LETTER

RE: “An Estimation of the Risk of Pseudotumor Cerebri Among Users of the Levonorgestrel Intrauterine Device”

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ABSTRACT

The current letter to the editor describes some of the limitations of Valenzuela et al.'s study on the association between levonorgestrel-releasing intrauterine system use and pseudotumor cerebri/idiopathic intracranial hypertension and further reinforces the authors' interpretations of the findings.

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Valenzuela et al.¹ explored an association between levonorgestrel-releasing intrauterine system (LNG-IUS) use and pseudotumor cerebri/idiopathic intracranial hypertension (PTC/IIH). As the authors state, their investigation does not indicate that LNG-IUS can cause PTC/IIH or that LNG-IUS use is an independent risk factor for PTC/IIH. Here, we discuss additional methodologic limitations of the study that further reinforce the authors' interpretations.

Using data from the University of Utah Health Sciences Center (USA) and from Rigshospitalet (Denmark), Valenzuela et al. retrospectively compared LNG-IUS exposure in PTC/IIH cases and controls. In Utah, cases of PTC/IIH newly diagnosed between 2008 and 2013 in females aged 18–55 were identified from the University PTC/IIH database. In Rigshospitalet, ascertainment of newly diagnosed cases between 2008 and 2014 in females aged 18–55 was done through hospital case review and the PTC/IIH database of the Department of Ophthalmology. Women aged 18–55 with at least one clinical encounter between 2008 and 2013 in the University of Utah Electronic Billing database and between 2008 and 2014 at Rigshospitalet were selected as controls, respectively. Based on this information, the crude odds ratios (ORs) of PTC/IIH associated with LNG-IUS use were 7.70 (95% confidence interval [CI]: 3.7–16.0) in Utah and 3.91 (95% CI: 1.89–8.06) in Denmark.

As authors also recognized, these results are likely to be affected by the potential confounding effect of the established risk factors – including obesity, recent weight gain, and tetracycline antibiotic use. One important potential confounder not mentioned by the authors was age. While both cases and controls had the same age range of 18–55 years, there is no indication that the study or the analyses accounted for the potential confounding effect of age either in the design or in the analyses. PTC/IIH patients were on average 30 years old (approximately 28 in Denmark and 32 in Utah). This figure parallels other published datasets.² Controls, on the other hand, were selected from any female aged 18–55 who had at least one clinical encounter at the study sites during the study period. As increasing age correlates with increased healthcare utilization, it is likely that the control group enrolled more women from the upper end of the age range. Assuming that controlling for age was not performed, it is likely that the different distribution of age between cases and controls could additionally inflate the calculated ORs.

The different methods of exposure ascertainment in cases and controls in both Utah and Denmark resulted in differential misclassification of exposure to LNG-IUS between the groups and consequently lead to overestimation of effect sizes. To determine whether PTC/IIH patients had used an LNG-IUS,

the authors conducted telephone interviews (Utah) and reviewed medical files (Denmark). Exposure ascertainment for controls was different, however. In Utah, the authors used University of Utah billing data to identify LNG-IUS insertion in that university healthcare system in controls between 2008 and 2013. This would miss those LNG-IUS users who received their IUS outside of the billing system of the University (such as at Planned Parenthood or any community practice not included within the University of Utah billing system) or who received their LNG-IUS before 2008 but were still using it during the study period and would misclassify them as non-users. In Rigshospitalet, an extrapolation of the 2014 national sales and census data was used to estimate the LNG-IUS exposure among controls. Specifically, the authors divided the number of LNG-IUS units sold in Denmark in 2014 by the number of reproductive-age women in Denmark. As LNG-IUS has an intended duration of use of five years, this method captures incident use for a single year only and disregards any LNG-IUS that was inserted during the period prior to 2014 and was still in use in 2014. Both methods of exposure assessment therefore lead to an underestimation of LNG-IUS use among the controls and subsequently a higher effect size for LNG-IUS use in relation to PTC/IIH. Published data on the contraceptive use in both study populations further support this argument:

Recent data on contraceptive use in the Nordic countries estimated the prevalence of LNG-IUS use in Denmark at approximately 10% (closer to 12% approaching the year 2014) for women in fertile age,³ in line with earlier published figures.⁴ The 3.5% prevalence for LNG-IUS in the Rigshospitalet study, extrapolated from 2014 sales figures in Denmark, is therefore a significant underestimation of the actual prevalence of LNG-IUS use in the control population. For the USA, the national average intrauterine device (IUD) use during 2006–2010 and 2011–2013 was 3.5% and 6.4% of women of child-bearing age, respectively.⁵ The Centers for Disease Control's Behavioral Risk Factor Surveillance System (BRFSS) survey has collected state-specific information on self-reported contraceptive use from 17 states as a part of the BRFSS Family Planning module in 2011 or as state-added questions in 2012 or 2013.⁶ According to the 2013 BRFSS data,⁶ prevalence of long-acting reversible contraceptive (LARC) use

among women aged 18–44 “at last intercourse” was 18.9% in Utah, the highest of any state surveyed. Sanders et al.⁷ reported that 75.1% of LARC use within the University of Utah healthcare system consisted of LNG-IUS and to a lesser degree of copper IUD (13.2%) or etonogestrel implant (11.7%). These sources indicate an overall LNG-IUS prevalence in Utah which is higher than the US national average and considerably higher than that identified by the authors (2%, or 4408/220,904).

Based on published data on LNG-IUS use in both populations and using a 10% estimate for LNG-IUS use in controls in both study sites (as published for Denmark,³ and as a cautious estimate for Utah assuming above-national average LNG-IUS use as supported by the surveys^{5,6}), we calculated a crude OR (95% CI) of 1.41 (0.67–2.98) for the Utah site and of 1.29 (0.61–2.70) for the Danish site. None of these crude ORs shows a significant association between LNG-IUS use and PTC/IIH.

In addition to the crude ORs, the authors present several other statistics, including disease prevalence and measures of risk such as relative risk and attributable risk. At both study sites, women with PTC/IIH who were enrolled from the PTC/IIH databases are likely to have been referred to the centres for specialist care, resulting in an artificial enrichment of cases in the study population compared to the general population. As a result, the disease frequency in the LNG-IUS exposed and unexposed group would not be proportional to the actual disease frequency in the population. This approach does not yield a valid estimate of the PTC/IIH prevalence in LNG-IUS use and cannot be used to calculate relative or attributable risks.

In summary, we agree with the authors that the study does not indicate that LNG-IUS can cause PTC/IIH. Additionally, taking into consideration the underestimated LNG-IUS rate among controls along with other limitations of the study including those mentioned above, the current study does not suggest an association between LNG-IUS and PTC/IIH.

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Conflict of interest

AG and JSch were both employees of Bayer AG.

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