BMJ Open

Trends of vital signs with gestational age in normal pregnancies: A systematic review protocol.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008769
Article Type:	Protocol
Date Submitted by the Author:	14-May-2015
Complete List of Authors:	Loerup, Lise; University of Oxford, Department of Engineering Science Pullon, Rebecca; University of Oxford, Department of Engineering Science Birks, Jacqueline; University of Oxford, Centre for Statistics in Medicine Fleming, Susannah; University of Oxford, Nuffield Department of Primary Care Health Sciences MacKillop, Lucy; Oxford University Hospitals NHS Trust, Nuffield Department of Obstetrics & Gynaecology Watkinson, Peter; Oxford University Hospitals NHS Trust, Nuffield Department of Clinical Neurosciences
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Evidence based practice, Health informatics, Intensive care
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Maternal medicine < OBSTETRICS

TRENDS OF VITAL SIGNS WITH GESTATIONAL AGE IN NORMAL PREGNANCIES: A SYSTEMATIC REVIEW PROTOCOL

Authors:
Lise Loerup
Department of Engineering Science, University of Oxford, Oxford, UK

Rebecca M. Pullon
Department of Engineering Science, University of Oxford, Oxford, UK

Jacqueline Birks
Centre for Statistics in Medicine, University of Oxford, Oxford, UK

Susannah Fleming
Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

Lucy H. Mackillop
Nuffield Department of Obstetrics & Gynaecology, Oxford University Hospitals NHS Trust, Oxford, UK

Peter J. Watkinson
Nuffield Department of Clinical Neurosciences, Oxford University Hospitals NHS Trust, Oxford, UK

Corresponding author:
Lise Loerup

Postal address: Institute of Biomedical Engineering, Old Road Campus Research Building, Off Roosevelt Drive, Headington, Oxford, OX3 7DQ, UK

Email: lise.loerup@eng.ox.ac.uk

Phone: +44 (0)7734341661

Key words (max. 5, preferably MeSH terms):
Pregnancy (MeSH), vital signs (MeSH), maternal physiology, modified obstetric early warning score

Word count (excluding title page, abstract, references, figures and tables):
1,997 words

ABSTRACT

Introduction: Vital signs (blood pressure, heart rate, temperature, oxygen saturation and respiratory rate) are thought to undergo changes during and immediately after pregnancy. However, these physiological changes are not taken into account in the normal ranges, which themselves are not evidence-based, used in routine and acute care monitoring. We aim to synthesise the existing evidence base for changes in vital signs during pregnancy derive new centile charts for each stage of pregnancy and the immediate post-partum period.

Methods and analysis: We will search the MEDLINE, EMBASE and CINAHL databases from their inception to April 2015 for vital signs from pregnant, intrapartum or postpartum women who were recruited as "healthy". Assessment of bias will be conducted using a predefined set of independently agreed methodological criteria, which assigns an overall quality score to each study. Whether vital signs measurement was undertaken with measurement devices validated for use in pregnancy and in a standard posture will be recorded. We will use regression methods to construct centile charts of vital signs across pregnancy and the immediate postpartum period for each vital sign. We will compare existing reference ranges to those derived from our centile charts.

Dissemination: The systematic review will be published in a peer-reviewed journal and disseminated electronically and in print.

Registration reference: PROSPERO, registration number CRD42014009673.

Strengths and limitations of this study

Strengths

- This is the first review to synthesise the evidence base of vital sign changes during pregnancy, taking into account the gestational age.

Limitations

- The quality of published information may limit the study findings
- Combining different methods of measurement of the same vital sign may prove difficult

INTRODUCTION

Rationale

Heart rate, blood pressure, respiratory rate, oxygen saturations and temperature are key vital signs used to assess the physiological status of women presenting acutely throughout pregnancy, intrapartum, during anaesthesia and in the early postpartum period. The perceived normal ranges of these vital signs underpin modified early obstetric warning scores developed to assist in early recognition of deterioration.[1,2] Using these vital signs to detect physiological deterioration is complicated by the normal dynamic changes in maternal vital sign physiology that occur both during pregnancy and immediately after delivery. In the case of modified early obstetric warning scores, they define the thresholds that determine if a woman requires review.

Yet currently, normal ranges are either not referenced, or reference a core textbook (which references data from small individual studies published between 1970 and the mid-1990s).[3] None of the clinical guidelines take account of expected changes in different stages of pregnancy, intrapartum and the early postpartum period. The evidence underpinning current guidance is therefore weak, and ranges used in clinical practice to detect physiological deterioration appear to be adapted from those established for the non-pregnant population or based on clinical consensus.[1,4] As apparently small changes in thresholds make substantial differences to the ability of clinical scores to identify physiological deterioration,[5,6] accurate reference ranges that take into account changes for each stage of pregnancy, the intrapartum and early postpartum periods, are essential to using vital signs to provide high quality clinical care.

As vital signs are commonly recorded at a particular stage of pregnancy in many different types of clinical studies, large quantities of data may already be available to inform these vital sign ranges.

Objectives

We aim to report on existing gestation-specific centiles for vital signs in pregnancy, intrapartum and the early postpartum period using studies of women recruited as "healthy", who undertook vital sign measurements using non-invasive techniques used by health care professionals. We will compare the reported centiles with existing reference ranges for each stage of pregnancy, intrapartum and the postpartum period. If the collected data allows, we will attempt to synthesise the reported vital sign data to develop new gestation-specific centile charts.

METHODS

Registration reference

This systematic review has been registered on PROSPERO (registration number CRD42014009673).

Criteria for inclusion of studies in this review

Types of studies

Prospective and retrospective longitudinal, cross-sectional and case control studies and randomized control trials will be included.

Types of participants

Pregnant women aged 14 years or older, with singleton, normal pregnancies and without illnesses likely to affect the cardiac or respiratory systems will be included.

Types of measurements

We will include objective measurement of heart rate, respiratory rate, blood pressure, oxygen saturations or temperature, taken from the start of the antenatal period (early pregnancy) up to two weeks postpartum. Self-monitoring or other measurements not taken by a healthcare professional, or measurements taken using invasive measurement techniques, will not be included. Gestational age at which the measurements were taken must be reported.

A complete list of inclusion and exclusion criteria has been included in Appendix 1 (Table 1), together with a list of acceptable measurement techniques (Table 2).

Types of outcome measures

Primary outcome measures

Where centiles are presented, we will report these for each gestational age. Otherwise, where data is not presented as centiles but a sufficient amount of data is available, we will calculate the median and representative centiles (1^{st}, 10^{th}, 25^{th}, 75^{th}, 90^{th}, 99^{th}) for changes in vital signs with respect to gestational age using data from each included study, subject to assessment of normal distributions of vital sign data.

Secondary outcome measures

A quality assessment will be performed and a score for the risk of bias for each study will be reported.

Where subgroup analyses suggest that the subgroups have clinically different centile distributions, we will, where sufficient data exists, present subgroup-specific centile-distributions.

Search methods for identifying the studies

Electronic searches

Three databases will be searched, from their inception until April 2015: MEDLINE (1950– April 2015), EMBASE (1980–April 2015), CINAHL (1982– April 2015). Specific search strategies will be developed for each database between clinicians and a qualified librarian from the Oxford University Healthcare Libraries, who will carry out the search. The strategies will use both MeSH terms and free text with no language restrictions. An example search strategy is shown in Appendix 2 (Table 3).

Searching other sources

We will perform non-electronic searches of our own files of articles and of the reference lists of all included studies to identify studies not captured in the initial electronic search.

Identification of reference guidelines

PW and LM will identify sources of existing reference ranges by reviewing obstetric, physiology and anaesthetic textbooks, international guidelines, standardised clinical training courses and maternal early warning scores to mirror the likely exposure of clinicians to reference ranges.

Data collection

Study selection

The retrieved titles and, where available, abstracts will be reviewed by two reviewers (LL and RP) to exclude studies that clearly fall outside the scope of the review, such as fetal studies or studies not performed on humans. Following this initial sift, the remaining titles and, where available, abstracts will be assessed by two reviewers (PW and LM) against the inclusion and exclusion criteria. The full texts of all potentially relevant articles will be retrieved for data extraction where appropriate. Figure 1 summarises the study selection process.

Assessment of bias and heterogeneity

A quality assessment of studies that meet our inclusion and exclusion criteria will be performed independently by two reviewers. Disagreements will be resolved by recourse to the original data. The quality assessment will be undertaken in line with the QUADAS-2 assessment,[7] following the methodology of Ioannou et al. (2012).[8] This assessment has been designed to evaluate the methodological quality of observational studies, performed with pregnant subjects. Where required, the specific assessment criteria will be adapted for our purpose. Results of this quality assessment, which assigns an overall quality score to each study, will be presented in tabular and graphical form.

Data extraction and management

Two reviewers will independently perform data extraction (LL and RP). Data will be extracted into a pre-piloted electronic spreadsheet (Microsoft ExCel). Disagreements will be resolved by recourse to the original data. Data will be extracted from tables, text or graphs. Appropriate software will be used to ensure accurate transcription of data from graphs, subject to predefined criteria to resolution of graphically presented data (as defined in Appendix 1, Table 2). For each period of pregnancy defined in a paper, the number of women in the group will be extracted, along with the following statistical data about the vital signs of interest (blood pressure, heart rate, temperature, oxygen saturation or respiratory rate), where reported:

- Mean value
- Median value
- Standard deviation
- Centiles, percentiles, quartiles etc.
- Confidence intervals
- Standard error of the mean

The period of pregnancy will be extracted as weeks of gestation and the method used to determine gestational age will be recorded. Data for a given period of pregnancy that is reported separately, for example for different ethnic groups or subgroups defined based on a medical diagnosis, will be classified independently. Data from subgroups with a medical diagnosis that could affect their measurement will only be included if the women are described as healthy at the start of the study. When multiple measurements at the same time point are reported for a single physiological variable (for example lying and sitting heart rates), a single data point will be selected to avoid over-representation using the pre-specified rules summarized in Appendix 3.

In addition, the following data will be extracted from each included paper, if the data is present: date of the study; period of data collection; demographic information about participants (age range, weight, BMI, ethnicity, reason for measurements); details of pregnancy (parity, number of gestations); country of study (with subsequent assignment to economic development status, according to the UNDP Human Development Index [9]); study setting and details of measurement (subject position, method of measurement, device details).

Data extraction from papers of a different language

In order to extract data from studies published in a language other than English, assistance will be sought from people within our research groups (preferably with a medical background) with native proficiency in the relevant language. Data from such studies will be extracted in consultation with one of the two reviewers (LL or RP).

Dealing with missing data

In cases where relevant data has not been adequately reported, or presented in a format that is not suitable for extraction, the original authors will be contacted and the data requested. We will in the first instance use contact details from the original paper, but where these are no longer valid, contact details will be sought from more recent publications on PubMed, from institutional websites or through general online search engines. Authors will be contacted twice; initially a request for data will be sent via electronic mail, and if no response is received after 4 weeks, authors will be contacted a second time.

Data analysis

Data synthesis

We will analyse cross sectional and longitudinal studies separately and combine the vital sign data if appropriate.

Cross sectional studies

Each cross sectional study will provide a mean response at one or more accurately known GA time points. When a study reports for more than one time point there will be no dependence between any data point as each person will contribute only one assessment.

Assuming no significant heterogeneity between studies, the centiles and other statistics for each value of gestational age will be reported. If possible, the analysis will pool results from the studies using regression techniques. Each study will contribute mean of vital signs and gestational age, taking into account differences in population size. There may be multiple data from cross sectional studies with independent estimates at more than one value of gestational age. The mean response curve as a function of gestational age will be estimated. If the relationship between the response and gestational age does not appear to have a functional form other non-parametric methods of curve fitting will be used.

Longitudinal studies

A longitudinal study measures the response at several time points for each participant. The set of time points may be unique for each participant, or identical across participants. The mean response curve over time for each study will be presented graphically, with the equation if a parametric method was used and the equation is reported.

Sensitivity analysis

If there is significant heterogeneity at any time point sensitivity analyses will be attempted by dropping outlying studies from the analysis.

Subgroup analysis

Where data is available, we will attempt to conduct the following subgroup analyses:

- BMI (or weight) class
- Ethnicity
- Development status of country of study
- Parity
- Position of measurement
- The method of measurement (for example blood pressure device)
- Measurement setting
- The year of assessment
- Pregnancy complications

DISCUSSION

This systematic review will summarise the current state of evidence for trends in maternal physiology in pregnancy. Where sufficient data is available, centile charts of vital sign longitudinally in pregnancy, intrapartum and the post-partum period will be derived. The knowledge of normal distributions of such data in a low-risk population of women for a *particular stage of pregnancy* is an essential pre-requisite both to the development of an evidence-based Modified Early Obstetric Warning Score (MEOWS) and for best practice use of these vital signs throughout clinical practice.

COMPETING INTERESTS

Nothing to declare

AUTHORS' CONTRIBUTIONS AND ACKNOWLEDGEMENTS

This protocol was prepared by LL and PW. LM advised on study selection. JB, SF and RP assisted with design of the methodology and analysis plan.

The authors would also like to acknowledge Tatjana Petrinic, Oxford University Health Care Libraries, University of Oxford, for help with designing the initial search strategy.

FUNDING STATEMENT

The NIHR Biomedical Research Centre, Oxford, UK, supported this work. LL and RP were supported by the RCUK Digital Economy Programme grant number EP/G036861/1 (Oxford Centre for Doctoral Training in Healthcare Innovation) and the Clarendon Fund (LL only).

COMPETING INTERESTS STATEMENT

No competing interests to declare.

REFERENCES

[1] Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ. on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–12. Oxford, UK: National Perinatal Epidemiology Unit, University of Oxford; 2014.

[2] Isaacs RA, Wee MYK, Bick DE, Beake S, Sheppard ZA, Thomas S, et al. A national survey of obstetric early warning systems in the United Kingdom: five years on. Anaesthesia 2014;69(7):687-692.

[3] Chamberlain G., Pipkin, FB. Clinical Physiology in Obstetrics. 3rd ed. Oxford, UK: Blackwell Science; 1998.

[4] McGlennan AP, Sherratt K. Charting change on the labour ward. Anaesthesia 2013;68(4):338-342.

[5] Smith GB, Prytherch DR, Schmidt PE, Featherstone PI, Higgins B. A review, and performance evaluation, of single-parameter "track and trigger" systems. Resuscitation 2008 10;79(1):11-21.

[6] Smith GB, Prytherch DR, Schmidt PE, Featherstone PI. Review and performance evaluation of aggregate weighted 'track and trigger' systems. Resuscitation 2008 5;77(2):170-179.

[7] Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Annals of Internal Medicine 2011;155:529-536.

[8] Ioannou C, Talbot K, Ohuma E, Sarris I, Villar J, Conde-Agudelo A, et al. Systematic review of methodology used in ultrasound studies aimed at creating charts of fetal size. BJOG 2012;119(12):1425-1439.

[9] HDRO (Human Development Report Office). Sustaining Human Progress: Reducing Vulnerabilities and Building Resilience. United Nations Development Programme, New York, USA, 2014. Retrieved 26 February 2015.

[10] O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. Journal of Hypertension 2003; 21(5): 821-848

[11] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, the PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 349: g7647

APPENDICES

Appendix 1 – Inclusion and exclusion criteria

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Cross-sectional, case-control or longitudinal study	Measurements from women with illnesses likely to affect the cardiac or respiratory systems
Minimum of 50 patients	Measurements from women with risk factors for developing complications
Age 14 years or older	Measurements from women known to be taking medication which could affect the measurements
Objective measurement[1] of heart rate, blood pressure, respiratory rate, oxygen saturation or temperature	Measurements from women where the reported gestational age at the point of measurement not defined in terms of days or weeks of gestation
Measurements taken during the antenatal period, up to the start of the intrapartum period[2]	Measurements from women where the reported period of gestation exceeded 16 weeks
Raw data or average measure reported and possible to extract within minimum accuracy	Measurements from self-monitoring or other measurements not taken by a healthcare professional
	Measurements from women with less than 10% singleton pregnancies
	For women known to undergo fertility procedures, any measurements taken prior to a positive pregnancy test
	Any of the following measurements (without valid baseline): • Measurements taken using ambulatory technologies • Measurements taken using invasive technologies • Measurements taken during anesthesia • Measurements taken during sleep • Measurements taken during exercise • Measurements taken at heights greater than 1000m above sea level

[1] *An overview of acceptable measurement techniques is provided in Table 2*
[2] *Defined as progressive cervical dilatation with regular contractions*

Table 2: Acceptable methods of measurement

Vital sign	Acceptable methods	Not acceptable methods	Minimum accuracy when presented in graph
Blood pressure	Non-invasive cuff Korotkoff sounds	Intra-arterial Echocardiography Impedance cardiography	2 mm Hg
Heart rate	Pulse oximeter Blood pressure monitor Electrocardiography	–	2 beats minute^{-1}
Oxygen saturation	Non-invasive pulse oximeter	Blood gas analysis	1%
Temperature	Oral Tympanic Auxiliary Forehead Rectal	Intrauterine Other invasive methods	0.1 ^{o}C
Respiratory rate	Count by viewing Count by stethoscope	Impedance pneumography	1 beat minute^{-1}

Appendix 2 – Search terms

A draft search strategy is presented in Table 1. It has been designed with assistance of a qualified librarian in the Oxford University Health Care Libraries, following an initial search by two reviewers (LL and RP), review of the findings of the initial search with clinicians (PW and LM) and adjustment to improve detection of papers known to us.

Table 3: Search criteria

Population	Physiological variables	Measurement
pregnan*.ti; maternal.ti; obstetric*.ti; "expectant mother*".ti; "expecting mother*".ti; peripartum.ti; "peri partum".ti; antepartum.ti; "ante partum".ti; postpartum.ti; "post partum".ti; intrapartum.ti; "intra partum".ti; puerperium.ti; trimester*.ti; perinatal*.ti; antenatal*.ti; postnatal*.ti	"vital sign*".ti; "early warning".ti; EWS*.ti; *"modified early obstetric warning".ti;* *score*.ti;* *MEOWS.ti;* *chart*.ti* physiolog*.ti; haemodynam*.ti; hemodynam*.ti; normogram*.ti; "heart rate*".ti; "pulse rate*".ti; "pulse oximetry".ti; "oxygen saturation*".ti; SpO2.ti; Sp02.ti; "blood pressure*".ti; (temperature AND body).ti; "respirat* rate*".ti; *"breath* rate*".ti;* *temperature*.ti;* *breath*.ti;* *respirat*.ti;* *"cardiac rate*".ti;* *oximetry.ti;*	trend*.ti; pattern*.ti; range*.ti; change*.ti; measur*.ti; monitor*.ti; record*.ti; assess*.ti; evaluat*.ti; observ*.ti; guidance.ti; guideline*.ti; technique*.ti; method*.ti; systematic*.ti; Chart*

Limits applied to search:

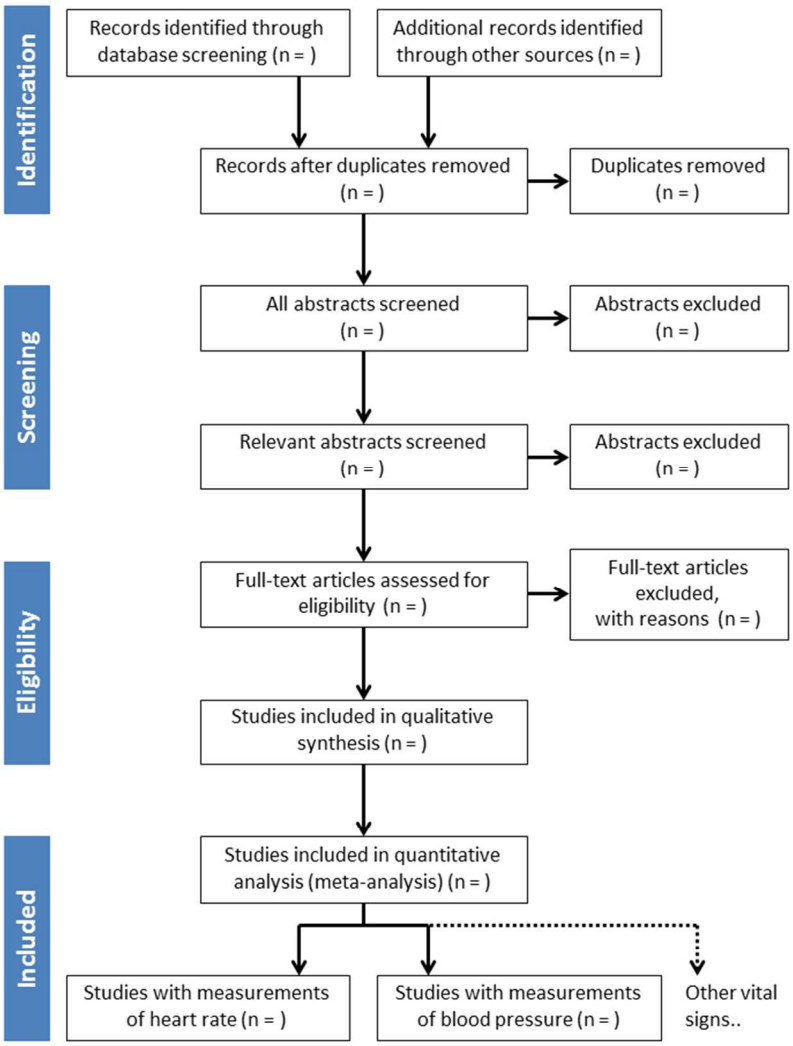
- Human subjects
- Databases: Medline, Embase, CINAHL
- Publication date: Database inception – April 2015
- Abstract available in English
- Journal papers only (exclude reviews, letters, comments, editorials, conference papers)

Appendix 3 – Rules for selection of vital sign measurements

To avoid overrepresentation, the following rules for selection of a single data point have been agreed:

1. Where measurements are recorded in different positions, measurements made in the seated position (or position closest to it) will be recorded, according to the hierarch of positions by the European Hypertension Society.[10] For blood pressure, only measurements made in the sitting or left lateral positions (or close to it) will be recorded.
2. When more than one baseline measurement is reported, the first reported measurement will be recorded.
3. Where measurements are recorded at different times of day, the measurements closest to midday will be recorded.
4. Where measurement methods are compared to a non-invasive gold standard the gold standard measurement will be used.
5. Where Korotkoff stage 4 and 5 diastolic blood pressures are reported, stage 5 will be recorded in line with the European Hypertension Society guidelines.[10]
6. Where vital signs are reported both in the form of empirical and modeled values, empirical values will be used.
7. Where data are reported for several variations of subgroups, longitudinally measured data will be prioritised over single data points, even if this will involve excluding measurements from certain subgroups.

These rules were developed to ensure that ranges are relevant to normal clinical practice for intermittent observations undertaken by clinicians.



Flow diagram of the study selection process, adapted from [11]

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2/3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2/3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3/4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	12
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4/5 + fig
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6/7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	n/r
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	n/r
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/r
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/r
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/r
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/r
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/r
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	n/r
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	n/r
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	n/r
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	7

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

BMJ Open

Trends of vital signs with gestational age in normal pregnancies: A systematic review protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-008769.R1
Article Type:	Protocol
Date Submitted by the Author:	18-Sep-2015
Complete List of Authors:	Loerup, Lise; University of Oxford, Department of Engineering Science Pullon, Rebecca; University of Oxford, Department of Engineering Science Birks, Jacqueline; University of Oxford, Centre for Statistics in Medicine Fleming, Susannah; University of Oxford, Nuffield Department of Primary Care Health Sciences MacKillop, Lucy; Oxford University Hospitals NHS Trust, Nuffield Department of Obstetrics & Gynaecology Watkinson, Peter; Oxford University Hospitals NHS Trust, Nuffield Department of Clinical Neurosciences
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Evidence based practice, Health informatics, Intensive care
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Maternal medicine < OBSTETRICS

TRENDS OF VITAL SIGNS WITH GESTATIONAL AGE IN NORMAL PREGNANCIES: A SYSTEMATIC REVIEW PROTOCOL

Authors:
Lise Loerup
Department of Engineering Science, University of Oxford, Oxford, UK

Rebecca M. Pullon
Department of Engineering Science, University of Oxford, Oxford, UK

Jacqueline Birks
Centre for Statistics in Medicine, University of Oxford, Oxford, UK

Susannah Fleming
Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

Lucy H. Mackillop
Nuffield Department of Obstetrics & Gynaecology, Oxford University Hospitals NHS Trust, Oxford, UK

Peter J. Watkinson
Nuffield Department of Clinical Neurosciences, Oxford University Hospitals NHS Trust, Oxford, UK

Corresponding author:
Lise Loerup

Postal address: Institute of Biomedical Engineering, Old Road Campus Research Building, Off Roosevelt Drive, Headington, Oxford, OX3 7DQ, UK

Email: lise.loerup@eng.ox.ac.uk

Phone: +44 (0)7734341661

Key words (max. 5, preferably MeSH terms):
Pregnancy (MeSH), vital signs (MeSH), maternal physiology, modified obstetric early warning score

Word count (excluding title page, abstract, references, figures and tables):
1,999 words

ABSTRACT

Introduction: Vital signs (blood pressure, heart rate, temperature, oxygen saturation and respiratory rate) are thought to undergo changes during and immediately after pregnancy. However, these physiological changes are not taken into account in the normal ranges, which themselves are not evidence-based, used in routine and acute care monitoring. We aim to synthesise the existing evidence base for changes in vital signs during pregnancy derive new centile charts for each stage of pregnancy and the immediate post-partum period.

Methods and analysis: We will search the MEDLINE, EMBASE and CINAHL databases from their inception to April 2015 for vital signs from pregnant, intrapartum or postpartum women who were recruited as "healthy". Assessment of bias will be conducted using a predefined set of independently agreed methodological criteria, which assigns an overall quality score to each study. Whether vital signs measurement was undertaken with measurement devices validated for use in pregnancy and in a standard posture will be recorded. We will use regression methods to construct centile charts of vital signs across pregnancy and the immediate postpartum period for each vital sign. We will compare existing reference ranges to those derived from our centile charts.

Dissemination: The systematic review will be published in a peer-reviewed journal and disseminated electronically and in print.

Registration reference: PROSPERO, registration number CRD42014009673.

Strengths and limitations of this study

Strengths

- This is the first review to synthesise the evidence base of vital sign changes during pregnancy, taking into account the gestational age.

Limitations

- The quality of published information may limit the study findings
- Combining different methods of measurement of the same vital sign may prove difficult

INTRODUCTION

Rationale

Heart rate, blood pressure, respiratory rate, oxygen saturations and temperature are key vital signs used to assess the clinical status of women presenting acutely throughout pregnancy, intrapartum, during anaesthesia and in the early postpartum period. The perceived normal ranges of these vital signs underpin modified early obstetric warning scores developed to assist in early recognition of deterioration.[1,2] Using these vital signs to detect physiological deterioration is complicated by the normal dynamic changes in maternal vital sign physiology that occur both during pregnancy and immediately after delivery. In the case of modified early obstetric warning scores, they define the thresholds that determine if a woman requires review.

Yet currently, normal ranges are either not referenced, or reference a core textbook (which references data from small individual studies published between 1970 and the mid-1990s).[3] None of the clinical guidelines take account of expected changes in different stages of pregnancy, intrapartum and the early postpartum period. The evidence underpinning current guidance is therefore weak, and thresholds used in clinical practice to detect physiological deterioration appear to be adapted from those established for the non-pregnant population or based on clinical consensus.[1,4] As apparently small changes in thresholds make substantial differences to the ability of clinical scores to identify physiological deterioration,[5,6] accurate reference ranges that take into account changes for each stage of pregnancy, the intrapartum and early postpartum periods, are essential to using vital signs to provide high quality clinical care.

As vital signs are commonly recorded at a particular stage of pregnancy in many different types of clinical studies, large quantities of data may already be available to inform these vital sign thresholds.

Objectives

We aim to report on existing gestation-specific centiles for vital signs in pregnancy, intrapartum and the early postpartum period using studies of women recruited as "healthy", who undertook vital sign measurements using non-invasive techniques used by health care professionals. We will compare the reported centiles with existing reference ranges for each stage of pregnancy, intrapartum and the postpartum period. If the collected data allow, we will attempt to synthesise the reported vital sign data to develop new gestation-specific centile charts.

METHODS

Registration reference

This systematic review has been registered on PROSPERO (registration number CRD42014009673).

Criteria for inclusion of studies in this review

Types of studies

Prospective and retrospective longitudinal, cross-sectional and case control studies and randomized control trials will be included.

Types of participants

Pregnant women aged 14 years or older, with singleton, normal pregnancies and without illnesses likely to affect the cardiac or respiratory systems will be included.

Types of measurements

We will include objective measurement of heart rate, respiratory rate, blood pressure, oxygen saturations or temperature, taken from the start of the antenatal period (early pregnancy) up to two weeks postpartum. Self-monitoring or other measurements not taken by a healthcare professional, or measurements taken using invasive measurement techniques, will not be included. Gestational age at which the measurements were taken must be reported.

A complete list of inclusion and exclusion criteria has been included in Appendix Table 1, together with a list of acceptable measurement techniques in Appendix Table 2.

Types of outcome measures

Primary outcome measures

Where centiles are presented, we will report these for each gestational age. Otherwise, where data are not presented as centiles but a sufficient amount of data are available, we will calculate the median and representative centiles (1st, 10th, 25th, 75th, 90th, 99th) for changes in vital signs with respect to gestational age using data from each included study, subject to assessment of normal distributions of vital sign data.

Secondary outcome measures

A quality assessment will be performed and a score for the risk of bias for each study will be reported.

Where subgroup analyses suggest that the subgroups have clinically different centile distributions, we will, where sufficient data exist, present subgroup-specific centile-distributions.

Search methods for identifying the studies

Electronic searches

Three databases will be searched, from their inception until April 2015: MEDLINE (1950– April 2015), EMBASE (1980–April 2015), CINAHL (1982– April 2015). Specific search strategies will be developed for each database between clinicians and a qualified librarian from the Oxford University Healthcare Libraries, who will carry out the search. The strategies will use both MeSH terms and free text with no language restrictions. An example search strategy is shown in Appendix Table 3.

Searching other sources

We will perform non-electronic searches of our own files of articles and of the reference lists of all included studies to identify studies not captured in the initial electronic search.

Identification of reference guidelines

PW and LM will identify sources of existing reference ranges by reviewing obstetric, physiology and anaesthetic textbooks, international guidelines, standardised clinical training courses and maternal early warning scores to mirror the likely exposure of clinicians to reference ranges.

Data collection

Study selection

The retrieved titles and, where available, abstracts will be reviewed by two reviewers (LL and RP) to exclude studies that clearly fall outside the scope of the review, such as fetal studies or studies not performed on humans. Following this initial sift, the remaining titles and, where available, abstracts will be assessed by two reviewers (PW and LM) against the inclusion and exclusion criteria. The full texts of all potentially relevant articles will be retrieved for data extraction where appropriate. Figure 1 shows a PRISMA flow diagram [7] that summarises the study selection process.

Assessment of bias and heterogeneity

A quality assessment of studies that meet our inclusion and exclusion criteria will be performed independently by two reviewers. Disagreements will be resolved by recourse to the original data. The quality assessment will be undertaken in line with the QUADAS-2 assessment,[8] following the methodology of Ioannou et al. (2012).[9] This assessment has been designed to evaluate the methodological quality of observational studies, performed with pregnant subjects. Where required, the specific assessment criteria will be adapted for our purpose. Results of this quality assessment, which assigns an overall quality score to each study, will be presented in tabular and graphical form.

Data extraction and management

Two reviewers will independently perform data extraction (LL and RP). Data will be extracted into a pre-piloted electronic spreadsheet (Microsoft ExCel). Disagreements will be resolved by recourse to the original data. Data will be extracted from tables, text or graphs. Appropriate software will be used to ensure accurate transcription of data from graphs, subject to predefined criteria to resolution of graphically presented data as defined in Appendix Table 2. For each period of pregnancy defined in a paper, the number of women in the group will be extracted, along with the following statistical data about the vital signs of interest (blood pressure, heart rate, temperature, oxygen saturation or respiratory rate), where reported:

- Mean value
- Median value
- Standard deviation
- Centiles, percentiles, quartiles etc.
- Confidence intervals
- Standard error of the mean

The period of pregnancy will be extracted as weeks of gestation and the method used to determine gestational age will be recorded. Data for a given period of pregnancy that are reported separately, for example for different ethnic groups or subgroups defined based on a medical diagnosis, will be classified independently. Data from subgroups with a medical diagnosis that could affect their measurement will only be included if the women are described as healthy at the start of the study. When multiple measurements at the same time point are reported for a single physiological variable (for example lying and sitting heart rates), a single data point will be selected to avoid over-representation using the pre-specified rules summarized in Appendix 3.

In addition, the following data will be extracted from each included paper, if the data are present: date of the study; period of data collection; demographic information about participants (age range, weight, BMI, ethnicity, reason for measurements); details of pregnancy (parity, number of gestations); country of study (with subsequent assignment to economic development status, according to the UNDP Human Development Index [10]); study setting and details of measurement (subject position, method of measurement, device details).

Data extraction from papers of a different language

In order to extract data from studies published in a language other than English, assistance will be sought from people within our research groups (preferably with a medical background) with native proficiency in the relevant language. Data from such studies will be extracted in consultation with one of the two reviewers (LL or RP).

Dealing with missing data

In cases where relevant data have not been adequately reported, or presented in a format that is not suitable for extraction, the original authors will be contacted and the data requested. We will in the first instance use contact details from the original paper, but where these are no longer valid, contact details will be sought from more recent publications on PubMed, from institutional websites or through general online search engines. Authors will be contacted twice; initially a request for data will be sent via electronic mail, and if no response is received after 4 weeks, authors will be contacted a second time.

Data analysis

Data synthesis

We will analyse cross sectional and longitudinal studies separately and pool the vital sign data if appropriate.

Cross sectional studies

Each cross sectional study will provide a mean response at one or more accurately known gestational age time points. Where a study reports cross-sectional measurements at multiple gestational ages (multiple samples from the same population) the data points will be treated as independent because each subject only contributes one assessment.

Assuming no significant heterogeneity between studies, the centiles and other statistics for each value of gestational age will be reported. If possible, the analysis will pool results from the studies using regression techniques. Where potential confounding factors are reported, such as BMI, malnutrition, and hemoglobin values, we will consider incorporating these factors in a meta-regression. Each study will contribute mean of vital signs and gestational age, taking into account differences in population size. The mean response curve as a function of gestational age will be estimated. If the relationship between the response and gestational age does not appear to have a functional form other non-parametric methods of curve fitting will be used.

Longitudinal studies

A longitudinal study measures the response at several time points for each participant. The set of time points may be unique for each participant or identical across participants. The mean response curve over time for each study will be presented graphically, with the equation if a parametric method was used and the equation is reported.

Sensitivity analysis

If there is significant heterogeneity at any time point sensitivity analyses will be attempted by dropping outlying studies from the analysis.

Subgroup analysis

Where data are available, we will attempt to conduct the following subgroup analyses:

- BMI (or weight) class
- Ethnicity
- Development status of country of study
- Parity
- Position of measurement
- The method of measurement (for example blood pressure device)
- Measurement setting
- The year of assessment
- Pregnancy complications

DISCUSSION

This systematic review will summarise the current state of evidence for trends in maternal physiology in pregnancy. Where sufficient data are available, centile charts of vital sign longitudinally in pregnancy, intrapartum and the post-partum period will be derived. The knowledge of normal distributions of such data in a low-risk population of women for a *particular stage of pregnancy* is an essential pre-requisite both to the development of an evidence-based Modified Early Obstetric Warning Score (MEOWS) and for best practice use of these vital signs throughout clinical practice.

COMPETING INTERESTS

Nothing to declare

AUTHORS' CONTRIBUTIONS AND ACKNOWLEDGEMENTS

This protocol was prepared by LL and PW. All authors contributed to the design of the methodology and analysis plan and have reviewed the final manuscript.

The authors would also like to acknowledge Tatjana Petrinic, Oxford University Health Care Libraries, University of Oxford, for help with designing the initial search strategy.

FUNDING STATEMENT

The NIHR Biomedical Research Centre, Oxford, UK, supported this work. LL and RP were supported by the RCUK Digital Economy Programme grant number EP/G036861/1 (Oxford Centre for Doctoral Training in Healthcare Innovation) and the Clarendon Fund (LL only).

COMPETING INTERESTS STATEMENT

No competing interests to declare.

REFERENCES

[1] Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ. on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–12. Oxford, UK: National Perinatal Epidemiology Unit, University of Oxford; 2014.

[2] Isaacs RA, Wee MYK, Bick DE, Beake S, Sheppard ZA, Thomas S, et al. A national survey of obstetric early warning systems in the United Kingdom: five years on. Anaesthesia 2014;69(7):687-692.

[3] Chamberlain G., Pipkin, FB. Clinical Physiology in Obstetrics. 3rd ed. Oxford, UK: Blackwell Science; 1998.

[4] McGlennan AP, Sherratt K. Charting change on the labour ward. Anaesthesia 2013;68(4):338-342.

[5] Smith GB, Prytherch DR, Schmidt PE, Featherstone PI, Higgins B. A review, and performance evaluation, of single-parameter "track and trigger" systems. Resuscitation 2008 10;79(1):11-21.

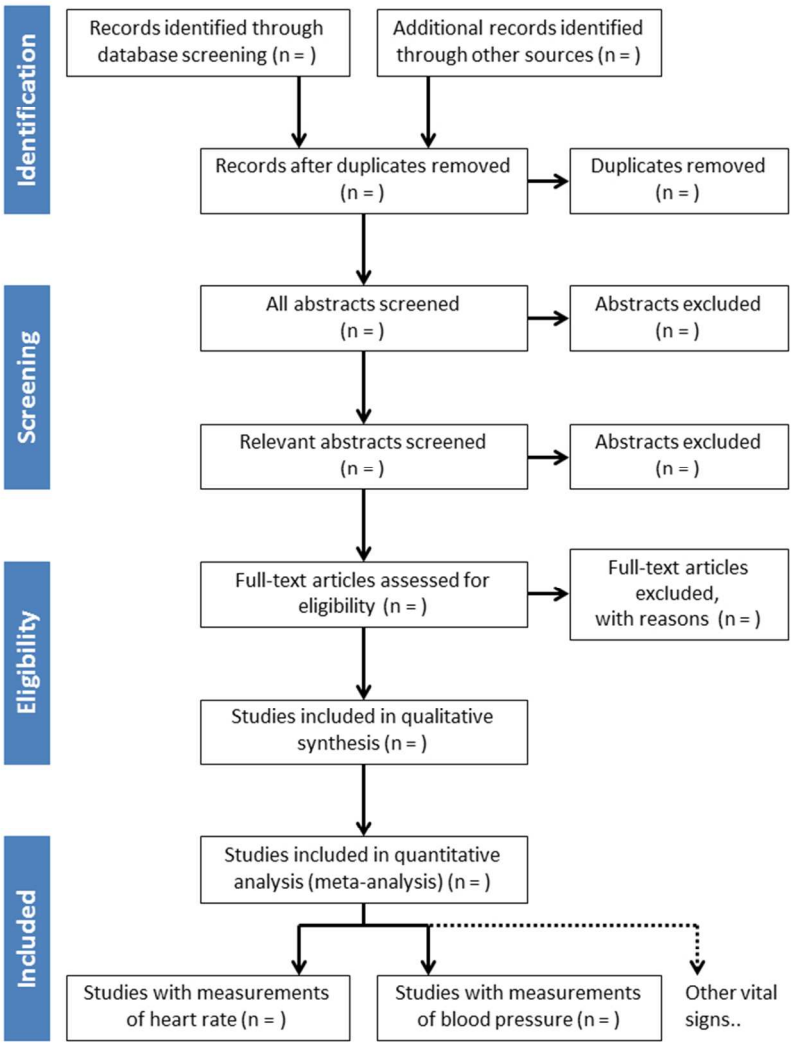
[6] Smith GB, Prytherch DR, Schmidt PE, Featherstone PI. Review and performance evaluation of aggregate weighted 'track and trigger' systems. Resuscitation 2008 5;77(2):170-179.

[7] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, the PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 349: g7647

[8] Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Annals of Internal Medicine 2011;155:529-536.

[9] Ioannou C, Talbot K, Ohuma E, Sarris I, Villar J, Conde-Agudelo A, et al. Systematic review of methodology used in ultrasound studies aimed at creating charts of fetal size. BJOG 2012;119(12):1425-1439.

[10] HDRO (Human Development Report Office). Sustaining Human Progress: Reducing Vulnerabilities and Building Resilience. United Nations Development Programme, New York, USA, 2014. Retrieved 26 February 2015.



The study selection process, here illustrated by a PRISMA flow diagram

APPENDICES

Appendix 1 – Inclusion and exclusion criteria

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Cross-sectional, case-control or longitudinal study	Measurements from women with illnesses likely to affect the cardiac or respiratory systems
Minimum of 50 patients	Measurements from women with risk factors for developing complications
Age 14 years or older	Measurements from women known to be taking medication which could affect the measurements
Objective measurement[1] of heart rate, blood pressure, respiratory rate, oxygen saturation or temperature	Measurements from women where the reported gestational age at the point of measurement not defined in terms of days or weeks of gestation
Measurements taken during the antenatal period, up to the start of the intrapartum period[2]	Measurements from women where the reported period of gestation exceeded 16 weeks
Raw data or average measure reported and possible to extract within minimum accuracy	Measurements from self-monitoring or other measurements not taken by a healthcare professional
	Measurements from women with less than 10% singleton pregnancies
	For women known to undergo fertility procedures, any measurements taken prior to a positive pregnancy test
	Any of the following measurements (without valid baseline): • Measurements taken using ambulatory technologies • Measurements taken using invasive technologies • Measurements taken during anesthesia • Measurements taken during sleep • Measurements taken during exercise • Measurements taken at heights greater than 1000m above sea level

[1] *An overview of acceptable measurement techniques is provided in Table 2*
[2] *Defined as progressive cervical dilatation with regular contractions*

Table 2: Acceptable methods of measurement

Vital sign	Acceptable methods	Not acceptable methods	Minimum accuracy when presented in graph
Blood pressure	Non-invasive cuff Korotkoff sounds	Intra-arterial Echocardiography Impedance cardiography	2 mm Hg
Heart rate	Pulse oximeter Blood pressure monitor Electrocardiography	–	2 beats minute^{-1}
Oxygen saturation	Non-invasive pulse oximeter	Blood gas analysis	1%
Temperature	Oral Tympanic Auxiliary Forehead Rectal	Intrauterine Other invasive methods	0.1 ^{o}C
Respiratory rate	Count by viewing Count by stethoscope	Impedance pneumography	1 beat minute^{-1}

Appendix 2 – Search terms

A draft search strategy is presented in Table 1. It has been designed with assistance of a qualified librarian in the Oxford University Health Care Libraries, following an initial search by two reviewers (LL and RP), review of the findings of the initial search with clinicians (PW and LM) and adjustment to improve detection of papers known to us.

Table 3: Search criteria

Population	Physiological variables	Measurement
pregnan*.ti; maternal.ti; obstetric*.ti; "expectant mother*".ti; "expecting mother*".ti; peripartum.ti; "peri partum".ti; antepartum.ti; "ante partum".ti; postpartum.ti; "post partum".ti; intrapartum.ti; "intra partum".ti; puerperium.ti; trimester*.ti; perinatal*.ti; antenatal*.ti; postnatal*.ti	"vital sign*".ti; "early warning".ti; EWS*.ti; *"modified early obstetric warning".ti;* *score*.ti;* *MEOWS.ti;* *chart*.ti* physiolog*.ti; haemodynam*.ti; hemodynam*.ti; normogram*.ti; "heart rate*".ti; "pulse rate*".ti; "pulse oximetry".ti; "oxygen saturation*".ti; SpO2.ti; Sp02.ti; "blood pressure*".ti; (temperature AND body).ti; "respirat* rate*".ti; *"breath* rate*".ti;* *temperature*.ti;* *breath*.ti;* *respirat*.ti;* *"cardiac rate*".ti;* *oximetry.ti;*	trend*.ti; pattern*.ti; range*.ti; change*.ti; measur*.ti; monitor*.ti; record*.ti; assess*.ti; evaluat*.ti; observ*.ti; guidance.ti; guideline*.ti; technique*.ti; method*.ti; systematic*.ti; Chart*

Limits applied to search:

- Human subjects
- Databases: Medline, Embase, CINAHL
- Publication date: Database inception – April 2015
- Abstract available in English
- Journal papers only (exclude reviews, letters, comments, editorials, conference papers)

Appendix 3 – Rules for selection of vital sign measurements

To avoid overrepresentation, the following rules for selection of a single data point have been agreed:

1. Where measurements are recorded in different positions, measurements made in the seated position (or position closest to it) will be recorded, according to the hierarch of positions by the European Hypertension Society.[A1] For blood pressure, only measurements made in the sitting or left lateral positions (or close to it) will be recorded.
2. When more than one baseline measurement is reported, the first reported measurement will be recorded.
3. Where measurements are recorded at different times of day, the measurements closest to midday will be recorded.
4. Where measurement methods are compared to a non-invasive gold standard the gold standard measurement will be used.
5. Where Korotkoff stage 4 and 5 diastolic blood pressures are reported, stage 5 will be recorded in line with the European Hypertension Society guidelines.[A1]
6. Where vital signs are reported both in the form of empirical and modeled values, empirical values will be used.
7. Where data are reported for several variations of subgroups, longitudinally measured data will be prioritised over single data points, even if this will involve excluding measurements from certain subgroups.

These rules were developed to ensure that data are relevant to normal clinical practice for intermittent observations undertaken by clinicians.

REFERENCES FOR APPENDIX

[A1] O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. Journal of Hypertension 2003; 21(5): 821-848

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2/3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2/3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3/4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	12
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4/5 + fig
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6/7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	n/r
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	n/r
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/r
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/r
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/r
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/r
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/r
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	n/r
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	n/r
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	n/r
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	7

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

BMJ Open

Trends of vital signs with gestational age in normal pregnancies: A systematic review protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-008769.R2
Article Type:	Protocol
Date Submitted by the Author:	10-Nov-2015
Complete List of Authors:	Loerup, Lise; University of Oxford, Department of Engineering Science Pullon, Rebecca; University of Oxford, Department of Engineering Science Birks, Jacqueline; University of Oxford, Centre for Statistics in Medicine Fleming, Susannah; University of Oxford, Nuffield Department of Primary Care Health Sciences MacKillop, Lucy; Oxford University Hospitals NHS Trust, Nuffield Department of Obstetrics & Gynaecology Watkinson, Peter; Oxford University Hospitals NHS Trust, Nuffield Department of Clinical Neurosciences
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Evidence based practice, Health informatics, Intensive care
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Maternal medicine < OBSTETRICS

TRENDS OF VITAL SIGNS WITH GESTATIONAL AGE IN NORMAL PREGNANCIES: A SYSTEMATIC REVIEW PROTOCOL

Authors:
Lise Loerup
Department of Engineering Science, University of Oxford, Oxford, UK

Rebecca M. Pullon
Department of Engineering Science, University of Oxford, Oxford, UK

Jacqueline Birks
Centre for Statistics in Medicine, University of Oxford, Oxford, UK

Susannah Fleming
Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

Lucy H. Mackillop
Nuffield Department of Obstetrics & Gynaecology, Oxford University Hospitals NHS Trust, Oxford, UK

Peter J. Watkinson
Nuffield Department of Clinical Neurosciences, Oxford University Hospitals NHS Trust, Oxford, UK

Corresponding author:
Lise Loerup

Postal address: Institute of Biomedical Engineering, Old Road Campus Research Building, Off Roosevelt Drive, Headington, Oxford, OX3 7DQ, UK

Email: lise.loerup@eng.ox.ac.uk

Phone: +44 (0)7734341661

Key words (max. 5, preferably MeSH terms):
Pregnancy (MeSH), vital signs (MeSH), maternal physiology, modified obstetric early warning score

Word count (excluding title page, abstract, references, figures and tables):
1,999 words

ABSTRACT

Introduction: Vital signs (blood pressure, heart rate, temperature, oxygen saturation and respiratory rate) are thought to undergo changes during and immediately after pregnancy. However, these physiological changes are not taken into account in the normal ranges, which themselves are not evidence-based, used in routine and acute care monitoring. We aim to synthesise the existing evidence base for changes in vital signs during pregnancy derive new centile charts for each stage of pregnancy and the immediate post-partum period.

Methods and analysis: We will search the MEDLINE, EMBASE and CINAHL databases from their inception to April 2015 for vital signs from pregnant, intrapartum or postpartum women who were recruited as "healthy". Assessment of bias will be conducted using a predefined set of independently agreed methodological criteria, which assigns an overall quality score to each study. Whether vital signs measurement was undertaken with measurement devices validated for use in pregnancy and in a standard posture will be recorded. We will use regression methods to construct centile charts of vital signs across pregnancy and the immediate postpartum period for each vital sign. We will compare existing reference ranges to those derived from our centile charts.

Dissemination: The systematic review will be published in a peer-reviewed journal and disseminated electronically and in print.

Registration reference: PROSPERO, registration number CRD42014009673.

Strengths and limitations of this study

Strengths

- This is the first review to synthesise the evidence base of vital sign changes during pregnancy, taking into account the gestational age.

Limitations

- The quality of published information may limit the study findings
- Combining different methods of measurement of the same vital sign may prove difficult

INTRODUCTION

Rationale

Heart rate, blood pressure, respiratory rate, oxygen saturations and temperature are key vital signs used to assess the clinical status of women presenting acutely throughout pregnancy, intrapartum, during anaesthesia and in the early postpartum period. The perceived normal ranges of these vital signs underpin modified early obstetric warning scores developed to assist in early recognition of deterioration.[1,2] Using these vital signs to detect physiological deterioration is complicated by the normal dynamic changes in maternal vital sign physiology that occur both during pregnancy and immediately after delivery. In the case of modified early obstetric warning scores, they define the thresholds that determine if a woman requires review.

Yet currently, normal ranges are either not referenced, or reference a core textbook (which references data from small individual studies published between 1970 and the mid-1990s).[3] None of the clinical guidelines take account of expected changes in different stages of pregnancy, intrapartum and the early postpartum period. The evidence underpinning current guidance is therefore weak, and thresholds used in clinical practice to detect physiological deterioration appear to be adapted from those established for the non-pregnant population or based on clinical consensus.[1,4] As apparently small changes in thresholds make substantial differences to the ability of clinical scores to identify physiological deterioration,[5,6] accurate reference ranges that take into account changes for each stage of pregnancy, the intrapartum and early postpartum periods, are essential to using vital signs to provide high quality clinical care.

As vital signs are commonly recorded at a particular stage of pregnancy in many different types of clinical studies, large quantities of data may already be available to inform these vital sign thresholds.

Objectives

We aim to report on existing gestation-specific centiles for vital signs in pregnancy, intrapartum and the early postpartum period using studies of women recruited as "healthy", who undertook vital sign measurements using non-invasive techniques used by health care professionals. We will compare the reported centiles with existing reference ranges for each stage of pregnancy, intrapartum and the postpartum period. If the collected data allow, we will attempt to synthesise the reported vital sign data to develop new gestation-specific centile charts.

METHODS

Registration reference

This systematic review has been registered on PROSPERO (registration number CRD42014009673).

Criteria for inclusion of studies in this review

Types of studies

Prospective and retrospective longitudinal, cross-sectional and case control studies and randomized control trials will be included.

Types of participants

Pregnant women aged 14 years or older, with singleton, normal pregnancies and without illnesses likely to affect the cardiac or respiratory systems will be included.

Types of measurements

We will include objective measurement of heart rate, respiratory rate, blood pressure, oxygen saturations or temperature, taken from the start of the antenatal period (early pregnancy) up to two weeks postpartum. Self-monitoring or other measurements not taken by a healthcare professional, or measurements taken using invasive measurement techniques, will not be included. Gestational age at which the measurements were taken must be reported.

A complete list of inclusion and exclusion criteria has been included in Appendix Table 1, together with a list of acceptable measurement techniques in Appendix Table 2.

Types of outcome measures

Primary outcome measures

Where centiles are presented, we will report these for each gestational age. Otherwise, where data are not presented as centiles but a sufficient amount of data are available, we will calculate the median and representative centiles (1^{st}, 10^{th}, 25^{th}, 75^{th}, 90^{th}, 99^{th}) for changes in vital signs with respect to gestational age using data from each included study, subject to assessment of normal distributions of vital sign data.

Secondary outcome measures

A quality assessment will be performed and a score for the risk of bias for each study will be reported.

Where subgroup analyses suggest that the subgroups have clinically different centile distributions, we will, where sufficient data exist, present subgroup-specific centile-distributions.

Search methods for identifying the studies

Electronic searches

Three databases will be searched, from their inception until April 2015: MEDLINE (1950– April 2015), EMBASE (1980–April 2015), CINAHL (1982– April 2015). Specific search strategies will be developed for each database between clinicians and a qualified librarian from the Oxford University Healthcare Libraries, who will carry out the search. The strategies will use both MeSH terms and free text with no language restrictions. An example search strategy is shown in Appendix Table 3.

Searching other sources

We will perform non-electronic searches of our own files of articles and of the reference lists of all included studies to identify studies not captured in the initial electronic search.

Identification of reference guidelines

PW and LM will identify sources of existing reference ranges by reviewing obstetric, physiology and anaesthetic textbooks, international guidelines, standardised clinical training courses and maternal early warning scores to mirror the likely exposure of clinicians to reference ranges.

Data collection

Study selection

The retrieved titles and, where available, abstracts will be reviewed by two reviewers (LL and RP) to exclude studies that clearly fall outside the scope of the review, such as fetal studies or studies not performed on humans. Following this initial sift, the remaining titles and, where available, abstracts will be assessed by two reviewers (PW and LM) against the inclusion and exclusion criteria. The full texts of all potentially relevant articles will be retrieved for data extraction where appropriate. Figure 1 shows a PRISMA flow diagram [7] that summarises the study selection process.

Assessment of bias and heterogeneity

A quality assessment of studies that meet our inclusion and exclusion criteria will be performed independently by two reviewers. Disagreements will be resolved by recourse to the original data. The quality assessment will be undertaken in line with the QUADAS-2 assessment,[8] following the methodology of Ioannou et al. (2012).[9] This assessment has been designed to evaluate the methodological quality of observational studies, performed with pregnant subjects. Where required, the specific assessment criteria will be adapted for our purpose. Results of this quality assessment, which assigns an overall quality score to each study, will be presented in tabular and graphical form.

Data extraction and management

Two reviewers will independently perform data extraction (LL and RP). Data will be extracted into a pre-piloted electronic spreadsheet (Microsoft ExCel). Disagreements will be resolved by recourse to the original data. Data will be extracted from tables, text or graphs. Appropriate software will be used to ensure accurate transcription of data from graphs, subject to predefined criteria to resolution of graphically presented data as defined in Appendix Table 2. For each period of pregnancy defined in a paper, the number of women in the group will be extracted, along with the following statistical data about the vital signs of interest (blood pressure, heart rate, temperature, oxygen saturation or respiratory rate), where reported:

- Mean value
- Median value
- Standard deviation
- Centiles, percentiles, quartiles etc.
- Confidence intervals
- Standard error of the mean

The period of pregnancy will be extracted as weeks of gestation and the method used to determine gestational age will be recorded. Data for a given period of pregnancy that are reported separately, for example for different ethnic groups or subgroups defined based on a medical diagnosis, will be classified independently. Data from subgroups with a medical diagnosis that could affect their measurement will only be included if the women are described as healthy at the start of the study. When multiple measurements at the same time point are reported for a single physiological variable (for example lying and sitting heart rates), a single data point will be selected to avoid over-representation using the pre-specified rules summarized in Appendix 3.

In addition, the following data will be extracted from each included paper, if the data are present: date of the study; period of data collection; demographic information about participants (age range, weight, BMI, ethnicity, reason for measurements); details of pregnancy (parity, number of gestations); country of study (with subsequent assignment to economic development status, according to the UNDP Human Development Index [10]); study setting and details of measurement (subject position, method of measurement, device details).

Data extraction from papers of a different language

In order to extract data from studies published in a language other than English, assistance will be sought from people within our research groups (preferably with a medical background) with native proficiency in the relevant language. Data from such studies will be extracted in consultation with one of the two reviewers (LL or RP).

Dealing with missing data

In cases where relevant data have not been adequately reported, or presented in a format that is not suitable for extraction, the original authors will be contacted and the data requested. We will in the first instance use contact details from the original paper, but where these are no longer valid, contact details will be sought from more recent publications on PubMed, from institutional websites or through general online search engines. Authors will be contacted twice; initially a request for data will be sent via electronic mail, and if no response is received after 4 weeks, authors will be contacted a second time.

Data analysis

Data synthesis

We will analyse cross sectional and longitudinal studies separately and pool the vital sign data if appropriate.

Cross sectional studies

Each cross sectional study will provide a mean response at one or more accurately known gestational age time points. Where a study reports cross-sectional measurements at multiple gestational ages (multiple samples from the same population) the data points will be treated as independent because each subject only contributes one assessment.

Assuming no significant heterogeneity between studies, the centiles and other statistics for each value of gestational age will be reported. If possible, the analysis will pool results from the studies using regression techniques. Where potential confounding factors are reported, such as BMI, malnutrition, and hemoglobin values, we will consider incorporating these factors in a meta-regression. Each study will contribute mean of vital signs and gestational age, taking into account differences in population size. The mean response curve as a function of gestational age will be estimated. If the relationship between the response and gestational age does not appear to have a functional form other non-parametric methods of curve fitting will be used.

Longitudinal studies

A longitudinal study measures the response at several time points for each participant. The set of time points may be unique for each participant or identical across participants. The mean response curve over time for each study will be presented graphically, with the equation if a parametric method was used and the equation is reported.

Sensitivity analysis

If there is significant heterogeneity at any time point sensitivity analyses will be attempted by dropping outlying studies from the analysis.

Subgroup analysis

Where data are available, we will attempt to conduct the following subgroup analyses:

- BMI (or weight) class
- Ethnicity
- Development status of country of study
- Parity
- Position of measurement
- The method of measurement (for example blood pressure device)
- Measurement setting
- The year of assessment
- Pregnancy complications

DISCUSSION

This systematic review will summarise the current state of evidence for trends in maternal physiology in pregnancy. Where sufficient data are available, centile charts of vital sign longitudinally in pregnancy, intrapartum and the post-partum period will be derived. The knowledge of normal distributions of such data in a low-risk population of women for a *particular stage of pregnancy* is an essential pre-requisite both to the development of an evidence-based Modified Early Obstetric Warning Score (MEOWS) and for best practice use of these vital signs throughout clinical practice.

AUTHORS' CONTRIBUTIONS AND ACKNOWLEDGEMENTS

This protocol was prepared by LL and PW. All authors contributed to the design of the methodology and analysis plan and have reviewed the final manuscript.

The authors would also like to acknowledge Tatjana Petrinic, Oxford University Health Care Libraries, University of Oxford, for help with designing the initial search strategy.

FUNDING STATEMENT

The NIHR Biomedical Research Centre, Oxford, UK, supported this work. LL and RP were supported by the RCUK Digital Economy Programme grant number EP/G036861/1 (Oxford Centre for Doctoral Training in Healthcare Innovation) and the Clarendon Fund (LL only).

COMPETING INTERESTS STATEMENT

No competing interests to declare.

REFERENCES

[1] Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ. on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–12. Oxford, UK: National Perinatal Epidemiology Unit, University of Oxford; 2014.

[2] Isaacs RA, Wee MYK, Bick DE, Beake S, Sheppard ZA, Thomas S, et al. A national survey of obstetric early warning systems in the United Kingdom: five years on. Anaesthesia 2014;69(7):687-692.

[3] Chamberlain G., Pipkin, FB. Clinical Physiology in Obstetrics. 3rd ed. Oxford, UK: Blackwell Science; 1998.

[4] McGlennan AP, Sherratt K. Charting change on the labour ward. Anaesthesia 2013;68(4):338-342.

[5] Smith GB, Prytherch DR, Schmidt PE, Featherstone PI, Higgins B. A review, and performance evaluation, of single-parameter "track and trigger" systems. Resuscitation 2008 10;79(1):11-21.

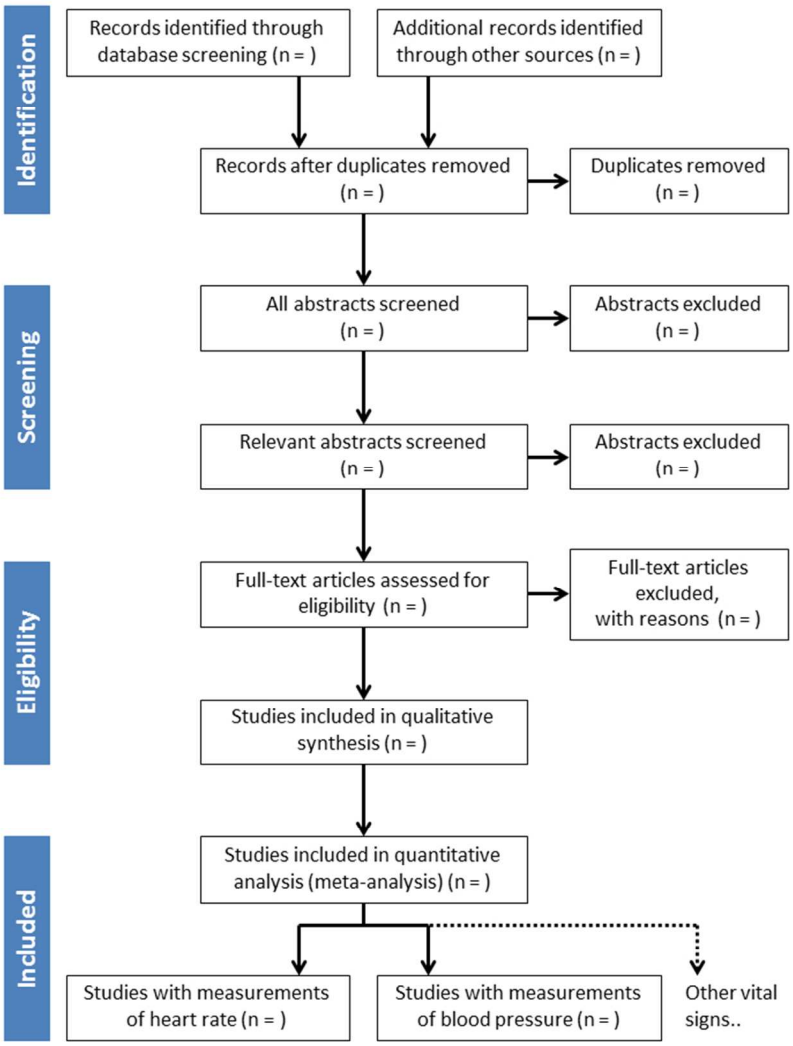
[6] Smith GB, Prytherch DR, Schmidt PE, Featherstone PI. Review and performance evaluation of aggregate weighted 'track and trigger' systems. Resuscitation 2008 5;77(2):170-179.

[7] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, the PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 349: g7647

[8] Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Annals of Internal Medicine 2011;155:529-536.

[9] Ioannou C, Talbot K, Ohuma E, Sarris I, Villar J, Conde-Agudelo A, et al. Systematic review of methodology used in ultrasound studies aimed at creating charts of fetal size. BJOG 2012;119(12):1425-1439.

[10] HDRO (Human Development Report Office). Sustaining Human Progress: Reducing Vulnerabilities and Building Resilience. United Nations Development Programme, New York, USA, 2014. Retrieved 26 February 2015.



The study selection process, here illustrated by a PRISMA flow diagram

APPENDICES

Appendix 1 – Inclusion and exclusion criteria

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Cross-sectional, case-control or longitudinal study	Measurements from women with illnesses likely to affect the cardiac or respiratory systems
Minimum of 50 patients	Measurements from women with risk factors for developing complications
Age 14 years or older	Measurements from women known to be taking medication which could affect the measurements
Objective measurement[1] of heart rate, blood pressure, respiratory rate, oxygen saturation or temperature	Measurements from women where the reported gestational age at the point of measurement not defined in terms of days or weeks of gestation
Measurements taken during the antenatal period, up to the start of the intrapartum period[2]	Measurements from women where the reported period of gestation exceeded 16 weeks
Raw data or average measure reported and possible to extract within minimum accuracy	Measurements from self-monitoring or other measurements not taken by a healthcare professional
	Measurements from women with less than 10% singleton pregnancies
	For women known to undergo fertility procedures, any measurements taken prior to a positive pregnancy test
	Any of the following measurements (without valid baseline): • Measurements taken using ambulatory technologies • Measurements taken using invasive technologies • Measurements taken during anesthesia • Measurements taken during sleep • Measurements taken during exercise • Measurements taken at heights greater than 1000m above sea level

[1] *An overview of acceptable measurement techniques is provided in Table 2*
[2] *Defined as progressive cervical dilatation with regular contractions*

Table 2: Acceptable methods of measurement

Vital sign	Acceptable methods	Not acceptable methods	Minimum accuracy when presented in graph
Blood pressure	Non-invasive cuff Korotkoff sounds	Intra-arterial Echocardiography Impedance cardiography	2 mm Hg
Heart rate	Pulse oximeter Blood pressure monitor Electrocardiography	–	2 beats minute^{-1}
Oxygen saturation	Non-invasive pulse oximeter	Blood gas analysis	1%
Temperature	Oral Tympanic Auxiliary Forehead Rectal	Intrauterine Other invasive methods	0.1 ^{o}C
Respiratory rate	Count by viewing Count by stethoscope	Impedance pneumography	1 beat minute^{-1}

Appendix 2 – Search terms

A draft search strategy is presented in Table 1. It has been designed with assistance of a qualified librarian in the Oxford University Health Care Libraries, following an initial search by two reviewers (LL and RP), review of the findings of the initial search with clinicians (PW and LM) and adjustment to improve detection of papers known to us.

Table 3: Search criteria

Population	Physiological variables	Measurement
pregnan*.ti; maternal.ti; obstetric*.ti; "expectant mother*".ti; "expecting mother*".ti; peripartum.ti; "peri partum".ti; antepartum.ti; "ante partum".ti; postpartum.ti; "post partum".ti; intrapartum.ti; "intra partum".ti; puerperium.ti; trimester*.ti; perinatal*.ti; antenatal*.ti; postnatal*.ti	"vital sign*".ti; "early warning".ti; EWS*.ti; *"modified early obstetric warning".ti;* *score*.ti;* *MEOWS.ti;* *chart*.ti* physiolog*.ti; haemodynam*.ti; hemodynam*.ti; normogram*.ti; "heart rate*".ti; "pulse rate*".ti; "pulse oximetry".ti; "oxygen saturation*".ti; SpO2.ti; Sp02.ti; "blood pressure*".ti; (temperature AND body).ti; "respirat* rate*".ti; *"breath* rate*".ti;* *temperature*.ti;* *breath*.ti;* *respirat*.ti;* *"cardiac rate*".ti;* *oximetry.ti;*	trend*.ti; pattern*.ti; range*.ti; change*.ti; measur*.ti; monitor*.ti; record*.ti; assess*.ti; evaluat*.ti; observ*.ti; guidance.ti; guideline*.ti; technique*.ti; method*.ti; systematic*.ti; Chart*

Limits applied to search:

- Human subjects
- Databases: Medline, Embase, CINAHL
- Publication date: Database inception – April 2015
- Abstract available in English
- Journal papers only (exclude reviews, letters, comments, editorials, conference papers)

Appendix 3 – Rules for selection of vital sign measurements

To avoid overrepresentation, the following rules for selection of a single data point have been agreed:

1. Where measurements are recorded in different positions, measurements made in the seated position (or position closest to it) will be recorded, according to the hierarch of positions by the European Hypertension Society.[A1] For blood pressure, only measurements made in the sitting or left lateral positions (or close to it) will be recorded.
2. When more than one baseline measurement is reported, the first reported measurement will be recorded.
3. Where measurements are recorded at different times of day, the measurements closest to midday will be recorded.
4. Where measurement methods are compared to a non-invasive gold standard the gold standard measurement will be used.
5. Where Korotkoff stage 4 and 5 diastolic blood pressures are reported, stage 5 will be recorded in line with the European Hypertension Society guidelines.[A1]
6. Where vital signs are reported both in the form of empirical and modeled values, empirical values will be used.
7. Where data are reported for several variations of subgroups, longitudinally measured data will be prioritised over single data points, even if this will involve excluding measurements from certain subgroups.

These rules were developed to ensure that data are relevant to normal clinical practice for intermittent observations undertaken by clinicians.

REFERENCES FOR APPENDIX

[A1] O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. Journal of Hypertension 2003; 21(5): 821-848

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			**n/r = not relevant**
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	cover
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/r
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Abstract & 2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	cover
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	6
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/r
Support:			
Sources	5a	Indicate sources of financial or other support for the review	6
Sponsor	5b	Provide name for the review funder and/or sponsor	6
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	6
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	1
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2-3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	2-3
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be	appendix

		repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4-6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4-6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6 + appendix
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5-6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5-6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	6-7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5-6**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/r**

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

**Comments:

16. We have adressed selective reporting by considering the drop-out rates within studies (i.e. the number analysed compared to the number recruited) as part of our quality assessment. It is not possible to assess publication bias using a funnel plot or similar for this type of meta-analysis.

17. This is not appropriate for this type of meta-analysis.