Peer Community In Ecology

Stress and stress hormones' transmission from mothers to offspring

Matthieu Paquet *based on peer reviews by 2 anonymous reviewers*

Amin, B., Fishman, R., Quinn, M., Matas, D., Palme, R., Koren, L., Ciuti, S. (2024) Sex differences in the relationship between maternal and neonate cortisol in a free-ranging large mammal. bioRxiv, ver. 4, peer-reviewed and recommended by Peer Community in Ecology. https://doi.org/10.1101/2023.05.04.538920

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Individuals can respond to environmental changes that they undergo directly (within-generation plasticity) but also through transgenerational plasticity, providing lasting effects that are transmitted to the next generations (Donelson et al. 2012; Munday et al. 2013; Kuijper & Hoyle 2015; Auge et al. 2017, Tariel et al. 2020). These parental effects can affect offspring via various mechanisms, notably via maternal transmission of hormones to the eggs or growing embryos (Mousseau & Fox 1998). While the effects of environmental quality may simply carry-over to the next generation (e.g., females in stressful environments give birth to offspring in poorer condition), parental effects may also be a mechanism that adjusts offspring phenotype in response to environmental variation and predictability, and thereby match offspring's phenotype to future environmental conditions (Gluckman et al. 2005; Marshall & Uller 2007; Dey et al. 2016; Yin et al. 2019), for example by preparing their offspring to an expected stressful environment.

When females experience stress during gestation or egg formation, elevations in glucocorticoids (GC) are expected to affect offspring phenotype in many ways, from the offspring's own GC levels, to their growth and survival (Sheriff et al. 2017). This is a well established idea, but how strong is the evidence for this? A meta-analysis on birds found no clear effect of corticosterone manipulation on offspring traits (38 studies on 9 bird species for corticosterone manipulation; Podmokła et al. 2018). Another meta-analysis including 14 vertebrate species found no clear effect of prenatal stress on offspring GC (Thayer et al. 2018). Finally, a meta-analysis on wild vertebrates (23 species) found no clear effect of GC-mediated maternal effects on offspring traits (MacLeod et al. 2021). As often when facing such inconclusive results, context dependence has been suggested as one potential reason for such inconsistencies, for exemple sex specific effects (Groothuis et al. 2019, 2020). However, sex specific measures on offspring are scarce (Podmokła et al. 2018). Moreover, the literature available is still limited to a few, mostly "model" species.

With their study, Amin et al. (2024) show the way to improve our understanding on GC transmission from mother to offspring and its effects in several aspects. First they used innovative non-invasive methods (which could broaden the range of species available to study) by quantifying cortisol metabolites from faecal samples collected from pregnant females, as proxy for maternal GC level, and relating it to GC levels from hairs of their neonate offspring. Second they used a free ranging large mammal (taxa from which literature is missing): the fallow deer (Dama dama). Third, they provide sex specific measures of GC levels. And finally but importantly, they are exemplary in their transparency regarding 1) the exploratory nature of their study, 2) their statistical thinking and procedure, and 3) the study limitations (e.g., low sample size and high within individual variation of measurements). I hope this study will motivate more research (on the fallow deer, and on other species) to broaden and strengthen our understanding of sex specific effects of maternal stress and CG levels on offspring phenotype and fitness.

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Amin, B., Fishman, R., Quinn, M., Matas, D., Palme, R., Koren, L., & Ciuti, S. (2024). Sex differences in the relationship between maternal and foetal glucocorticoids in a free-ranging large mammal. bioRxiv, ver. 4 peer-reviewed and recommended by Peer Community in Ecology. https://doi.org/10.1101/2023.05.04.538920

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Reviews

Evaluation round #2

DOI or URL of the preprint: https://doi.org/10.1101/2023.05.04.538920
Version of the preprint: 3

Authors' reply, 13 February 2024

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Decision by Matthieu Paquet, posted 19 October 2023, validated 19 October 2023

Minor revision

Dear Authors,

Many thanks for your revised preprint entitled "Sex differences in the relationship between maternal and neonate cortisol in a free-ranging large mammal". It has now been reviewed by one of the previous reviewers and their comments are appended below. These comments will need to be adressed before your preprint can be recommended.

Regarding the statistical procedure, to be clear,I was not asking for a change of procedure (and I do not think it should be changed) but simply asking for justification and explanation for the readers with references. The justification and references in the response are great to me but I don't see any associated changes for the reader in the main text (justification of such choice, e.g. statistical power required for testing interactions) and the associated references, so please update those aspects as well. I do appreciate that the description of the procedure itself is now more detailed.

Similarly, the results regarding the new repeatability analysis seem worth mentioning in the main text, together with the references that make the authors think that such low repeatability was “expected”, and a short statement regarding the implications of such low (and statistically “non-significant”) intra individual repeatability for the investigation of the relationship between maternal and neonate cortisol.

I look forward to reading the revised version of this preprint.
Best wishes,
Matthieu

Reviewed by anonymous reviewer 2, 13 October 2023

I was pleased to review the revised version of the manuscript entitled “Sex-specific differences in the relationship between maternal and neonate foetal cortisol glucocorticoids in a free-ranging large mammal”.

First, I have to highlight the great work conducted by the authors to revise their manuscript according to the feedback of the Editor and the 2 Reviewers.

Modifications clarify the fact that this article is a research article rather than a methodological one. However, according to me, it requires to go a bit further to anchor the issue in its research theme. In the introduction notably (~ lines 70-73), I would describe in more details the foetal programming concept, and the associated maternal GC effects on offspring phenotype, as it is the key concept below your research issue. Concretely, I would give some striking examples, indicating exactly how maternal GC levels influence cited offspring features (is it a positive or a negative relationship? Is it species-specific? Is it age-dependent?).

To note, I didn’t perfectly understand the answers provided by the authors to justify why they couldn’t switch the statistical analyses order and the associated presentation of results (i.e., from the most completed model with both sexes in a unique model and then the two distinct sex-specific models to characterize in more details the relationship between maternal GC levels and foetal ones).

Finally, the discussion would be more coherent with the introduction by adding a part dealing with the highlighted relationship in the stress context (line 69-70).

Here are line-to-line corrections:

Line 47: have shown

Line 48: I would rephrase: “However, how maternal GC levels precisely relate to foetal levels is still not completely understood.”

Line 50: I would add one or two sentences describing the methods as it is an innovative and original one, as well as the sample size.

Lines 51-52: Your relationship of interest should be described in the same order all along the manuscript, i.e. maternal GC levels with foetal GC levels (or the contrary) but being consistent.

Line 78: in utero should be written in italics.

Line 77-81: it is unclear here why you are dealing with steroid hormones in these two examples while you started this part with stress. This information would be important to add here.

Line 100-101: (Regarding the cited examples) some predictions could be emitted. At least, all possible relationship would be described.

Line 111: Fallow deer is a hider species.

Line 111: per should be written in italics (to correct all along the manuscript).

Line 137: How old are the fawns at capture? Do you measure cortisol on the entire hair or do you exclude a part of it to not measure the GC levels accumulated after birth?

Line 170-175: This adding increases the complexity of comprehension according to me and it is quite repetitive (with line 190-191 notably). I would place such sentences at the beginning of each part describing in details the statistical analyses achieved, as an “introduction” sentence.

Line 185: mid-May

Line 207: Homogenize the format (italics or not) of the word “post-hoc”.

Line 210: Be clearer about which outlier you are considered here (the male fawn GCS vs the FCMs value for one mother).

Between the previous and the current Figure 1B (males), one point has changed (the one ~600 maternal FCMs in the previous Figure 1B), why such change occurred between the two versions of the manuscript.

Line 235-239: This part should be placed in the introduction.

Line 245-251: Such part could support one prediction for your study. If such part would be keep in the Discussion part, transition with the previous/next argument should be rewritten to be easier to read.

Line 252: what is this hormone? A steroid produced by the HPA axis? Is it only produced by placenta? Transitions with previous part should be rewritten to be easier to read.

Line 274: hypotheses which should be tested.

Evaluation round #1

DOI or URL of the preprint: https://doi.org/10.1101/2023.05.04.538920

Version of the preprint: 2

Authors’ reply, 20 September 2023

Download author’s reply

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Decision by Matthieu Paquet, posted 26 July 2023, validated 26 July 2023

Dear Authors,

Your preprint entitled “Sex-specific relationship between maternal and neonate cortisol in a free-ranging large mammal” has now been reviewed and the reviewers’ comments are appended below. As you will see, both reviewers are positive about the study, notably regarding the way it is written, its ecological relevance and its scientific robustness. Additionally, the code was easy to read, ran smoothly, and the results from the code matched those presented in the main text (but see below for some small omissions and discrepancies). Yet the reviewers have several comments that need to be addressed carefully before your preprint can be recommended.

One main comment shared by both reviewers is that the research question and the biological context are not clear. More particularly, regarding potential sex specific effects, apart from mentioning the possible existence of such effects, I could not see any prediction made in the introduction regarding the direction of such effect, and the findings of the work cited when mentioning the possibility for sex differences (Braithwaite et al., 2018; Fishman et al., 2022; Liu et al., 2001) could be briefly developed.

If the authors had no predictions apart from a possible existence of sex specific effects, then it should be clearly stated.

I also agree with reviewer 1 on the fact that the statistical procedure to investigate the sex specific effects is not common. They may be a rationale as for why this approach was taken, in which case it needs to be justified and explained to the reader step by step (first a t test, then separate analyses for each sex, then both sexes analyzed together to estimate the sex difference i.e., interaction), with references recommending it if any.

I also have some more specific comments:

Line 55-56: it seems inaccurate to ”label” parental effects as maternal effects solely because maternal effects are expected to be stronger than paternal effects. I’d recommend to clarify, or rephrase as e.g., ”Parental

phenotypes can be drivers of offspring variation, and in many mammalian species, these parental effects are often assumed to be mainly maternal effects since it is the mother that mostly takes care of the offspring." or any other accurate rewording.

Line 135: is there any estimate of individual repeatability of this measure (from this data or previously published)? Could it be mentioned in the dataset which data values come from one sample vs averaged from several samples (ideally, the raw dataset with multiple measures per female and their respective sampling days could be provided)?

Line 138: how was this value defined as "extreme outlier"? Is it from the goodness of fit diagnostic of the male linear model? Perhaps "outlier" is enough (no need for "extreme"), especially since the value does not look particularly unrealistic?

Line 140-141: although the estimates of the effects are similar, it seems that the interaction is no longer statistically clear when discarding the "outlier"? Please confirm and clarify.

Lines 146-147: please add these t-tests in the R code.

Line 169: also specify the value of the "outlier" here.

Figure 1: start the y axis at zero. I would also suggest showing the outlier in the figure (e.g. in light gray and/or with another shape) and mentioning in the figure legend that this data point was discarded from the main analyses.

I look forward to reading the revised version of this preprint.

Best wishes,

Matthieu

Reviewed by anonymous reviewer 1, 03 July 2023

The preprint provides new insights on the relationship between maternal glucocorticoid and foetal glucocorticoid levels. The sex-specific pattern of the relationship found in the preprint is ecologically-relevant and robust, especially in this free-ranging large mammal, the fallow deer.

However, I find it a bit hard to grasp the research questions and the whole picture from the introduction part. I would suggest to reformulate and add several key information (see below).

Title

The authors used 'neonate cortisol' in the title but 'foetal glucocorticoid' in the abstract and the main text. Given the description of how the authors sample the young, I think 'foetal glucocorticoid' should be used throughout the text, including the title.

Abstract

I miss a sentence clarify the biological relevance/functions of the GC in determining the offspring phenotype in the abstract.

Introduction

L. 57 References need to be added for the first sentence of the introduction.

L.57-61 References in these sentences are only concern the effects of maternal stress/GC on offspring phenotypes. Yet, the authors are talking about maternal effects in general here. Please see and add reviews from Groothuis et al, 2005, 2010, 2015 and others that reviewed more broadly on the maternal effects.

L.62 I doubt whether the authors are looking as acute stress or chronic stress in this study, since the GC accumulated in maternal fecal samples and foetal hairs would reflect a long term and average stress level.

L.66 citation error "(e.g.8)", please correct

Materials and methods

L.124 citation error "(e.g. 15,25)", please correct

L.134 it is not clear in the introduction or here in the methods whether the Fallow mother only produce one fawn per pregnancy.

L.146-147 A confusing sentence, please reformulate. and I wonder if the authors are comparing the GC levels or the FCMs of the mothers? If they are comparing the GC levels of the mother, an explanation of how they convert FCMs to GC levels is necessary. In addition, it is not clear what is the relationship between maternal FCMs and GC levels at this point. How well can FCMs represent the GC levels of the mothers?

L.151-153 Where is the results/parameters from the model assumption check?

L. 154-155 Specify include these factors as what in the model.

". During the preliminary analysis, we included the number of days between the collection of mothers' faeces and the day of fawn birth in our models."

L.157-158 Please give the value of AICs or delta AIC of the models compared, instead of "higher AIC".

L.160-164 It is counterintuitive to me that the authors ran a post-hoc test by "including both sexes" in the same/previous model. On the contrary, a linear model with neonate GC as response variable and maternal FCMs, fawn sea and heir interaction as explanatory variables should be the overall/main model. Other potential covariates such as the number of days between the collection of mothers' faeces and the day of fawn birth should also be tested in this model. Thereafter, a post-hoc testing the relationship of neonate GC and maternal FCMs separately for two sexes should be carried out.

Results

L.172- 178. Like I suggested in the method section. If the statistical analysis changed, this corresponding result section should also be reformulated.

Tables and figures

Figure 1B, I am concerning the potential outliners in this panel. There is one data point where the maternal FCM is above 600 ng/g. Please check and re-do the statistics.

Discussion

L190.-194. This should be consisted and move to introduction, as it is necessary for the reader to know why the authors would expect a sexual difference in the first place.

L.194-195 I don't fully understand the sentence until I read the paragraph below. Need to reformulate these information.

L.204-207. It seems that it is the male foetusese that control its own GC exposure environment instead of the mother actively adjust how much GC her foetus would expose to. This is very interesting and important. I

would suggest the authors add a stand-alone sentence to declare this.

L.211-214 It seems that the authors are suggesting that the GC level of the fetal are extraneous (that is to say. maternally-derive). If this is true, the authors should clarify by which point the fetal can also have endogenous GC? To what extend this endogenous GC would affect the fetal development comparing to the maternal GC. If it is a mixture of maternal GC and endogenous GC that influencing the fetal development. The authors should clarify how maternal GC would affect the embryonic endogenous GC?

Furthermore, it is still not clear to me what is the relationship between maternal FCMs and her GC levels. How well can FCMs represent the GC levels of the mothers?

Reviewed by anonymous reviewer 2, 24 July 2023

I was pleased to review the article entitled "Sex-specific relationship between maternal and neonate cortisol in a free-ranging large mammal" written by Amin and colleagues.

This manuscript describes an innovative non-invasive ecophysiological method used to link foetal and maternal glucocorticoid levels in mammal. The manuscript is quite well-written, and easy to read and to understand.

I have one crucial comment to address to the authors before recommending their manuscript. I'm not entirely sure to understand whether this manuscript aims 1) to describe a new methodology validated to work on maternal effects in mammals, using the deer or 2) to highlight a sex-difference in the link between maternal and fetal glucocorticoid levels in one given mammalian species through the use of an innovative method. Indeed, on one side, technical and methodological details are missing to be considered as a methodological paper (and some are described in the supplementary material or by citing previous work). On the other side, biological context and discussions would be clearer to be considered as a research paper.

To help increasing the impact of this manuscript, here are some questions I would recommend the authors to answer in their manuscript:

- For the technical/methodological aspects:

Regarding the "circulating glucocorticoids", did you check that glucocorticoids levels measured in feces are representative to glucocorticoids levels circulating in plasma? Because you have wide variations in your sampling protocol, did you verify/consider the potential effect of the time of the day on GC variations? How were stored the feces before being placed in the freezers? How long did the feces were kept in a cooler bag before being placed in a freezer? Did you consider the effect of the duration between collection and freezer storage on GC measurements? How did you determine the gestation stage? Could you confirm that samples were collected before determining the mother-fawn pairing (June vs July respectively)? How did you select the individuals to sample in such scenario?

- For the biological/ecological aspects:

In the introduction, I would clarify why studying GC (and/or the associated stress?) would be relevant in the gestation context. Moreover, I would describe in more details how maternal GC levels play a key role during gestation and can affect offspring phenotype. In addition, whether the aim of your manuscript is to deal with a GC sex-response, I would develop some examples already found in other vertebrate species.

Moreover, I would detail how and why can maternal circulating and fetal accumulated glucocorticoid levels be related. Which maternal information is obtained from this relationship between GC (which are accumulated over a couple of weeks) and FCM (which are the immediate/present levels, i.e. when the foetus is already covered in fur, meaning after the synthesis of the hair and the associated GC accumulation). How maternal FCMs vary all along the gestation?

The discussion part would be reorganize or slightly rewritten to be more precise and clear regarding the different hypotheses that could be emitted regarding both the link between offspring GC and maternal FCMs as well as between female and male progeny.

I also have a couple of comments line-by-line:
All along the manuscript: I would use the singular when designating ‘parental/maternal phenotype’.
Line 42: foetal levels are
Line 80: there is an extra space at the beginning of the paragraph
Line 170: no clear sex difference
Line 187: than
Line 191: per year