Association between increased versus normal antenatal vaginal pH and preterm birth: protocol for a systematic review

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Review question
Is an increased vaginal pH > 4.5 significantly associated with preterm birth before 37 completed weeks gestation?

Searches
We searched the following electronic bibliographic databases and platforms: SCOPUS, MEDLINE, EMBASE, PsycINFO, PubMed, Web of Science and OVID. Furthermore, the search was applied to the Cochrane Central Register of Controlled Trials (CENTRAL), the Database of the Centre for Review and Dissemination (CRD), the Clinical Trials Registry and ProQuest Dissertations and Theses Global.
The search strategy followed the PICO approach and was tailored to each database or platform.
Search terms included English and German keywords. No publication date or publication status restrictions were imposed. There were no language restrictions for the search. All searches will be re-applied before completion of the analyses to identify further studies for inclusion. The search strategy for PubMed and OVID is available as Appendix to the published protocol.

Types of study to be included
Inclusion: original research including randomised controlled trials and non-randomised studiesExclusion: Non-original research such as reviews

Condition or domain being studied
Preterm birth before 37 completed weeks gestation.

Participants/population
Inclusion: All pregnant women before the onset of labour.
Exclusion: Non-pregnant women, women in labour.

Intervention(s), exposure(s)
Inclusion: Vaginal pH measurement in pregnancy at any gestational age is increased > 4.5. All methods of measurement will be included (self-measurement or by health care professional, various techniques).
Exclusion: Other diagnostic tests of the urogenital tract without pH measurement.

Comparator(s)/control
Inclusion: Vaginal pH measurement in pregnancy at any gestational Age is physiological < or = 4.5. All methods of measurement will be included (self-measurement or by health care professional, various techniques)
Exclusion: Other diagnostic tests of the urogenital tract without pH measurement.

Main outcome(s)
The primary outcome measure will be preterm birth, which is defined as birth before 37 completed weeks gestation (37 weeks + 0 days).
Studies, which do not include term / preterm birth as an outcome will be excluded.

Additional outcome(s)
Gestational age at preterm birth (<35, <32, <28 weeks).

Data extraction (selection and coding)

A standardised form will be used to extract data from included studies. The extracted information will include the following:
1) Characteristics of the publication (study type, country of data collection, publication language and time of data collection),
2) Information on definition for preterm birth, definition for pathological pH, who measured the pH, how was the pH measured, discrimination of measurement method, regime of measurement, range of gestational age at study entry and mean maternal age,
3) Absolute numbers of the sample, groups and outcome (n[total], n[case group], n[control group], n[missing], n[preterm births in case group] and n[preterm births in control group]), and
4) Information on the inclusion criteria, exclusion criteria, whether only singleton pregnancies were included, whether women with history of preterm birth were included and whether only nulliparous women were included).
The extraction table will include the initials of the persons who will undertake the extraction and the persons who will review the extraction (15%), as well as the date of extraction. 15% of the extracted data will be reviewed by a second investigator and possible discrepancies will be resolved through discussion and consultation of a third investigator if necessary.
Missing data will be requested from study authors. Those responsible for the included studies will be asked to supply the following information, based on what is missing: definition for preterm birth, definition for pathological pH, how was the pH measured, and absolute numbers of the sample, groups and outcome (n[total], n[case group], n[control group], n[missing], n[preterm births in case group] and n[preterm births in control group]).

Risk of bias (quality) assessment

Risk of bias of included studies will be assessed by two researchers. In case of conflicts, consensus will be sought. Where no consensus will be achieved, a third researcher will be involved for arbitration. Randomised controlled trials will be assessed with the Cochrane Tool for Risk of bias Assessment (Higgins et al., 2011). Non-randomised studies will be assessed with the Newcastle-Ottawa Scale (Wells et al., 2008). Results on both the risk of bias tools will be further used to investigate the robustness of the primary analysis results on the exclusion of poor-quality studies. As poor-quality study we define a study with at least two items of high risk of bias according to the risk of bias tool for the randomised controlled studies or a study rated with a total score of <7 according to the Newcastle-Ottawa Scale tool for the non-randomised controlled studies.

Strategy for data synthesis

Randomised controlled trials (RCTs) will be synthesized in a random-effects meta-analysis model. The primary outcome will be evaluated using the odds ratio scale where odds ratio >1 implies higher preterm birth risk in the intervention (increased pH >4.5) compared to comparator (pH < or = 4.5). The extent of heterogeneity will be measured using the I-squared and tau-squared; the former reflects the percentage of total variation attributed to heterogeneity rather than to simple chance and the latter provides an estimate of the magnitude of statistical heterogeneity. The analytic framework and the heterogeneity estimator will be decided upon the number of eligible RCTs: in case of more than 10 studies, the Paul-Mandel heterogeneity estimator will be preferred as better alternative to the DerSimonian and Laird method for its superior simulative performance alongside the Q-profile method for the estimation of the uncertainty of the heterogeneity variance. In addition, a predictive interval will be provided to indicate the range of averaged effect estimates expected in a future similar trial.
However, in case of less than 10 studies, we will opt for Bayesian random-effects meta-analysis as a more appropriate analysis framework in the light of few studies since external evidence in the form of prior distribution can be jointly synthesized with the observed data to provide more proper posterior distributions for the unknown meta-analytic parameters. We will use informative prior on the heterogeneity variance parameter to compensate for the inadequacy in the observed evidence. Such informative priors have been already proposed by research setting (i.e. outcome type, intervention-comparator type and disease area).
Forest plots will be used to present the meta-analysis results. Both study raw data (i.e. number of term/preterm births and sample size per arm) and effect estimates alongside the 95% confidence/credible intervals will be presented.
When at least 10 studies are included in the meta-analysis, then funnel plot will be drawn to investigate the presence of possible small-study effects.
Non-randomised controlled trials (NRCTs) will be analyzed narratively since larger heterogeneity than in

RCTs is expected due to methodological diversions across the included studies (e.g. variations on whether and how confounding has been addressed in the analysis, greater risk of biases due to poor trial design and execution). The primary outcome will be evaluated using the odds ratio scale where odds ratio >1 implies higher preterm birth risk in the intervention (increased pH >4.5) compared to comparator (pH =4.5). A forest plot will be used to present the study results (i.e. point estimates and 95% confidence intervals). Within the forest plots, studies will be grouped according to specific characteristics (definition of physiological pH if included studies use different cut-offs; gestational age at preterm birth <37 weeks, <35 weeks, <32 weeks, <28 weeks; and type of measurement (self-measurement or through physician)). No pooling of the studies will be attempted within each subgroup for the above-mentioned reasons.

Analysis of subgroups or subsets
If the necessary data are available and they are derived from randomized controlled trials, subgroup analyses are planned for different gestational ages, such as < 35 weeks gestation, < 32 and <28. It is not possible to specify in advance, whether these analyses will be feasible.

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Type and method of review
Systematic review

Anticipated or actual start date
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Conflicts of interest
None known

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Germany

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Stage of review
Review Completed published

Details of final report/publication(s) or preprints if available

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Subject indexing assigned by CRD

Subject index terms

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13 October 2016

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12 August 2018

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

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