, with trends in risk for the latter variable being statistically significant.[9]

THYROID CANCER

In 2008 a Danish study[10] concluded: "Clomiphene and possibly progesterone may increase thyroid cancer risk, particularly among parous women. Longer follow-up is needed to confirm our findings."

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[5] Jensen, *et al*. 2009 "Use of fertility drugs and risk of ovarian cancer: Danish population based cohort study." *British Medical Journal* 338;b249.
[6] Lerner-Geva, *et al*. 2006. "Infertility, Ovulation Induction Treatments and the Incidence of Breast Cancer—a Historical Prospective Cohort of Israeli Women." *Breast Cancer Research and Treatment* 100, 201-212.
[7] Venn A, *et al*., 1999. "Risk of cancer after use of fertility drugs with in-vitro fertilization. *Lancet* 346. 995-1000.
[8] Modan, *et al.* 1998. "Cancer incidence in a cohort of infertile women. *American Journal of Epidemiology* 147. 1038-1042.
[9] Althuis, M.D., *et al*. 2005 "Uterine cancer after use of clomiphene citrate to induce ovulation." *American Journal of Epidemiology* 161, 607-615.
[10] Hannibal, C.G., *et al*. 2008. "Risk of thyroid cancer after exposure to fertility drugs: results from a large Danish cohort study," *Human Reproduction*, Volume 23, No. 2, pp. 451-456.

UTERINE CANCER

A 2005 study[11] concluded, "In summary, our study is the first known to suggest that clomiphene increases uterine cancer risk and to demonstrate evidence of both a dose-response and latency effect." The study also includes the statement that "… all ovulation-stimulating drugs may increase uterine cancer risk."

OVERALL CANCER RISKS

NCI's Dr. Louise Brinton recently (2007:42 See footnote #4 for complete reference) summarized research on long-term effects of ovulation-stimulating drugs on cancer risk as follows:

"There has been little attention focused on the long-term effects of assisted reproductive technologies, which often involve much higher exposures to gonadotrophins than were received by women in previous eras. In addition, most IVF protocols include luteal phase support for several weeks with supplemental progestogens, which raises concern since these agents have been linked in several studies to increases in breast cancer risk. Since in-vitro techniques have become common only in the last couple of decades, it may be some time before epidemiological studies can amass the follow-up times required to fully address long-term effects." ….

"Although most attention has focused on effects of fertility drugs on ovarian cancer risk, more recent investigations support the need for further attention on breast and endometrial cancers. The need is supported by the recognition that ovulation stimulating drugs are effective at increasing both oestrogen and progestin concentrations, alterations that have been linked with both of these cancers. Further, a relationship with breast cancer would parallel findings of an increased risk of this tumor among mothers exposed to diethylstilbestrol during pregnancy."

NEW STUDY ON OVERALL CANCER RISK – Nov. 2008[12]

A long-term population-based historical cohort study of parous [having given birth one or more times] Israeli women concluded: "Women who used drugs to induce ovulation (n=567) had increased risks of cancer at any site…" An increased risk of

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[11] Althuis, M.D. *et al*., "Uterine Cancer after Us of Clomiphene Citrate to Induce Ovulation." *American Journal of Epidemiology*, pp. 607-615.
[12] Calderon-Margalit, R. *et al*. 2008. "Cancer Risk After Exposure to Treatments for Ovulation Induction." *American Journal of Epidemiology*, (Advance Access published November 26, 2008).

uterine cancer was found among women treated with ovulation-inducing agents…" ….”In conclusion the present study demonstrated an association between treatment for ovulation induction and overall risk of cancer, particularly cancer of the uterus.”

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