The Nordic Health Registries: an important part of modern medical research

Sir,

Human Reproduction published an editorial (Evers et al., 2015) and two invited commentaries (Grimes, 2015; van Wely, 2015) to accompany our recent article, entitled ‘Cancer Risk among Parous Women Following Assisted Reproductive Technology’ (Reigstad et al., 2015). We are honored by the additional exposure, rendering opportunity to engage in further discussions about cancer and fertility treatment. The commentary by van Wely presents considerations on many important strengths, but also limitations, of our study. The following letter is a response to the commentary of Dr Grimes (Grimes, 2015).

We appreciate Dr Grimes’ thorough review of our article and for pointing out some of the complexities involved with assessing the relationship of fertility treatments to cancer risk. Although challenging, the issue is clearly of interest and public health importance given that the use of assisted reproductive technology (ART) is on the rise and that there are strong commercial interests associated with the ART industry (Health Care Finance, 2012; The New York Times, 2013). While linked registries have their limitations, they do offer some advantages over other observational studies from which conclusions regarding possible effects of ART have derived. Thus, record linkage studies can provide larger numbers of exposed women as well as documented (rather than recalled) information on drug exposures, as well as complete data on cancer outcomes. Unfortunately, carrying out a randomized controlled trial (RCT) is not feasible for assessing cancer outcomes, largely because of the long induction times involved, as well as the rarity of cancers in the population. Most importantly, it would be considered unethical to perform a RCT of different fertility treatments with cancer as the outcome.

The Nordic registries provide a rich resource by which a variety of exposures and outcomes can be linked through a common personal identification number. Neither registries used in the present study were founded for administrative purposes; on the contrary, the Cancer Registry was established with the intention of facilitating cancer research concerning incidence, prevalence, survivorship and causality. The Medical Birth Registry of Norway (MBRN) was founded with the purpose of monitoring the health and well-being of newborns, and its establishment was in fact instigated by the Thalidomide scandal in the spring of 1962 (Rodin et al., 1962; Speirs, 1962). While there are some limitations to linked registry studies, as we extensively discussed in our article, record linkage efforts have previously provided a number of important public health insights. This includes the demonstration that low birthweight individuals are at an increased risk of coronary heart disease later in life (Leon et al., 1998; Eriksson et al., 1999), and that women with preeclamptic pregnancies subsequently experience reduced risks of developing breast cancers (Vatten et al., 2002). Another noteworthy discovery, based on several epidemiological studies (Engelberts and Dejonge, 1990) is that prone sleeping positions increase the risk of sudden infant death syndrome (SIDS); a finding also confirmed by a prospective cohort study (Dwyer et al., 1991).

Dr Grimes questioned the extent to which our article complied with STROBE (STrengthening the Reporting of OBservational Studies in Epidemiology) guidelines. Although not explicitly mentioned as part of the article, all criteria were explicitly satisfied. In addition, we did have an a priori study hypothesis which was simple and clearly defined (Reigstad et al., 2015); namely whether women giving birth after ART have higher risks of cancer than those who conceive naturally. Many previous observational studies assessing the relationship of ART to cancer risk have relied on comparisons of infertile women with the general population, which can present interpretative problems given that it is well recognized that bearing children strongly influences the risk of many cancers. Thus, our study offered an advantage over these studies by being able to compare cancer incidence among a cohort of infertile women according to different types of ART exposures. We do recognize that we were not able to completely control for all sources of potential confounding, such as obesity and cigarette smoking, but we were able to control for the most important difference between infertile women and women in the general population, namely the number of children borne.

It is true that findings that emerge from epidemiologic studies are merely associations and that inferences regarding causality depend on many other factors. Discovering associations through epidemiologic studies is also of importance in pointing biological research in new directions. For instance, the observation of lower risks of breast cancer among preeclamptic women has stimulated research into novel hormonal mechanisms of the disease that may operate at early phases of women’s lives (Troisi et al., 2013; Rasmussen et al., 2015). It is also correct that the relative risks that derive from most epidemiological studies are small, but may still have great importance in terms of attributable risk, particularly for common exposures and diseases.

Given that we observed only a few significant findings in our investigation, we believe that the Norwegian data are largely reassuring regarding the effects of ART exposures on subsequent cancer risks. In our paper, one of the findings related to a potential excess risk of central nervous system (CNS) tumors in ART-exposed patients, a finding that we interpreted cautiously and recommended be examined in future studies. The failure to replicate this association in future research would provide further reassurance of the safety of ART exposures. We thus believe it is critical that researchers continue to pursue research leads where findings may be difficult to explain—as ignoring a potentially elevated risk of cancer is as unwise as possibly making a false interpretation.

References


M.M. Reigstad1,*, I.K. Larsen2, T.Ä. Myklebust2, T.E. Robsahm2, N.B. Oldereid2, A.K. Omland2, S. Vangen1 and R. Storeng1
1Norwegian National Advisory Unit on Women’s Health, Oslo University Hospital, Rikshospitalet, Oslo, Norway
2Institute of Population-based Cancer Research, Cancer Registry of Norway, Oslo, Norway
3Section of Reproductive Medicine, Oslo University Hospital, Rikshospitalet, Oslo, Norway
*Correspondence address. martereigstad@gmail.com
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The absence of evidence is not the evidence of absence

Sir,

The debate opened by Moffett and Shreeve (2015) offers an excellent updated introduction on uterine natural killer (NK) cells. However, it contains many inaccuracies with respect to immunomodulation and intravenous gammaglobulin (IVIg) in particular, which we would like to clarify:

Moffett and Shreeve refer to the lack of evidence to use immunomodulatory drugs in recurrent reproductive failure (RRF). Patients with RRF represent a heterogeneous group encompassing diverse autoimmune and inflammatory causes, among others. Antiphospholipid syndrome (aPS) is the most frequent cause of RRF. In a subgroup of patients with aPS, in which miscarriage occurs despite adequate antithrombotic prophylaxis with acetylsalicylic acid (AAS) and low molecular weight heparin (LMWH), IVIg has been used with beneficial clinical effects in terms of the mother’s health and their baby’s survival (Wijetilleke et al., 2012). Moreover, peripheral blood (pb)NK cells expansions are associated with aPS (Oliver-Mirarro et al., 2009). An ongoing effort is being done to better identify other autoimmune causes of RRF, namely, coeliac disease, hypothyroidism and proinflammatory profiles by pbNK cells expansion with increased Th1 and Th17 cytokines, and specific NK cell receptors (Kwak-Kim et al., 2014). Further translational research is necessary to better elucidate the precise role of these alterations on pregnancy failure, and to propose more targeted therapies.

Moffett and Shreeve state that IVIg global adverse effects (AEs) are up to 40%, but they omit to say that AEs are related to high-dose and high speed infusion. In a recent review of AE of high-dose IVIg (with 5-fold dosage used in RRF) transitory headaches (16.6%), fever (6.6%), hypertension (4.6%), chills (3.3%) and nausea (3.2%) are reported (Lunemann et al., 2015). It is well-known by clinical immunologists that slow infusion of low-dose IVIg results in ≏5% of patients exhibiting mild AE without moderate or severe AEs. Moffett and Shreeve mention anaphylaxis as an AE of IVIg. Anaphylaxis is an unpredictable AE as for any known drug (it is very rare in IVIg and related to anti-IgA antibodies in IgA-deficient patients, which is not the case here).

For more than 30-years IVIg has been in use during pregnancy for primary immunodeficiency and autoimmune diseases, and according to international consensus and expert committees, diverse autoimmune diseases are treated with off-label IVIg, such as multiple sclerosis, myasthenia gravis, immune thrombocytopenia, systemic lupus erythematosus, congenital heart block, as a steroid-sparing potent immunomodulatory agent (defined as good clinical practice) (Elovaara et al., 2008).

Moffett and Shreeve highlight the high cost of IVIg, which is true. The mean hospital medical cost of a miscarriage for the Spanish Social Security System, however, is estimated to be 7246€ (1198€ for curettage plus 6048€ for hospitalization and patient care) (http://www.msssi.gob.es/estadEstudios/estadisticas/docs/pesosCostes2004ResumenNotas.pdf). The global cost of IVIg for the whole pregnancy is less than these ciphers (~5445€ for a patient of 60 kg body-weight): not to mention the psychological, family and social impact of RRF.

There are at least 70 indications for IVIg off-label use; some of them, such as Alzheimer disease, will present a serious problem to IVIg available resources if proven effective. Why would the low dosage and 9-months period of IVIg dosing used in RRF patients, if proven effective (in terms of mother’s health and baby’s life-births), merit a different treatment?

Contradictory results were observed in a recent meta-analysis of the IVIg use in secondary recurrent miscarriage without immunologic selection of patients (Egerup et al., 2014). The authors concluded on the necessity to identify a subgroup of patients in whom the benefit