Reviewer’s report

Title: Neurodevelopmental profile of Fetal Alcohol Spectrum Disorder: A systematic review

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Reviewer: Heather Carmichael Olson

Reviewer's report:

This systematic review focuses on finding, evaluating and discussing the existing literature aimed at identifying a behavioral phenotype of the set of conditions termed FASD. This is a worthy goal. From a large number of peer-reviewed studies, the few studies that evaluated the classification function of an identified neurodevelopmental profile were included. Findings were that two approaches have been taken to this research question, including: (1) studies that used subsets of norm-referenced caregiver ratings of child behavior; and (2) selected subtest scores from standardized test batteries assessing wide-ranging neurodevelopmental domains. The authors deemed both approaches as promising, though the current reviewer notes that neither approach consistently pairs both good specificity with good sensitivity. Conclusions were that research in this area is limited and that a profile of FASD has not yet been established. The authors provide a set of recommendations for future research.

This manuscript is very well-written, leading the reader through an explanation of what is a complex scientific problem and relevant research findings in an understandable manner. The literature search was comprehensive (even including all publication languages and a manual review of content page in major journals covering neurodevelopmental disorders). A surprisingly small number of studies meeting criteria of the review protocol were identified (N=9), with only a few investigators attempting to accomplish this challenging research aim, which is an interesting finding in itself. Results of these fairly small but programmatic research efforts are described logically and with clarity, and study limitations are highlighted and explained. Table 2 is especially helpful in summarizing the NST data, and Tables 3 through 5 useful in summarizing test scores used in the test battery approach. The conclusion is drawn that the NST should still be considered in the validation stage and is intended for screening purposes, a cautious interpretation which seems quite accurate. What is known about the use of the BRIEF for this classification purpose is interpreted as in the exploratory stages, again an appropriately cautious interpretation. Limitations of the several attempts so far to use standardized test batteries to define a neurodevelopmental profile are carefully pointed out.

It is quite useful that the authors clearly point out the diagnostic systems or PAE criteria used in most of the studies. The systems utilized in the reviewed studies range from the 2005 version of the Canadian guidelines, the 4-Digit Diagnostic Code, a definition of PAE in the Nguyen et al. study, to an almost identical definition of PAE as that used by Nguyen coupled with subsequent physical characteristics criteria used by Mattson and colleagues. (To be complete, it is
recommended that the authors also mention the diagnostic code or method used to define FASD in the Haynes et al. study.) The authors also mention the important point that the classification of individuals in the Mattson et al. programmatic research is not reflective of how FAS is classified elsewhere.

But the authors do not raise and discuss the vital issue that the use of these different methods of diagnosing FAS, conditions under the umbrella term of FASD, or particular levels of PAE mean that the screening tools being evaluated are, de facto, aimed at classifying different groups of affected individuals. This means that the problem of identifying the neurodevelopmental profile of FASD goes well beyond the challenges of the sensitivity and specificity of different tools, or even the issues currently raised in the Discussion section. It seem crucial for the authors to comment on how their findings may be impacted by: (1) the recent Coles et al. findings that different FASD diagnostic systems may be identifying different groups of affected individuals; and (2) the fact that classifying individuals based on PAE alone, or on PAE plus physical characteristics, will generate different groups than classifying individuals based on a defined diagnostic system. In addition to commentary on this issue, a recommendation in the Discussion section about resolving this thorny issue seems necessary.

There are a few other issues that the authors might clarify to enhance the manuscript. The authors characterize lower levels of specificity or sensitivity as "varying," rather than pointing out that some of the levels found are quite low— for instance, the NST has been found in some studies to have a rather low level of probability of correctly identifying individuals who do not have the condition. The current reviewer is not a psychometrics expert… but might it be useful to compute the confidence intervals for sensitivity and specificity, at least for the programmatic research on the NST, to better characterize the state of the data?

Besides the major missing recommendation about how to handle the use of different diagnostic systems/PAE criteria, the authors do a good job of making recommendations for improving the literature. A minor point is that the seventh recommendation in the Discussion section is unclear. What specifically do the authors mean by exploring the possible heritability of some of the neurodevelopmental symptoms attributed to PAE? Also, the eighth recommendation may beg the question of whether it is even possible to identify and validate a neurodevelopmental profile of FASD. If the authors believe that finding a behavioral phenotype (at least for screening purposes) is achievable, what practical steps do they suggest to accomplish this eighth goal (and the sixth goal)? Are the authors suggesting big data strategies, where very large groups of individuals are brought together and identified using a common diagnostic system (or at least with data available so they are classifiable according to several different, well-defined, reproducible diagnostic systems)... and then neurodevelopmental profiles are examined with statistical adjustment for adverse prenatal and postnatal experiences... and divided into subgroups depending on dosage and timing of exposure, and genetic factors/differences in fetal susceptibility? The current reviewer is very interested in the practical recommendations the authors would make for concrete steps to establish at least a usable screening tool for FASD.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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