Use of GRADE for Journal Club to Combat Fake News: A Case Study of Influenza Vaccination in Pregnancy

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Abstract

The purpose of this report is two-fold. First, we review the interpretation of observational studies from the standpoint of an internal medicine journal club format. A Second purpose is to share/provide an example using the GRADE criteria. GRADE is a validated tool used to quantitively assess the overall quality of a study. To illustrate, we selected a study assessing the risk of spontaneous abortion (SAB) after influenza vaccine administration. Since 2004, the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practice (ACIP) have recommended influenza vaccination of pregnant women. Previous studies have not found an association between influenza vaccination and SAB. However, in a recent case-control study by Donahue.J. et al, a correlation for SAB in women who received the H1N1 influenza vaccine was identified. This correlation was observed in the first 28 days after influenza vaccine administration. Our goal is to enable our learners to critique the published literature using appropriate evaluation tools.
Background

In September of 2017 multiple news outlets reported on an article published in the journal Vaccine. The article implied a possible link between H1N1 influenza vaccine and SAB during the first trimester of pregnancy. [1] In response, the Centers for Disease Control and Prevention (CDC) launched a study to address the safety of the H1N1 vaccine in pregnant women. Results from the study will be available at a future date.

The present review provides a critique of the study[1], using it as an example to demonstrate the steps in the GRADE[2] evaluation framework for analyzing an observational case-control study. One of the authors (YH) had a recent personal experience with the issue of influenza vaccine and SAB. Dr. H's spouse was 5 weeks pregnant when she visited her primary care physician, who advised against the influenza vaccine. The couple were reluctant to this advice and consulted the obstetrics and gynecology (OBGYN) specialist. The specialist advised vaccine administration in accordance with current CDC's recommendations. The vaccine was administered in week 5. At week 6, she experienced spotting. An ultrasound confirmed the miscarriage. Although the reason of the miscarriage was not determined, it is critical to understand the impact of such a study on clinical practice and the resulting dichotomous advice provided to patients based on media outlets and fake news.
Brief review of Donahue J. et al study

The study is designed as an observational retrospective case-control study. Pregnant women with SAB were the target population of the study. Eligibility criteria included SAB, diagnosed by clinical examination or ultrasound; age of 18-44; date of LMP; and continuous enrollment with a healthcare provider for the past 12 months. Subjects with ectopic pregnancy, therapeutic abortion, and history of SAB in women less than 5 weeks gestation were excluded from the study. [1]

Cases included 485 women who had SAB and 485 pregnant women in the control group. Both groups were compared to determine whether women with SAB were more likely to have received the 2010-2011 and/or 2011-2012 seasonal flu vaccine in the proceeding 28 days of SAB. The control cases were selected based on similar characteristics to cases of SAB which included maternal age group (less than 30 or more than 30 years), had an approximately similar date of last menstrual period (LMP), and were enrolled in the same health care plan. Adjustments between the cases and controls on smoking during pregnancy, diabetes type 1 or 2, obesity with body mass index (BMI) more than 30, and healthcare utilization in the prior one year were made.

The exposure in this study is having received H1N1 influenza vaccine and the observed outcome is SAB during the first trimester of pregnancy. [1] Vaccine safety data was collected by the Vaccine Safety Datalink (VSD). VSD is a monitoring tool established in 1990 through a collaboration between CDC's Immunization Safety Office (ISO) and several integrated healthcare organizations across the US. [3] VSD is able to utilize electronic health information from more than 9 million people, which is approximately 3% of the US population, and abstract information for monitoring and research.

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purposes.[3] The authors of the study abstracted some information from the VSD records such as demographics, vaccination history and medical outcomes.[1] Significant differences in demographics that may affect internal validity are summarized in Table 1.

| Table 1. Significant differences in demographics between cases and controls that may affect internal validity. |
|-------------------------------------------------|--------|--------|
| Age 35-44                                       | Cases  | Controls |
|                                                | 157 (32) | 128 (26) |
| BMI ≥ 30                                        | 134 (28) | 112 (23) |
| Race- African American                          | 42 (9)  | 20 (4)  |
| Previous SAB                                    |        |        |
| ≥ 1                                             | 138 (29) | 125 (26) |
| ≥ 2                                             | 43 (9)   | 26 (5)   |
| Smoked during pregnancy                         | 52 (11)  | 34 (7)   |

Based on abstracted data from VSD, the authors calculated the adjusted odds ratio (OR) of 2.0 (95% confidence interval (CI), 1.1-3.6) of SAB within 28 days after the administration of the flu vaccine. The aOR for 2010-2011 and 2011-2012 were 3.7 and 1.4, respectively. For women who received H1N1-containing vaccine during the previous influenza season (2010-2011), the aOR was 7.7 (95%, CI, 2.2-27.3), whereas the aOR among women not vaccinated during the previous season was 1.3 (95% CI, 0.7-2.7). When women with previous SAB are excluded the aOR remained elevated at 6.5 (95% CI, 1.7-24.3); however, sample size was small which is represented by the wide CI value (95%, CI, 2.2-27.3).

The study concludes that there is a correlation between SAB and influenza vaccination in the preceding 1-28 days, particularly among women who had been vaccinated in the previous year.

Analyzing and interpreting the study using GRADE
To combat the potential hype of distorted research study outcomes we recommend using GRADE as the tool for evaluating observational studies. In addition to its validated effectiveness for that purpose, GRADE provides a quantitative evaluation of the evidence.[2] There are five components evaluated in GRADE, these are type of evidence, quality, consistency, directness, and effect size. Next, we assign a value for each component.

**Type of Evidence:** Randomized clinical trials are assigned four points while observational studies receive a score of 2 points. [2] The design of case-control studies is based on matching a group of cases to one or more similar control group(s) to compare previous exposures between the groups. Case-control studies use the OR for statistical comparison between the groups.[4] Hence, the design of the study[1] as a case-control study has a score of 2 points.

**Quality:** This section addresses the methodology and execution of the study by assessing the blinding process, group allocations, follow-ups, and sparse data (missing data). One point is deducted for each problem identified in one of these elements with a maximum deduction of 3 points.[2] The study had two quality concerns. First, the two groups of case and control were not appropriately matched. Table 1, shows that the case group had more older women ≥ 30 years, a higher BMI of ≥ 30, more African Americans, ≥ two previous SAB, and more smokers during pregnancy.[1] Second, the matched case-control design is problematic as it raises concerns about selection bias due to the lack of appropriate matching and randomization.[5] A preferable study design would have been to use a cohort design to see if pregnant women who did get the vaccine had a higher risk of SAB. A cohort design would have been also more suitable
as the follow-up period is short and all data are available through VSD.[5, 6] Hence, we assigned a score of -2 for quality.

**Consistency:** Assessment of the consistency of outcomes. A point is deducted for inconsistent results, or a point is added for evidence of a dose response, or if adjustment for confounding variables would have increased the effect size.[2] Multiple previous studies have shown consistent results of influenza vaccine having no association with spontaneous abortion [7-9] which is inconsistent with the conclusion drawn from Donahue. J et al [1]. Hence, we assigned a score of -1 for this section.

**Directness:** Evaluation of issues that may hinder the generalizability of the reported outcomes for the specified population.[2] Notably, for the variable (≥ 2 previous SAB). Table 1 shows that previous SAB was twice as common in the SAB cases than in controls (9% vs. 5%, P=0.03).[1] The study did not adjust for previous SAB in their adjusted logistic regression models, consequently, this could be a confounding variable that was not accounted for.[1] It also seems quite plausible that women with previous SAB might have had conflicting decisions about whether or not to receive the flu vaccination compared to women who did not. Alternatively, it might be that those women could have had SAB regardless of flu vaccination status due to their increased risk of SAB from environmental or genetic risk factors.

Moreover, race was not adjusted for in the study model although a significant difference between cases and controls was observed in African Americans as shown in table 1(P=0.008). The mentioned rational for not adjusting for race in the study is that the adjusted and unadjusted OR were less than 10%. However, in some cases a lower cutoff of 5%, such as the case for the study may be more appropriate. [10] In such
observational studies, researchers should always be concerned about whether unmeasured confounding variables might be causing these results. For instance, could socioeconomic status influence results in such a study?

Having comparable groups and adjusting for variables have direct effect on internal validity of the study. Also, having a larger representative sample of the population can enhance precision and the external validity of the study.[4] Hence, we assigned a score of -1 for this section.

**Effect size:** Measuring the impact of OR, relative risk (RR), or hazard ratio (HR) to provide an estimate of the significance of the results.[2] OR is a measure of association between an exposure and outcome. An OR of 1.0, represents an equal incidence of outcome in both groups suggesting that the exposure is not a risk factor for that particular outcome, this is referred to as null value. An OR >1 reflects that the exposed population is more likely to have the observed outcome. An OR <1 means that the exposure is protective. OR is usually presented with a confidence interval (CI), the bigger the sample the smaller the CI. In the cases when the CI range crosses the value of 1.0, OR value will be impaired due to the possibility of having a null implies no relationship between exposure and disease. [6] OR in case-control studies should be interrupted with caution due to the nature of the study with only one period of observation. Also, the OR equation does not represent the total populations in the exposed and unexposed groups, therefore, it is not possible to directly determine disease rate in such studies.[6]
The study has multiple ORs that are lower than the value of two and some close to the value of one, which suggests that there is no difference between the groups. Hence, we assigned a score of zero for this section.

The GRADE tool provides a quantitative score based on the previously mentioned criteria. Table 2 provides the interpretation of the quantitative scores for GRADE. Our GRADE score for the study[1] is -2 points (+2 for observational study, -2 for quality, -1 consistency, -1 for directness, 0 for effect size). The total score of -2 indicates that the study is of very low evidence.

<table>
<thead>
<tr>
<th>GRADE Score</th>
<th>Quality</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>Very Low</td>
<td>Any estimate of effect is highly uncertain</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>≥ 4</td>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect</td>
</tr>
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**Discussion**

The present review has demonstrated the use of the GRADE framework to quantitively evaluate an observational study, which has been shown to be an efficient tool in assessing the study’s strengths and weaknesses. We recommend residents to use GRADE for journal club activities.
The study published by Donahue J et al [1] has several limitations as illustrated in Table 3. There were a small number of participants who received H1N1 vaccines which could affect the significance of the study and may lead to imprecise results. The data was collected through the VSD which only represents 3% of the general population.[3] Also, the study observed for an outcome that is rather common during first trimester of pregnancy, therefore the cause of SAB could be multifactorial and not due to the influenza vaccine. Miscarriages are most common during first trimester between 7th and 12th weeks.[11] However, there are multiple etiologies of SAB including chromosomal abnormalities, intrauterine fetal demise, molar pregnancy, maternal cervical conditions, and hormonal abnormalities. Some of these medical conditions could have made the miscarriage more likely. [11] It was noted on table 1 that more women in the case group had history of SAB when compared with the control group.[1]

<table>
<thead>
<tr>
<th>Limitations</th>
<th>Effect on the Study</th>
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</thead>
<tbody>
<tr>
<td>Small sample size</td>
<td>Precision, Sampling error</td>
</tr>
<tr>
<td>Post hoc analysis</td>
<td>Data dredging</td>
</tr>
<tr>
<td>Unprecise date of SAB</td>
<td>Information bias</td>
</tr>
<tr>
<td>clinically unrecognized SAB</td>
<td>Selection bias</td>
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<tr>
<td>Impeding SAB due to comorbidities</td>
<td>Protopathic bias</td>
</tr>
<tr>
<td>Misclassified vaccination status</td>
<td>Variability in measurements</td>
</tr>
<tr>
<td>Failed to adjust for variables such as race</td>
<td>Confounding variables</td>
</tr>
<tr>
<td>Mismatched cases and controls</td>
<td>Internal validity</td>
</tr>
<tr>
<td>Non-representative sample</td>
<td>External validity</td>
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The aOR was calculated by adjusting for some variables such as maternal age of more than 30, smoking during pregnancy, diabetes type 1 or 2, obesity with BMI more than 30, and healthcare utilization in the prior year. However, lack of adjustment for some
other variables, such as maternal age of 35 years or older and history of previous SAB, race, and any concurrent infectious illnesses, may have significant implications on the aOR.

Another limitation to consider is the possibility that some of the pregnant women included in the study might have had influenza vaccination in a non-traditional setting, such as in a pharmacy, and were not identified as recipients on their medical records.

Other issues in the study is the possible impact of the missing data from the data set, as there are a total of 66 (13%) missing data points from the cases and 35 (7%) missing data points from the control group. This is a significant number if we take into consideration the small sample size.

Although the authors comment on the use of post-hoc analysis, which refers to an outcome that was not planned for in the study design and was simply noted at a later stage. Physicians in practice should not base their practice on post-hoc findings as the results might be flawed due to chance. The study demonstrates that the case group actually had an older population, more SAB, higher BMI, and more smokers during pregnancy.

A recent survey conducted by the CDC in late 2017 found out that around two-thirds of pregnant women in the influenza season of 2017-18 had not been vaccinated against the influenza. Also only 15.6% of pregnant women who visited a medical provider since July 2017 had received a recommendation for the influenza vaccination, but not offered one. While 25.7% neither received a recommendation nor an offer for the influenza vaccination. 58.7% of pregnant women received recommendation and an offer to
administer the influenza vaccine.[12] The effects of main stream media highlighting the Donahue.J et al.[1] publication can impact clinical practice as we described. Despite multiple studies in the past demonstrating the safety of flu vaccine including H1N1 during pregnancy and CDC’s current recommendation to vaccinate all pregnant women, it is challenging to convince the public that the study had various limitation and cannot be generalized to all pregnant women after a media blitz. Information that is preliminary may have potential negative health impact in general population. The media have played a significant part in promoting this study, as multiple news outlets adopted this study findings with misleading headlines such as “Miscarriages linked to flu vaccine being administered during pregnancy in new study”. [13]

Media has a very strong impact on the way we think and act as a society.[14] We have yet to recover from the aftermath of a single publication by Wakefield, A.J. et al. [15] that linked Autism with MMR vaccine. Multiple studies were done immediately after the publication and they refuted the proposed link between Measles, Mumps, and Rubella (MMR) vaccine and Autism. [16] The negative effects from the MMR/autism study manifested in the recent measles outbreak in Minnesota[17] due to the reluctance to receive MMR vaccine.[15, 16]

Since this is an issue of public health, the CDC continues to recommend vaccination for all pregnant women; however, the CDC has also launched a new study to assess the safety of H1N1 vaccine in pregnant women.

As clinicians and researchers, we will be able to facilitate the use of GRADE to analyze the study and its statistical significance, but for patients it may not be that easy to find their way through the maze of variables, calculations, and adjusted rates.
Conclusion

GRADE is a validated tool used to quantitively assess the overall quality of a study. The best course of action will be to follow the CDC’s recommendations given the low GRADE score calculated for the Donahue.J. et al study. Journal clubs should be encouraged to adopt validated evidence-based tools to quantitively assess the overall quality of studies to provide evidence base practice.
References:

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