Author’s response to reviews

Title: The Short-Term Economic Burden of Gestational Diabetes Mellitus in Italy.

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Answer to reviewers

The authors are grateful to reviewers that provided useful comments to improve the quality of this article. Please find responses to each point below.

Donald Dudley (Reviewer 1)

The paper by Meregaglia, et al, is a cost analysis of diabetes care in Italy. Several issues need to be addressed:

1. Line 85: How much of the change in the incidence of GDM in Italy is due to changes in diagnostic criteria.

We specified the amount of this increase following the adoption of the new IADPSG criteria compared to the old ones. The increase in GDM prevalence has been reported by several Italian authors, although the amount of this growth may vary across studies. Moreover, IADPSG are being applied by an increasing number of countries, and this should facilitate the comparison of GDM prevalence worldwide.

2. Line 90: I believe they mean "short term" rather than "short run" in this sentence. But more importantly, how is "short term" defined? Over what time frame?
We modified “short-run” into “short-term” (and “long-run” into “long-term”) and clarified its meaning (i.e. from week 28th until and including childbirth).

3. Lines 111-121: A significant problem with the paper is that all of the neonatal costs are estimates. Are there any other proxy numbers that can used to identify infants of GDM mothers so that these costs can be more accurate?

Unfortunately, the database provided by the Italian Ministry of Health is designed to limit inference of sensitive information, particularly for newborns. It lacks unique identifiers for newborns, who receive their fiscal numbers after birth when one of the parents physically registers the birth with the appropriate government office. This identification number is not always communicated to the hospital, which therefore assigns a default common id number to the infant (in the national database more than 33% of the newborns has only this common default ID number). The age in days is not provided for the infant discharge records, nor is the date of birth of the infant recorded in the discharge record of the mother. The residency is listed at the municipal level, and therefore makes identification even using other stochastic methods virtually impossible, especially considering larger cities. We have adjusted the text to reflect this situation.

4. Lines 123-124: Are these true costs or are these charges? If costs, please note how these costs are determined. Also, the authors should state clearly that these are true costs and not charges. These terms are often used interchangeably and they are clearly different.

Thank you for pointing out this important distinction. The costs in the paper refer to reimbursement tariffs. We have adjusted the text in the manuscript to explain this situation. We also expanded the definition of the Italian health care system financing to include the fact that hospitals may also receive some general subsidies from the regions beyond the DRG and official outpatient tariff reimbursements.

5. Table 1: Women with GDM were more likely to be older than 35. Are costs of genetic screening/diagnosis included in the model?

Indeed, women above 35, regardless of their GDM status, are likely to undergo genetic screening during pregnancy; however, we did not consider these costs because they were out of the study scope.

6. Table 1: Women with GDM were more likely to be obese. Were the costs of obesity itself also factored into the model?

Similarly, it is likely that GDM women are also overweight or obese (Table 1), but the cost of obesity was considered out of scope.
7. Line 164: In the introduction, the authors note that some women are recommended to undergo screening at 16-18 weeks, but they only included women screened at 28 weeks. Cannot the number of women who would recommended to have the earlier screening be factored into the model?

Most of the diagnoses occur between the 24th and 28th gestational week, although some high-risk women (e.g., BMI>30) can be tested earlier. However, all GDM diagnoses should be captured at week 28. As reported in the study limitations, we underestimated some outpatient costs occurred between 16th and 28th week, but this conservative choice was justified by the difficulties in estimating the proportion of patients diagnosed at an earlier stage.

8. Lines 166-169: What proportion of women in Italy are completely compliant with the number of glucose determinations during their pregnancies? Couldn't this be estimated and factored into the model?

Thank you for this comment, but unfortunately there are no published data on that. We added this point to the limitations.

9. Line 170: Only aspart was factored into the model. What about other types? Could these have not been estimated?

This drug was selected based on expert opinion, since it is the one most frequently adopted by Italian gynecologists. It also has full reimbursements status from the Italian Medicines Agency.

10. Table 2: Glucometers are listed as free of charge. Surely this costs someone something.

In Italy, glucometers are usually given free of charge by the pharma companies, which boost the hospitals to buy their ‘strips’ (the effective revenue source). Thus, the glucometer is a cost for the company, but not for the healthcare system (the perspective adopted in this study).

11. Table 2: If the number of finger sticks is 4/day in women with GDM on insulin, they authors state total number of test strips to be 198. How was this number derived?

198 is not the number of strips, but instead their cost. It was derived as: 4 strips a day x 90 days (roughly, the last pregnancy term including childbirth) x 0.55 unitary cost = 198.

12. Table 2: Shouldn't "gynecologic visit" be "obstetrical visit"?

Yes, the term should be obstetric visit and has been corrected in the text.
13. Table 4: What about medical legal costs from shoulder dystocia? Is this a problem in Italy as in other countries?

It is likely that shoulder dystocia leads to legal costs. However, these would go beyond the time horizon of this study.

14. Line 277: "GMD" should be "GDM".

Thanks, the mistake has been corrected.

15. Line 284: Are oral hypoglycemic agents used in Italy for women with GDM? Shouldn't this be factored into the model?

According to the expert involved in this study, the use of oral hypoglycemic agents (e.g. metformin) is still not recommended in pregnancy, with few exceptions for women who were using the drug before getting pregnant. Thus, we removed this sentence: “moreover, we included only insulin as a drug cost, disregarding other medications that may be prescribed to control GDM”. Thanks for pointing this out.

16. Lines 300-306: The authors report on other costs analyses. How is their analysis different or better than the other reports?

We extended this part explaining the strengths and limitations of our study compared to the previous ones.

Maisa Feghali (Reviewer 2)

The authors report on the short-term economic burden of gestational diabetes mellitus (GDM) in Italy. They built a model primarily using maternal data from a national Italian database and neonatal data from a retrospective study in the United States of America and limited cost estimates to the 3rd trimester of pregnancy. The study highlights the financial burden of GDM at a national level. However, there were a few issues that warrant further attention:

1. The authors report a GDM prevalence rate of 10.9%. The maternal database used for cost estimation included 11,540 women diagnosed with GDM a rate of 2.6%. The authors report this discrepancy in the discussion session, but do not provide a sufficient explanation for this difference. Also, the authors do not comment about why they chose to proceed with the rate of 10.9% or how different rates may impact the model and cost estimation.

We tested the robustness of the estimate (10.9%) by comparing it with a new Italian study (now reported in the reference list) which showed a very closed value (11%) for GDM prevalence.
Moreover, we updated the text to reflect the under-reporting problems with using diagnostic codes in administrative data.

2. The authors described using rates of neonatal outcomes from a retrospective study because of a lack of a linked maternal-child database that would allow them to estimate the rate of neonatal outcomes. The study used is a retrospective study of 36,241 women with a singleton pregnancy at term who received prenatal care and delivered at the University of California San Francisco between 1982 and 2006. The authors are encouraged to compare the rates of neonatal outcomes of interest in Italy in 2014 to those extracted from the retrospective study given the difference in location and period of time.

This is a major limitation of the study. Unfortunately, we could not link mothers to infants in the HDD, and no recent Italian studies report a range of neonatal outcomes for GDM and normal pregnancies. In the discussion, more explanation has been given about the choice to refer to the study by Esakoff in order to estimate neonatal complications rates.