Author's response to reviews

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.

Authors:

Carlo Corchia (corchiacarlo@virgilio.it)
Monica Da Fre’ (monica.dafre@ars.toscana.it)
Domenico Di Lallo (dilallo@asplazio.it)
Luigi Gagliardi (l.gagliardi@neonatalnet.org)
Franco Macagno (macagno.franco@aoud.sanita.fvg.it)
Virgilio Carnielli (v.carnielli@univpm.it)
Silvana Miniaci (s.miniaci@virgilio.it)
Marina Cuttini (marina.cuttini@opbg.net)

Version: 3
Date: 12 November 2013

Author's response to reviews:

Dear Editor,

Please find attached a revised version of the paper:

Ref. MS: 1730835641103601

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.

Carlo Corchia, Monica Da Fre’, Domenico Di Lallo, Luigi Gagliardi, Franco Macagno, Virgilio Carnielli, Silvana Miniaci and Marina Cuttini.

The paper has been modified according to reviewers’ comments. As required, the name of the Ethics Committee that approved the study and the Authors’ contribution section have also been added.

We thank you and the reviewers for the pertinent comments, that have helped us to improve the paper and make it more focused.

The point-by-point responses to the reviewers are as follows.

Reviewer 1
Discretionary revisions:
1) Abstract: results section: definitely less clear than the figure; It could be perhaps shortened.

response: The abstract has been shortened
Minor essential revisions:
1) page 7: when was done the first ultrasound during pregnancy? What was decided if discrepancies with LMP?

response: Criteria used to obtain the best GA obstetrical estimate according to Italian guidelines have been specified and the relevant reference has been added. Information about the first ultrasound examination during pregnancy was not included in the original dataset.

2) page 7: definition of periventricular leukomalacia

response: Definition was “cystic periventricular leukomalacia”; it has been specified in the manuscript and the relevant reference has been added.


response: Thanks for suggestion. We have specified in the method section the reasons why the 10th percentile was used as cutoff; some relevant references have been included. The article cited by the referee reports the results of a consensus conference about the management of short children born small for gestational age. The suggested criterion (<2 birth weight z score), however, has been adopted less frequently than the 10th percentile in the literature, especially in population studies. For this reason and in order to assure comparison with other area-based studies we decided to use the 10th percentile.

4) page 9: what does mean "a shorter lenght of hospitalization? probably many confounders could interfere

response: A comment about the meaning of the shorter length of hospital stay in AC- than in naturally conceived multiples in relation to possible confounders, such as prenatal variables and infants’ morbidity, has been added in the discussion section.

5) page 12: chorionicity can not be taken into account. Therefore data regarding definite zygosity are incomplete, and it seems that the statistical analysis for this parameter should not be done.

response: Definite etherozygosity has been deleted from the variables under investigation and has not been taken into account in the analyses.

Reviewer 2
Design:
• The exclusion criteria should be made explicit

response: Only mothers with unknown mode of conception were excluded (n=131). This point is specified at the beginning of the results section and is
presented in the figure.

- Variables should be better defined

response: Further specification and definition of outcome and explanatory variables have been added in the method section.

- % of missing data for all the variables should be provided

response: In order to facilitate the reading, tables present the absolute frequencies of valid data and do not show missing data. In the method section it was added that missing data were always under 5% for all variables, with the exception of maternal age (7%) and education (14%). Missing data were considered as dummy variables in the multivariable analyses, as specified in the method section. Frequencies of neonatal morbidities were computed on infants surviving to diagnostic ascertainment, or to 36 weeks GA age for BPD.

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).

response: Multivariable logistic models were now used for the analyses. The “cluster” option was used to account for the non-independence of observations within NICUs, as specified in the method section.

- 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.

response: GA and SGA status have been added to the multivariable models.

Results

- Table 1 is redundant.

response: Table 1 has been deleted and results added to the old table 2 (now table 1).

- Table 2 should include parity

response: The variable “previous births” has been added to the table.
• Abbreviations (PDA, PVL, etc.) should appear below the tables.
response: Abbreviations have been added below the tables.

Discussion
• Sample size should be discussed as one of the limitations of the study
response: A comment about sample size has been added in the discussion.

Finally, after the amendments suggested by reviewers, the discussion section has been slightly modified accordingly, and some relevant references have been added. The English language has been extensively revised.

Carlo Corchia Monica Da Frè Domenico Di Lallo
Luigi Gagliardi Franco Macagno Virgilio Carnielli
Silvana Miniaci Marina Cuttini