Published in final edited form as:

Fertil Steril. 2013 June ; 99(7): 1853–1854. doi:10.1016/j.fertnstert.2013.02.047.

Epithelial ovarian tumors and fertility drugs—are we asking the right questions?

Pauline Mendola, Ph.D.

Eunice Kennedy Shriver National Institute of Child Health and Human Development, Division of Epidemiology, Statistics and Prevention Research, Epidemiology Branch, Bethesda, Maryland

The article by Dr. Asante and colleagues (1) in the current issue attempts to address the question whether or not infertility drugs increase ovarian tumor risk. This is a question of great interest to the reproductive health community—but it is not a simple question and the data to provide a clear answer appear elusive.

Although the historic literature is inconsistent, most recent studies (2, 3) as well as the current report find no increased risk for ovarian tumors associated with fertility drug use. Whereas many investigators speculate that earlier reports of increased risk were based on less well controlled studies, even recent studies frequently lack key data to address the question with more confidence. Confirmed infertility diagnosis(es) and detailed treatment data are often lacking. In addition, follow-up times are often insufficient to capture most diagnoses given that about half of ovarian cancers are expected to occur after age 63 years (4). If there are high risk groups (e.g., nulliparas, long-term fertility drug users), they have not been consistently identified. When data on the indication(s) for treatment, the drugs used (including type, dose, duration), and other important confounders are missing or poorly specified, it is challenging to identify risk at all, let alone if only a subgroup of women are impacted.

Case-control studies are the most efficient way to study rare events like cancer, but they suffer from inherent concerns about bias. Selection bias is the most worrisome concern in hospital-based studies. Ideally, cases represent the universe of all cases and control subjects arise from the same source population as the cases. The Mayo Clinic Ovarian Cancer Study has many strengths including frequency-matching on region, which is important as both cases and controls came from a six-state catchment area. However, region was not controlled for in the analyses, perhaps because it did not operate as a confounder, but it could bias the results toward the null to the extent that controls are more similar to cases in the study than the source population. Somewhat less reassuring, although cases might travel for specialized care and may represent cases in general, the control women all have access to health care and they also have the resources to travel for treatment of “general medical conditions.” It is not clear what implications this has for the findings, but in a null study these are factors worth thinking about. It may also be worth noting that the age distribution in the current study has a large SD. Although age is controlled for in the analysis, there is potential heterogeneity in the time between infertility treatment and diagnosis. We might expect a complex relationship where women who sought treatment and received fertility

drugs are likely younger on average than other cases, but they also experience a shorter latency.

At present, two main hypotheses—incessant ovulation and elevated gonadotropin levels—have been the primary drivers of research, both plausible and supported by animal and human evidence. Under these hypotheses, infertility presents a risk because women are less likely to be anovulatory due to pregnancy and lactation, as well as perhaps having shorter duration of hormonal contraceptive use with longer time attempting pregnancy. Among infertile women, the addition of drugs to stimulate ovulation creates both a condition of high gonadotropins and superovulation. This would seem to be a particular concern for women who are not anovulatory, as the stimulation would occur against a backdrop of incessant ovulation. In the current article (1), neither infertility nor infertility drug use were associated with increased risk of ovarian tumor. Whereas statistical power was modest, the study had the power to detect an effect for infertility and infertility drug use well below a risk of 2.0, which is in range of several previous reports. Some of the subgroup analyses are challenged by small numbers, with approximately half as many controls as cases and power to detect only large effects in the range of 2.7–4.6. Given that some other small studies have seen effects as large as 11, it might not seem implausible to conduct these tests, but does reinforce the inconsistent nature of the literature on subgroup risks where a few cases can drive a large association with poor precision and power is generally limited.

In contrast to the traditional causal hypotheses, new evidence is emerging to suggest that epithelial ovarian tumors have an extraovarian origin and divide into two types, one more indolent and the other more aggressive, both of which involve the ovary secondarily (5). To the extent that ovarian tumors arise from extragonadal tissue, then neither ovulation nor high levels of gonadotropins are tripping the switch—although they likely play some role given the strong and consistent reduction in risk associated with anovulatory states (e.g., oral contraceptive use, pregnancy).

Ovarian epithelial cancer is one of the most common gynecologic cancers and the fifth leading cause of cancer death in US women. Fortunately, the incidence of ovarian cancer has generally declined between 1975 and 2009, with a –1.5 annual percentage change reported between 2001 and 2009 (4). Coupled with the increase in fertility drug use over time, these secular trends are inconsistent with a large risk on the population level, even with some variation in latency. This factor, along with the accumulating null findings in recent studies of fertility drug use and ovarian tumors, is generally reassuring. To get a clearer answer, particularly for subgroups of interest, future retrospective studies should make use of the tools available to enhance the validity of self-reported fertility data including cognitive interviewing and review of infertility treatment records. Prospective studies that focus on patients with infertility should seek consent for future linkage with cancer registries and other databases.

Despite acknowledged limitations, the extant evidence appears to exclude a substantial risk of ovarian tumor associated with fertility drug use, particularly for invasive tumors. Whether a risk remains for certain subgroups of women is difficult to say without more data focused on those specific questions, including detailed treatment data and adequate follow-up time.

References

1. Asante A, Leonard PH, Weaver AL, Goode EL, Jensen JR, Stewart EA, et al. Fertility drug use and the risk of ovarian tumors in infertile women: a case-control study. *Fertil Steril*. 2013; 99:2031–6. [PubMed: 23552324]
2. Gadducci A, Guerrieri ME, Genazzani AR. Fertility drug use and risk of ovarian tumors: a debated clinical challenge. *Gynecol Endocrinol*. 2013; 29:30–5. [PubMed: 22946709]
3. Brinton LA, Sahasrabudhe VV, Scoccia B. Fertility drugs and the risk of breast and gynecologic cancers. *Semin Reprod Med*. 2012; 30:131–45. [PubMed: 22549713]
4. National Cancer Institute. [Accessed February 25, 2013] SEER stat fact sheets: ovary. Available at: <http://seer.cancer.gov/statfacts/html/ovary.html#risk>
5. Kurman RJ, Shih I-M. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer —shifting the paradigm. *Hum Pathol*. 2011; 42:918–31. [PubMed: 21683865]