Reviewer's report

Title: No difference in mortality and major morbidities in very preterm infants born from assisted conception or naturally conceived. Results of the area-based ACTION study.

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Reviewer: Francisco Bolumar

Reviewer's report:

Although several studies suggest an increased risk for neonatal morbidity after AC, the evidence is scant and mainly derived from retrospective hospital data. Further studies of specific morbidities, with sufficient sample size and good control of confounding variables, are needed to assess the independent effect of ART.

This is an interesting area-based prospective cohort study carried out in six Italian regions and aimed at assessing whether there are differences in neonatal outcomes between very preterm infants born after assisted conception or naturally conceived, separately for singletons and multiples.

The description of antecedents is adequate and the authors duly justify the need for carrying out the study. The study design (prospective area-based cohort study) and statistical analysis (Generalized Estimating Equations) is methodologically sound, but presentation of results could be improved (see specific points).

Sample size is small and probably some of the morbidities may not have achieved statistical significance because of the relatively small number of infants. In addition, the small size of the study precludes the identification of specific AC techniques, which may be associated with adverse outcomes, which is of particular interest.

There are a few issues that should be addressed:

Design:

• The exclusion criteria should be made explicit
• Variables should be better defined
• % of missing data for all the variables should be provided

Analysis

• For multivariable analyses, generalized estimating equations were used to account for the hierarchical nature of the database. This is true for multiple births but probably for single births it would have been better to use logistic regression
The results would be quite similar but at least to facilitate understanding to the average reader).

- The authors state that GA and SGA status may be intermediate outcomes between AC and infants’ mortality and morbidity, and therefore were not included in the multivariable models. However, the authors do not specify that in their view all the independent effect of AC on mortality and morbidity is mediated through gestational age. Otherwise, I believe that both gestational age and small for gestational age should be included as confounding variables in the model.

Results

- Table 1 is redundant.
- Table 2 should include parity
- Abbreviations (PDA, PVL, etc) should appear below the tables.

Discussion

- Sample size should be discussed as one of the limitations of the study

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests