Author’s response to reviews

Title: Perinatal outcomes of infants with congenital limb malformations: an observational study from a tertiary referral center in Central Europe

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Author’s response to reviews:

To

Angela Lupattelli
Associate Editor
BMC Pregnancy and Childbirth

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Dear Professor Lupattelli,

Thank you for the opportunity to submit our revised manuscript, entitled “Perinatal outcomes of infants with congenital limb malformations: an observational study from a tertiary referral center in Central Europe” (Manuscript ID: PRCH-S-19-01442.R1).

We have extensively adapted the manuscript and introduced all suggested changes. An English native speaker editing service finally checked the manuscript. Please find enclosed a detailed response to the reviewers’ comments, as well as the revised version of our manuscript (changes are highlighted).

Indeed, we hope that the manuscript, which we feel was significantly improved following the reviewers’ comments, is now suitable for publication in your highly esteemed journal.

Thank you for your consideration. We look forward to hearing from you.
Point-by-Point response on “Perinatal outcomes of infants with congenital limb malformations: an observational study from a tertiary referral center in Central Europe” (PRCH-S-19-01442.R1)

REVIEWER 1

Reviewer 1, Comment 1:

I agree totally with the authors (pg 11 ln247) that there is a selection bias and possible false conclusions. Referral policies from peripheral clinics, differences in counselling and decision-making for termination of pregnancy (TOP), huge differences in genetic testing opportunities between 2004-17 are factors that possibly influenced policy and outcomes.

Response to Reviewer 1, Comment 1:

We appreciate this comment of Reviewer 1. As mentioned in this comment, and as we have stated in the Limitations section of our manuscript, it cannot be ruled out that we have drawn some biased conclusions, e.g. due to the retrospective study design. With regard to the points that were criticized by the Reviewer (referral policies from peripheral clinics, differences in counseling and decision-making for TOP and genetic testing), we want to state that this is what we however consider common, real-life and realistic circumstances in daily practice. These points represent common potential biases in observational studies, and we are convinced that our approach was still the only reasonable approach to analyze the data. We consider it important to use realistic circumstances, such as to include referrals from peripheral clinics to our tertiary center, and we believe that our work is therefore still worthwhile to be published.

Reviewer 1, Comment 2:

Classification in LLM/ULM/BLM is descriptive and it is not totally clear how this coincides with diagnosis.

Response to Reviewer 1, Comment 2:
We thank Reviewer 1 for this valuable comment. As presented in the Results section of our revised manuscript, the study cohort comprised various different congenital deformities of either the upper or lower limbs (or both) with partially low sample sizes. Given the severely varying distribution of limb-reduction defects between upper and lower limbs, we decided to stratify our case cohort based on the location of deformity, as it has previously been performed by Makhoul et al. and Bedard et al., into upper vs. lower vs. both limbs. From a clinical perspective, this classification might be more useful than splitting the data into a multitude of different major or minor pathologies. Moreover, as highlighted by Kutuk et al., upper extremity malformations (with concomitant visceral malformations) show particularly poor perinatal outcomes and should therefore be examined separately. Finally, since the patient cohort examined in this study frequently needs to undergo further pediatric-orthopedic treatment, this also needs to be considered for data analysis. Current orthopedic practice usually involves a particular subspecialization into either upper limb or lower limb treating surgeons. We therefore believe that our approach of classifying the limb malformations is suitable for the multidisciplinary readership of this article. Nevertheless, we have displayed the diagnoses of our patients in detail in the newly added Figure 1 (see below).

Reviewer 1, Comment 3:

What is the take-up rate of routine screening ultrasound, is there any data on the cases missed? First diagnosis postnatally? Syndactyly, polydactyly or oligodactyly are not rarely overlooked, and although perhaps minor, may guide a syndrome diagnosis.

Response to Reviewer 1, Comment 3:

We absolutely agree with the Reviewer that many pathologies, especially of the hand and feet, may easily be overlooked. As shown by Piper et al. and Dicke et al., the sonographic detection rate is as high as 42% in the upper extremity, declining to only 4-19% when considering digits alone. Based on this information, these appropriate literature references were added to the revised manuscript. Unfortunately, we are not able to specifically assess the missed cases. Nevertheless, given the high expertise of prenatal diagnostics and sonographic imaging at our tertiary center, we believe that the detection rate should be rather high and in-line with those reported in the literature.

Reviewer 1, Comment 4:

Is there a cooperation with EUROCAT? In that case, report from this registry may be more worthwhile.

Response to Reviewer 1, Comment 4:

We thank Reviewer 1 for this important question. Unfortunately, our Department is not yet member of EUROCAT, neither is there any cooperation existing at the moment. In the introduction of our paper, we are mentioning this important network of population-based
registries for the epidemiological surveillance of congenital anomalies (page 3, lines 47–51). We would like to take the opportunity to discuss the need to become EUROCAT network member within our University and Department board.

Reviewer 1, Comment 5:

Outcomes of live-born, related to diagnosis is not complete and not clear described.

Response to Reviewer 1, Comment 5:

Indeed, the outcomes of live-born infants were not yet displayed in connection to the diagnosis. We intended to omit this information since there were so many different diagnoses that it would have been difficult to summarize them within a table; this might cause confusion of the readers. However, as suggested, we have now included Figure 1 that shows the detailed diagnoses and the outcomes, and also described them within the Results section of our revised manuscript (see below).

Reviewer 1, Comment 6:

A higher incidence of preterm labour is puzzling. Is it indeed related to polyhydramnions, or iatrogenic?

Response to Reviewer 1, Comment 6:

We totally agree that polyhydramnions are just one of many possible reasons for the high preterm delivery rate that we report within our paper. Therefore, we already stated that polyhydramnions only explain “in part” the increased risk for preterm delivery. As suggested, we have decided to soften this statement, including the following sentence at the end of this paragraph (page 10, line 232–235): “We are aware that many of the reported preterm deliveries might have been iatrogenic due to preeclampsia, cervical insufficiency, intrauterine growth retardation, maternal comorbidities, imminent fetal asphyxia or for various other reasons.”

Reviewer 1, Comment 7:

pg 3 In 60 needs reference.

Response to Reviewer 1, Comment 7:

Thank you for this remark. Unfortunately, we were unable to relate this statement to any of the references that we used. Consequently, we have therefore omitted this sentence, which we anyways did not consider to be very important in this context.
Reviewer 1, Comment 8:

pg 4 ln 82 omit "immense", "large" is already in ln 83.

Response to Reviewer 1, Comment 8:

We totally agree that “immense” has been misleading in this context. We therefore adapted the sentence to the following: “Therefore, in the present study, we aimed to contribute to the sparse available body of literature, offering data on congenital limb malformations at a large tertiary referral center in Austria.”

Reviewer 1, Comment 9:

pg 5 ln 98 "inclusion und(typo) exclusion" criteria? These are not described elsewhere.

Response to Reviewer 1, Comment 9:

We apologize for this typo and that we have not mentioned any inclusion or exclusion criteria. In the revised version of our manuscript, we now specified these criteria and added them where appropriate: “We included all pregnant women with no limitations to age and/or ethnicity; fetuses needed to be diagnosed with at least one limb malformation during the prenatal sonogram at our tertiary referral center. The only exclusion criterion was unclear imaging results.”

Reviewer 1, Comment 10:

pg 6 ln 133 20 lost to follow up, but if these were TOP, it should have been known?, so these were not TOP?

Response to Reviewer 1, Comment 10:

We thank Reviewer 1 for the feedback. As also stated in Response to Reviewer 3, Comment 5, we dedicate an entire paragraph on this topic in the Discussion section of our manuscript. Indeed, it should have been known if these cases underwent TOP; however, TOP could have been done in another hospital or institution (see also Response to Reviewer 3, Comment 3). Since we are the largest perinatal center in the region, affected cases are likely to be transferred to our hospital. Hence, we assumed that lost cases are likely to underwent TOP. Although it is likely that these cases underwent TOP, we are aware that this is just a suggestion. Hence we included the following sentence in the revised version of our manuscript: “Apart from this theory, there remains the possibility that patients were treated at outpatient departments or were only seeking a second opinion at our department, making it impossible to follow up their cases.” We hope that this is now clear for the readership.
Reviewer 1, Comment 11:

pg 7 ln 151, 21 had unknown sex, that is not registered or indifferent genitalia?

Response to Reviewer 1, Comment 11:

We apologize for using the misleading term “unknown sex”. Indeed, both reasons – unregistered and indifferent genitalia – were among these 21 cases. We therefore adapted the sentence to the following: “Thirty-one infants (29.8%) were female, 52 (50%) were male, and in 21 cases (20.2%), gender was either not registered or genitalia were indifferent.” Consequently, we adapted the word “sex” to “gender” within the entire manuscript. We believe that this should now be clear for the readers.

Reviewer 1, Comment 12:

pg 7 ln 154, 2 live born after unsuccessful TOP, this raises questions on gestational age, method of TOP. It is good that you are honest about this, but reading it, it raises questions that perhaps need some explanation.

Response to Reviewer 1, Comment 12:

We apologize if this sentence might have been misleading. The 2 cases that we report herein, were cases that underwent induced abortion at 20 and 23 gestational weeks, respectively, using mifepristone followed by misoprostol. The associated birthweight and Apgar-score were 185g and 450g, 2/0/0 and 1/1/0, respectively. In order to clarify this, we now included the following sentence in the revised version of our manuscript. “Of the 104 followed cases, 38 (36.5%) underwent TOP, of which ten (26.3%) were terminated by induced fetal demise (faeticide); 59 cases (56.7%) were born live, including two live-born cases after termination attempts using mifepristone followed by misoprostol.”

Reviewer 1, Comment 13:

pg 7, ln 157, fetal syndrome was identified, was a geneticist involved? Procedure?

Response to Reviewer 1, Comment 13:

We thank the Reviewer for this comment. At our Department, material that was obtained from invasive prenatal procedures is obligatory evaluated by a physician geneticist. In case of a complex or suspected syndrome, the gene assessment is carried out by microarray, whole exome or whole genome sequencing methods. Findings are discussed on a weekly basis within a multidisciplinary pre- and perinatal board, and genetic counseling of the affected parents involves a specialized psychologist in this field.
Reviewer 1, Comment 14:

pg 8 ln 188, yes, but see comment 10, then the follow up should be known?

Response to Reviewer 1, Comment 14:

We apologize but we negate that the follow-up should have been known, since patients might have undergone TOP at another institution. In contrast, it is very unlikely that they have delivered at another hospital. Please see Response to Reviewer 1, Comment 10 for a more detailed response regarding this statement.

Reviewer 1, Comment 15:

pg 10 ln 227 recurrent preterm delivery? Why so in this group?

Response to Reviewer 1, Comment 15:

We apologize for this misunderstanding. Our tertiary referral center is the largest center in Central Europe and we have strict criteria to be registered for a planned delivery: e.g. previous preterm delivery, increased maternal age, severe maternal comorbidities, multiple gestation, etc. In order to clarify this point to the readers, we now included the following sentence in the revised version of our manuscript: “In part, the increased rate of preterm delivery in our study might be explained by contributing risk factors for preterm delivery (e.g., previous preterm delivery) that are criteria for registration for a planned delivery at our tertiary referral center.”

Reviewer 1, Comment 16:

pg 10 ln 232 why preterm delivery with isolated clubfeet?

Response to Reviewer 1, Comment 16:

After having reviewed our dataset with special regard to the preterm delivery rate in cases with isolated clubfeet, we found that the following reasons for the preterm delivery: preterm contractions, cervical insufficiency, preeclampsia, intrauterine growth retardation, and twin gestation. We included the following sentence in the manuscript to make it clear to the readership: “Compared with the results of Sharma et al., we also found a rather high preterm delivery rate in cases with isolated clubfeet, attributed to the fact that we are the largest perinatal center in the region and that cases with other comorbidities and reasons for preterm delivery were included. We are aware that many of the reported preterm deliveries might have been iatrogenic due to preeclampsia, cervical insufficiency, intrauterine growth retardation, maternal comorbidities, imminent fetal asphyxia or for various other reasons.”

Reviewer 1, Comment 17:
table 2, mean umbilical cord pH and mean apgar scores are meaningless. If they say anything, they are a result of intrapartum management, which is not discussed here.

Response to Reviewer 1, Comment 17:

With regard to Comment 17, we disagree with Reviewer 1. As stated in the Introduction section of our manuscript, our study aimed to analyze perinatal outcomes of infants with congenital limb malformations. Of course, mean umbilical cord pH and median Apgar score are mostly attributing to the intrapartum management; they are also considered to be reliable (surrogate) markers for perinatal outcome, and both are well known among obstetricians AND neonatologists (Thongren-Jerneck et al. 2001). We would therefore appreciate if we could leave these two parameters within Table 2.

Reviewer 1, Comment 18:

fig 1, this is already in the text, can be omitted.

Response to Reviewer 1, Comment 18:

We considered the graphical presentation of our results as reasonable. However, as suggested by Reviewer 1, we have now omitted the flowchart of our 124 cases with congenital limb malformations during the study period and adapted the figure legends accordingly.

REVIEWER 2

Reviewer 2, Comment 1:

Line 52: Bedard reports limb deficiencies and does not include pathologies such as talipes - therefore it is not surprising that this is different from the current study. This should be clarified or the comparison removed.

Response to Reviewer 2, Comment 1:

Thank you for this important point to consider. As requested the text was adapted to: “According to Bedard et al., the lower limbs are less commonly affected than the upper limbs, and 10.8% of affected infants have malformations of both upper and lower limbs. However, it has to be mentioned that frequent lower limb diagnoses such as talipes equinovarus were not considered in this study, possibly resulting in a lower reported incidence of lower limb malformations in their study.” We hope that this is now clear for the readers.

Reviewer 2, Comment 2:
Lines 61-69. Quite a lot of numbers. Should consider shortening and use of a table.

Response to Reviewer 2, Comment 2:

Thank you for this comment. We reduced the numbers, however, it is in our opinion still not enough information to warrant a table. Please find attached the revised text: “To date, there have been very few studies that have examined the perinatal outcomes associated with congenital limb malformations. In a previously published study, the perinatal mortality of cases with ULM was reported to be 137 per 10,000 live births, compared with an overall infant mortality of 3.7 per 10,000 live births. Zelop et al. reported that the majority of patients examined did not survive (i.e., terminated pregnancies, neonatal deaths, and fetal demise). In the non-survivor group, 59% had aneuploidy detected by karyotype analysis.”

Reviewer 2, Comment 3:

Methods: I am not clear what the inclusion and exclusion criteria mentioned

Response to Reviewer 2, Comment 3:

Thank you for this important point. We specified these criteria an added them where appropriate: “We included all pregnant women with no limitations to age and/or ethnicity; fetuses needed to be diagnosed with at least one limb malformation during the prenatal sonogram at our tertiary referral center. The only exclusion criterion was unclear imaging results.”

Reviewer 2, Comment 4:

Line 224-228: I am not convinced that this can be attributed to polyhydramnios as this is not such a huge occurrence in most cases of limb abnormality. Suggest revise or remove.

Response to Reviewer 2, Comment 4:

We thank Reviewer 2 for this comment and we have to admit that the sentence on the possible effect of polyhydramnios might have been confusing. As suggested, we have therefore decided to remove this sentence. (Please see also Response to Reviewer 1, Comment 6.)

Reviewer 2, Comment 5:

In general this is a very useful set of data which are carefully phenotyped. However, I find it very unusual that the data are divided into upper limb, lower limb and both and that there is no reference within the text as the actually underlying pathologies/diagnoses as it is these that most relevant to outcomes. Especially as the range of the diagnoses that I am sure is within this dataset ranges from fatal to fully treatable. The authors should seriously consider re-working the data
and re-writing the paper to move away from the current upper/lower/both classificational and move towards a more descriptive analysis based on diagnosis. This would make a much stronger paper that would be more interesting and relevant to the reader.

Response to Reviewer 2, Comment 5:

Please see Response to Reviewer 1, Comment 2.

REVIEWER 3

Reviewer 3, Comment 1:

This is a well performed retrospective report on the outcome of limb-malformations in a tertiary centre in Vienna. I think information about location/level should be in the title; ie "Perinatal outcomes of infants with congenital limb malformations: an observational study from a tertiary centre in Vienna"

Response to Reviewer 3, Comment 1:

We thank the Reviewer for this constructive criticism. As “Vienna” might be too regional, we decided to adapt the title of the manuscript to the following: “Perinatal outcomes of infants with congenital limb malformations: an observational study from a tertiary referral center in Central Europe” We hope that the Reviewer agrees with this new title.

Reviewer 3, Comment 2:

I find that the expression "Perinatal outcomes are not well understood" is not quite covering the situation; the etiology, classification and reports are differing, and this study help to some extent in entangling these problems.

Response to Reviewer 3, Comment 2:

As suggested, we modified this sentence according to your valuable suggestion to the following: “Congenital malformations are rare and, to the best of our knowledge, perinatal outcomes of the affected patient population have not yet been described in detail.”

Reviewer 3, Comment 3:

As is stated in the EUROCAT reference "Survival to 1 week and 1 year varies enormously between countries mainly because of different legislation regarding termination". This calls for some explanation for the reader about the system in Austria: Are all women offered a first or
second trimester ultrasound screening? What are the rules for termination of pregnancies, what is the upper limit of gestational age.

Response to Reviewer 3, Comment 3:

In Austria, first and second trimester screenings are recommended but optional. Pregnant women have to be informed in time by their obstetrician about the existence of these screenings, mentioning advantages, related risks, and the eventuality of difficult decisions arising from these examinations. After having counseled the patient, obstetricians need to document this in the patient’s so-called “mother-child booklet”. In other words, screenings are offered on request if the pregnant woman decides to take these examinations but are neither compulsory, nor are they covered by health insurances (only in case of a high risk for fetal anomaly or aneuploidy). Indications for offering prenatal diagnosis for free include (i) age of the pregnant woman of 36 years or higher, (ii) having had a previous child with congenital anomaly, and/or (iii) a known aneuploidy or genetic disorder in parents and relatives. Therefore, in some sociodemographic levels, pregnant women have to face the question of whether they can afford prenatal diagnosis or not.

In the Austrian Criminal Code (StGb §97), the rules for termination of pregnancies (TOP) are laid out, stating that TOP before the beginning of labor is principally not punishable if (i) this is the only way to avoid a severe threat to the life or physical or mental health of the pregnant woman, or (ii) the mental or physical health of the fetus is heavily in danger, or (iii) the pregnant individual was &lt;14 years of age at the time of conception. In practice, there are two time periods in which different indications for TOP are defined. Before fetal viability (e.g., &lt;24 weeks of gestation) TOP is carried out on request for fetal anomaly or aneuploidy of sufficient severity. Minor forms of malformations or syndromes (e.g., hexadactyly, isolated clefts) will however not be terminated. After having reached a gestational age of potential fetal viability, TOP requests are accepted only in non-viable cases or late diagnosis of very severe congenital anomalies (e.g., anencephaly, schizencephaly, brain tumor). Within this time period, an isolated fetal trisomy 21 will not be an indication for TOP. In every single case, the decision whether pregnancy might be terminated or not, (i) needs to follow the mother’s and parent’s request, (ii) has to be decided by a local multidisciplinary board, and (iii) in case of a gestational age ≥23 weeks, feticide is carried out (EUROCAT 2010). In addition, pregnant women have the possibility, within the first 3 months after conception, to request TOP for any reason, which has then to be paid individually, and which is then undertaken in private clinics.

In order to make this clear to the readers of your journal, we included the following sentence in the revised version of our manuscript: “Of note, prenatal diagnosis is optional and not covered by insurance in Austria; termination of pregnancy (TOP) is allowed during the first three months after conception, and after that there needs to be a serious reason for TOP that is adjudicated by a multidisciplinary board.”

Reviewer 3, Comment 4:
I notice that the mean GA when the malformation is diagnosed is 20+5, this seems to be quite late, and could maybe be given a comment?

Response to Reviewer 3, Comment 4:

Thank you for this specific question. The diagnosis time of 20+5 weeks that we report within our paper coincides with the time period of 19 to 22 weeks of gestation, in which the second trimester organ scan might be carried out (see Response to Reviewer 3, Comment 3). It seems reasonable that most of the malformations are detected during this examination, due to several reasons. First of all, our university hospital takes care only of high-risk pregnancies (e.g., women with severe internal comorbidities or who have experienced preterm labor in the previous pregnancy) from the very beginning. Most of the pregnant women with later risky constellations (e.g., placenta previa, placenta accreta/increta/percreta, and fetal malformations and/or aneuploidy) planning their labor in our hospital are seen for the first time after the diagnosis has already been made by their private obstetrician and after referring them to our clinic for further pre- and/or postnatal care. Therefore, we rarely see these women in the early pregnancy.

There are defined levels of sonographic expertise in Austria. For the basic sonograms that are recommended by Austrian healthcare officials and undertaken in obstetric offices, level-1 is sufficient. Thus, it is comprehensible that not-severe malformations, such as limb malformations, are sometimes only detected when pregnancy is already in the advanced weeks of gestation or when the mother undergoes the organ scan, which is generally performed by (more specialized) level-2 or level-3 sonographers. Similarly, Kozlowsky et al. conclude in their recently published paper that only severe malformations such as an-/exencephaly, holoprosencephaly, omphalocele, gastroschisis, body stalk anomaly or a megacyst must be detected in an early (11 to 14 weeks of gestation) sonogram. Kozlowsky et al. identified a detection rate of severe malformations in early scans of only 44%.

As stated in Response to Reviewer 3, Comment 3, first trimester screening, which should only be performed by an experienced sonographer, is not covered by insurances in Austria (except for some individual reasons). Therefore, some women also refrain from this examination and just opt for the second trimester organ scan. Similarly, some women might opt to continue their pregnancy regardless of a fetal aneuploidy. A recent trend has emerged towards a basic sonogram combined with the routine use of cfDNA for non-invasive prenatal testing, followed by a routine organ scan at 20 weeks of gestation. Our own data on this topic are promising and have recently been published, challenging the conventional first trimester screening (Holzer et al., 2019).

Reviewer 3, Comment 5:

On page 8, line 179 it is stated that "It can be suggested that there is a high rate of induced abortion in pregnancies with congenital limb malformation", I think this needs a modification as this applies to the possibly quite selected group seen at the tertiary centre. They also seem to have a very high rate of syndromes (63.5%).
Response to Reviewer 3, Comment 5:

We totally agree with Reviewer 3 that this sentence needed to be revised, which we did as follows: “According to our data, cases with congenital limb malformations were shown to have a rather high rate of induced abortion, which is understandable, given the selected patient group and our high level of perinatal care.” We hope that this is now clear to the readership of your highly esteemed journal.

References


