

Gestation-Specific Vital Sign Reference Ranges in Pregnancy

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OBJECTIVE: To estimate normal ranges for maternal vital signs throughout pregnancy, which have not been well defined in a large contemporary population.

METHODS: We conducted a three-center, prospective, longitudinal cohort study in the United Kingdom from August 2012 to September 2017. We recruited women at less than 20 weeks of gestation without significant comorbidities with accurately dated singleton pregnancies. We measured participants' blood pressure (BP), heart rate, respiratory rate, oxygen saturation and temperature following standardized operating procedures at 4–6 weekly intervals throughout pregnancy.

RESULTS: We screened 4,279 pregnant women, 1,041 met eligibility criteria and chose to take part. Systolic and diastolic BP decreased slightly from 12 weeks of gestation: median or 50th centile (3rd–97th centile) 114 (95–138); 70 (56–87) mm Hg to reach minimums of 113 (95–136); 69 (55–86) mm Hg at 18.6 and 19.2 weeks of gestation, respectively, a change (95% CI) of -1.0 (-2 to 0); -1 (-2 to -1) mm Hg. Systolic and diastolic BP then rose to a maximum median (3rd–97th centile) of 121 (102–144); 78 (62–95) mm Hg at 40 weeks of gestation, a difference (95% CI) of 7 (6–9) and 9 (8–10) mm Hg, respectively. The median (3rd–97th centile) heart rate

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Each author has confirmed compliance with the journal's requirements for authorship.

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was lowest at 12 weeks of gestation: 82 (63–105) beats per minute (bpm), rising progressively to a maximum of 91 (68–115) bpm at 34.1 weeks. SpO₂ decreased from 12 weeks of gestation: median (3rd–97th centile) 98% (94–99%) to 97% (93–99%) at 40 weeks. The median (3rd–97th centile) respiratory rate at 12 weeks of gestation was 15 (9–22), which did not change with gestation. The median (3rd–97th centile) temperature at 12 weeks of gestation was 36.7 (35.6–37.5)°C, decreasing to a minimum of 36.5 (35.3–37.3)°C at 33.4 weeks.

CONCLUSION: We present widely relevant, gestation-specific reference ranges for detecting abnormal BP, heart rate, respiratory rate, oxygen saturation and temperature during pregnancy. Our findings refute the existence of a clinically significant BP drop from 12 weeks of gestation.

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Successive inquiries into maternal deaths call for an evidence-based early warning score to facilitate earlier recognition and treatment of the unwell pregnant woman.^{1–4} Recognition is complicated by the normal physiologic changes in vital signs during pregnancy.¹ Changes in normal ranges for blood pressure (BP) through pregnancy have been derived from routinely collected data—which may be biased by the reason for collection.⁵ Blood pressure trends without normal ranges have been investigated in smaller studies.⁶ Substantially fewer data exist for heart rate,^{7–11} temperature,^{12,13} respiratory rate^{14,15} and oxygen saturation^{14,16} patterns during pregnancy.

Parameters recommended internationally for normal ranges of vital signs in pregnancy ([United Kingdom, Confidential Enquiry into Maternal and Child Health¹; Ireland, Irish Maternity Early Warning System¹⁷; United States, National Partnership for Maternal Safety¹⁸]) and thresholds used for modified obstetric early warning scores^{19–22} are not gestation-specific or evidence-based, but based on expert opinion with wide local, national and international variation.

Using robust estimates of the outer centiles of vital sign distributions to generate early warning scores is reliable in nonpregnant adults.^{23,24} The approach may be particularly useful for pregnancy, where event rates are low. However, there are insufficient published data to generate evidence-based, gestation-specific reference ranges for vital signs.²⁵

A large-scale, contemporary prospective data set of vital signs in pregnancy is needed to provide gestation-specific normal ranges for use in clinical

practice. We included a pragmatic population, representative of women who would be monitored using a modified obstetric early warning score system derived from the normal vital sign ranges obtained.

The primary objective of the Pregnancy Physiology Pattern Prediction (4P) study was to develop a database of prospective vital sign measurements using standardized measurement techniques throughout pregnancy.²⁶ Estimates of population distributions and associated centiles were derived from this database. Secondary objectives of developing a centile-based early warning score and investigating new patterns in vital sign data will be explored in further work.

METHODS

This work is reported following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.²⁷ We registered the study (<https://doi.org/10.1186/ISRCTN10838017>). Detailed methods are reported in the published protocol²⁶ and in brief here. We conducted a multicenter, longitudinal, observational, cohort study across three centers in the United Kingdom. We collected vital sign data during the antenatal, intrapartum, and postnatal periods. Here we present data from the antenatal period.

Recruitment commenced in August 2012, and collection of vital sign data was completed in August 2017. The study started in Oxford as a substudy of the INTERBIO-21st Fetal Study, approved by Oxford South Central C Research Ethics Committee (REC):08/H0606/139,^{28,29} and then expanded to include two additional centers (Newcastle and London, South East Coast–Brighton and Sussex REC:14/LO/1312) continuing after completion of INTERBIO-21st (December 2015).

We approached women when they attended the ultrasound department or antenatal clinic at three university hospitals before 20 weeks of gestation. Women were eligible if they were aged 16 years or older, with a singleton pregnancy, and fell within category 1 of the American Society of Anesthesiologists' classification of physical status before pregnancy ("a normal healthy patient without any clinically important comorbidity and without clinically significant past or present medical history"³⁰). Gestational age was determined by ultrasound measurement of crown-rump length before 14 weeks of gestation. Full eligibility criteria can be found in Appendix 1, available online at <http://links.lww.com/AOG/B746>.

The primary outcome was gestation-specific reference ranges comprising centile distributions for vital

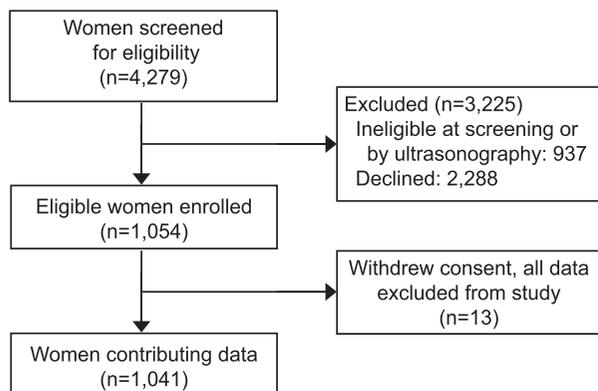


Fig. 1. Flowchart of participants through the study.

Green. Vital Sign Reference Ranges for Pregnancy. Obstet Gynecol 2020.

signs through pregnancy. We conducted sensitivity analyses to assess changes in performance of the sensors used to measure each vital sign over time. We assessed differences in methods for recording respiratory rate, agreement between two thermometers used and the effect of duplicate measurement.

We collected vital sign data at clinic visits every 4–6 weeks³¹ throughout pregnancy for five physiologic

parameters: BP, heart rate, SpO₂, temperature, and respiratory rate. We measured all vital signs following study standard operating procedures.²⁶ Blood pressure was measured with an automated BP monitor validated for use in pregnancy (Microlife 3BT0-A (2)/WatchBP Home). Heart rate and oxygen saturation were measured with a Bluetooth-enabled pulse oximeter (WristOx2 3150).

Temperature was measured with a tympanic thermometer (Genius 2). Temperature was also measured with a Bluetooth enabled tympanic thermometer (Fora IRb 20b) in the INTERBIO-21st subgroup. Respiratory rate was recorded using two different methods. Trained midwives observed chest wall movement over 15 seconds. From October 2015 onward, midwives also tapped in time with observed respiratory rate for 1 minute using bespoke software on an Android tablet. Research midwives entered vital sign data (or in the case of Bluetooth-enabled devices, automatically transmitted) onto a study-specific android tablet computer (Samsung Galaxy Tab 4.0²⁶).

We collected demographic information (age, height, weight, self-reported ethnicity, number of

Table 1. Baseline Maternal Characteristics

Characteristic	Study Center			
	Oxford (n=779 [74.8])	London (n=105 [10.1])	Newcastle (n=157 [15.1])	Total (N=1,041)
Age (y)	31.4±4.8	33.9±4.7	30.8±5.2	31.5±4.9
Weight (kg)	67.6±13.0	69.9±15.6	70.8±16.2	68.3±13.9
BMI (kg/m ²)	24.6±4.3	25.4±5.4	26±5.7	24.9±4.7
BMI category (kg/m ²)				
Normal (18.5–24.9)	467 (60.0)	63 (60.0)	81 (51.6)	611 (58.7)
Overweight (25.0–29.9)	220 (28.2)	22 (21.0)	43 (27.4)	285 (27.4)
Obese (30 or higher)	92 (11.8)	20 (19.0)	33 (21.0)	145 (13.9)
GA at first visit (wk)	12.6±2.5	14.4±2.4	15.2±1.0	13.1±2.4
Nulliparous	332 (42.6)	60 (57.1)	68 (43.3)	460 (44.2)
Ethnicity				
White	668 (85.8)	71 (67.6)	150 (95.5)	889 (85.4)
Asian	34 (4.4)	13 (12.4)	5 (3.2)	52 (5.0)
African or Caribbean	6 (0.8)	17 (16.2)	0 (0)	23 (2.2)
Mixed	14 (1.8)	3 (2.9)	1 (0.6)	18 (1.7)
Other	57 (7.3)	1 (1.0)	1 (0.6)	59 (5.7)
Smoker	62 (8.0)	6 (5.7)	11 (7.0)	79 (7.6)
Anemia*	3 (0.4)	3 (2.9)	1 (0.6)	7 (0.7)
Pregestational diabetes	2 (0.3)	1 (1.0)	3 (1.9)	6 (0.6)
Preexisting hypertension [†]	16 (2.1)	0 (0)	1 (0.6)	17 (1.6)
Cardiac disease [‡]	11 (1.4)	1 (1)	0 (0)	12 (1.2)
Preexisting renal disease	18 (2.3)	2 (1.9)	5 (3.2)	24 (2.3)

BMI, body mass index; GA, gestational age.

Data are mean±SD or n (%).

* Hb less than 110 g/L.

[†] Unmedicated.

[‡] Nonischemic noncongenital.

Table 2. Pregnancy Complications and Perinatal Outcomes

Complications and Outcomes	Study Center			Total (n=1,004)
	Oxford (n=762 [75.9])	London (n=96 [9.6])	Newcastle (n=146 [14.5])	
Gestational diabetes	26 (3.4)	4 (4.2)	8 (5.5)	38 (3.8)
Gestational hypertension	44 (5.8)	1 (1.0)	1 (0.7)	46 (4.6)
Preeclampsia	12 (1.6)	0 (0)	7 (4.8)	19 (1.9)
Severe preeclampsia, HELLP, eclampsia	2 (0.3)	0 (0)	3 (2.1)	5 (0.5)
Termination of pregnancy at less than 12 wk	0 (0)	0 (0)	0 (0)	0 (0)
Termination of pregnancy at more than 12 wk	3 (0.4)	0 (0)	0 (0)	3 (0.3)
Miscarriage at less than 12 wk	1 (0.1)	0 (0)	0 (0)	1 (0.1)
Late miscarriage 12–24 wk	8 (1)	1 (1.0)	0 (0)	9 (0.9)
Intrauterine death or stillbirth at more than 24 wk	3 (0.4)	0 (0)	0 (0)	3 (0.3)
Preterm delivery at less than 37 0/7 wk	50 (6.7)	4 (4.2)	13 (8.9)	67 (6.7)
Spontaneous vaginal birth	476 (63.6)	53 (56.4)	91 (64.5)	620 (59.6)
Assisted vaginal birth	133 (17.3)	14 (14.9)	11 (7.8)	158 (15.2)
Cesarean birth	138 (18.4)	28 (29.5)	39 (27.7)	205 (19.7)
Birth weight at 37 0/7 wk or more (g)	3,409±534	3,442±573	3,450±504	3,418±533
Term low birth weight (less than 2,500 g; 37 0/7 wk or more)	20/702 (2.8)	2/92 (2.2)	4/137 (2.9)	26/931 (2.8)

HELLP, hemolysis, elevated liver enzymes, low platelet count.
Data are n (%) or mean±SD.

previous pregnancies, smoking status), past medical and obstetric history, current health status, pregnancy-related health and current medications at the initial assessment. At each follow-up appointment we collected assessments of smoking status, current health status, pregnancy related health and current medications. We extracted medical and obstetric history from the participants' notes.

If participants did not respond to contact by research midwives during the study, they were treated as withdrawn after the third failed contact attempt. Data already collected from withdrawn participants were included in the final analysis, unless explicitly requested otherwise.

Trained research midwives undertook all antenatal observations and extracted all hospital data following study standard operating procedures. Research midwife coordinators performed frequent site visits to carry out midwife training and address any recruitment and equipment issues.

Vital sign measurements taken for the study were not included in the clinical record and were not communicated to the clinical team unless BP reached predefined values (systolic 140 mm Hg or higher or diastolic 90 mm Hg or higher) according to study standard operating procedures.

Duplicate measurements were recorded for a subset of participant visits to document the effect of using only the first recorded measurement for each vital sign parameter (as in clinical practice). To minimize

participant inconvenience, duplicate measurements were reviewed by study statisticians to decide when an adequate number of duplicate measurements had been collected.

Our sample size determination may be found in Appendix 2 (available online at <http://links.lww.com/AOG/B747>) and the published protocol.²⁶ In brief, a sample size of 1,000 women would achieve an SE of 0.05*SD at the 2.5 and 97.5 centiles, and even greater precision at the less extreme centiles. Adequate precision was also met for any subgroup analysis; for example, a sample size of 300 women would achieve an SE of 0.1*SD at the 2.5 and 97.5 centiles.

Vital sign data from all participants were included in the primary analysis. We constructed smoothed centiles for systolic and diastolic BP, heart rate, SpO₂, temperature and respiratory rate by gestational age. We constructed gestation-specific reference ranges comprising smoothed centiles for vital sign distribution (3rd, 10th, 50th, 90th and 97th as used by the World Health Organization Multicentre Growth Reference Study,^{32,33} with corresponding 95% CIs) for all women. We presented centiles from 12 to 40 weeks of gestation (because there were relatively few data at less than 12 and greater than 40 weeks of gestation) for each vital sign graphically and tabulated at fortnightly intervals, along with associated 95% CIs.

We used statistical methods to generate gestational age-specific centiles following those used in the INTERGROWTH-21st Project for fetal growth.^{34–37}

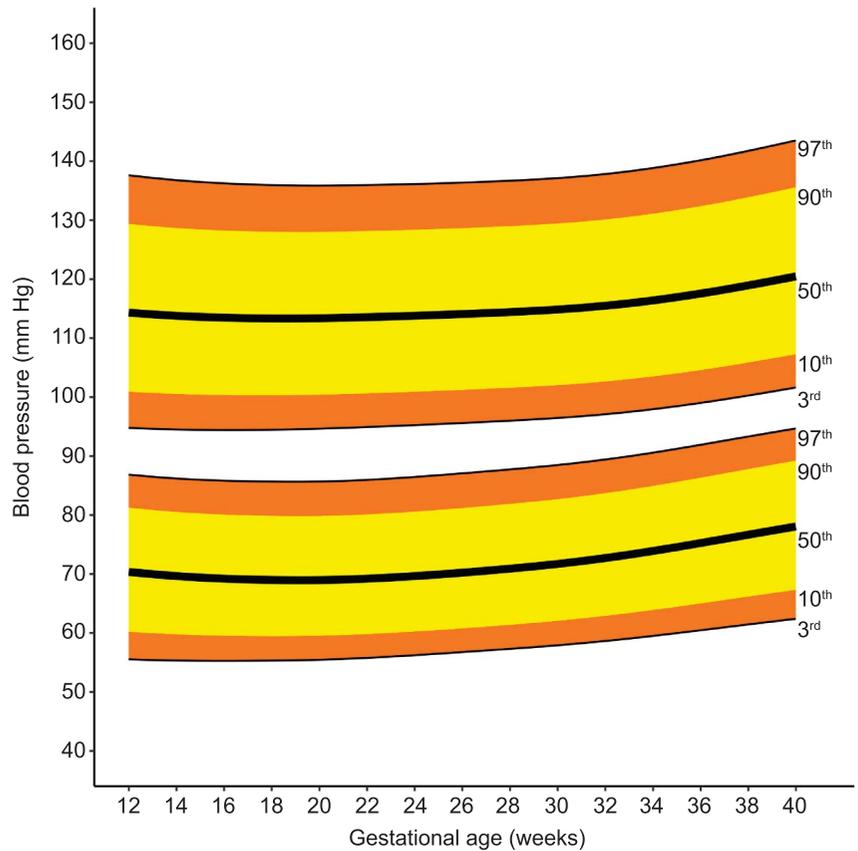


Fig. 2. Smoothed centiles for systolic blood pressure (*upper line and centiles*) and diastolic blood pressure (*lower line and centiles*) in mm Hg. Green. *Vital Sign Reference Ranges for Pregnancy. Obstet Gynecol 2020.*

Once enrolled, we did not exclude women who developed conditions that might affect their vital signs (to generate a pragmatic, representative sample of pregnant women, maximizing the clinical applicability of centiles generated). We explored different statistical methods to achieve the best fit to the data (see Appendix 2, <http://links.lww.com/AOG/B747>).

We expected some participants would become lost to follow-up or have missing measures. We included these participants in the analysis, unless all data were missing. We compared agreement between Fora and Genius thermometers using a Bland-Altman plot to assess whether it was possible to pool measures. We also compared data from the counting and tapping methods for recording respiratory rate before pooling.

We conducted sensitivity analyses to assess changes in sensor performance over time.

To explore whether limiting the population to those of optimal health would affect results, we defined a “restrictive” population of women aged younger than 40 years with body mass indexes (BMIs, calculated as weight in kilograms divided by height in meters squared) between 18.5 and 29.9, who did not smoke and did not have any medical comorbidities.

In this “restrictive” population, we excluded measures from women who developed a severe maternal condition during pregnancy (severe preeclampsia; hemolysis, elevated liver enzymes, and low platelet count [HELLP] syndrome; or eclampsia), from the time of diagnosis onward, in line with previous work.³⁸ We conducted a post hoc analysis using these definitions in comparison with the full “pragmatic” population.

To explore whether the small reduction in heart rate near term resulted from women with higher heart rates giving birth earlier, we conducted a post hoc analysis with all women who delivered at less than 37 weeks of gestation excluded. We undertook a prespecified subgroup analysis including only nulliparous women. Participants provided informed written consent and could withdraw from the study at any time.

RESULTS

We screened 4,279 women between August 1, 2012, and December 28, 2016, of whom 1,054 agreed to take part. Thirteen women subsequently withdrew consent for any data to be used and were excluded completely. This provided a total pragmatic study cohort of 1,041 women who contributed antenatal

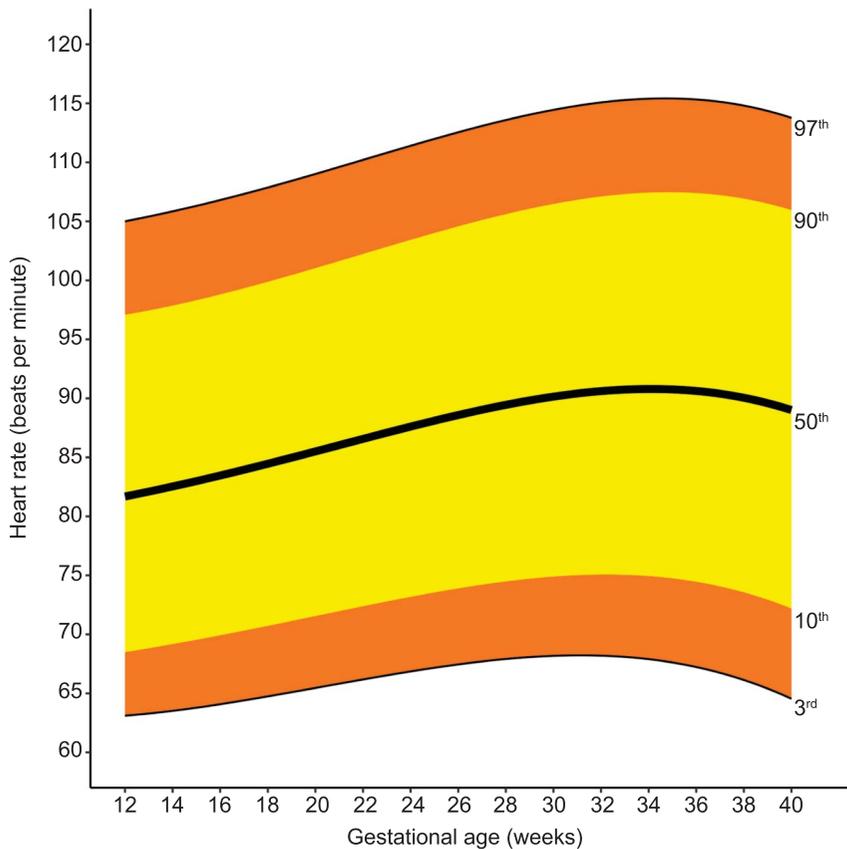


Fig. 3. Smoothed centiles for heart rate in beats per minute.

Green. *Vital Sign Reference Ranges for Pregnancy*. *Obstet Gynecol* 2020.

vital sign data (Fig. 1). Delivery information was unavailable for 37 women, who were either lost to follow-up (15 women) or discontinued participation (22 women) during the study period. Within this group, 36 women provided data at 12 weeks of gestation, 24 at 24 weeks, 12 at 28 weeks, and two at 32 weeks, beyond which they no longer participated.

Demographic characteristics of the study cohort were similar across sites (Table 1). Mean (SD) gestational age at the first antenatal visit was 13.2 (2.5) weeks; maternal age 31.5 (4.9) years, BMI 24.9 (4.7), and 44.2% (460/1,041) were nulliparous.

The median number of visits per woman where vital signs were taken was 6 (interquartile range 5–7). In total, vital sign data were recorded at 5,890 visits. Most women, (982/1,041, 94%) missed no more than one expected visit, with 926/1,041 (89%) always achieving expected visits within 6 weeks of each other (for baseline characteristics of women with missing visits see Appendix 3, available online at <http://links.lww.com/AOG/B748>). Blood pressure was recorded at nearly every visit (5,863/5,890), SpO₂ at 96% of visits (5,651/5,890) and respiratory rate at 91% of visits (5,370/5,890), using the tapping method

in 36% (2,125/5,890 from 477 women). Temperature was recorded at 97% of visits (5,742/5,890), using a Genius device at 93% (5,507/5,890) and a Fora device at 55% of visits (3,225/5,890). An abnormal BP recording necessitating referral to the woman's usual clinical team occurred at 0.2% of visits (11/5,863 observations; 10/1,041 women).

Delivery information was available for 1,004 women. Table 2 details pregnancy outcomes and perinatal events within the study cohort.

Systolic BP decreased from 12 weeks of gestation: median, or 50th centile (3rd–97th centile) 114 (95–138) mm Hg to reach its nadir of 113 (95–136) mm Hg at 18.6 weeks, a change (95% CI) of -1.0 (-2 to 0) mm Hg. Systolic BP then rose progressively from 19 weeks of gestation to a maximum median of (3rd–97th centile) 121 (102–144) mm Hg at 40 weeks, a difference (95% CI) of 7 (6 – 9) mm Hg from minimum to maximum systolic BP.

Diastolic BP decreased from 12 weeks of gestation: median (3rd–97th centile) 70 (56–87) mm Hg to its nadir of 69 (55–86) mm Hg at 19.2 weeks, a change (95% CI) of -1 (-2 to -1) mm Hg. Diastolic BP subsequently increased to a maximum median of

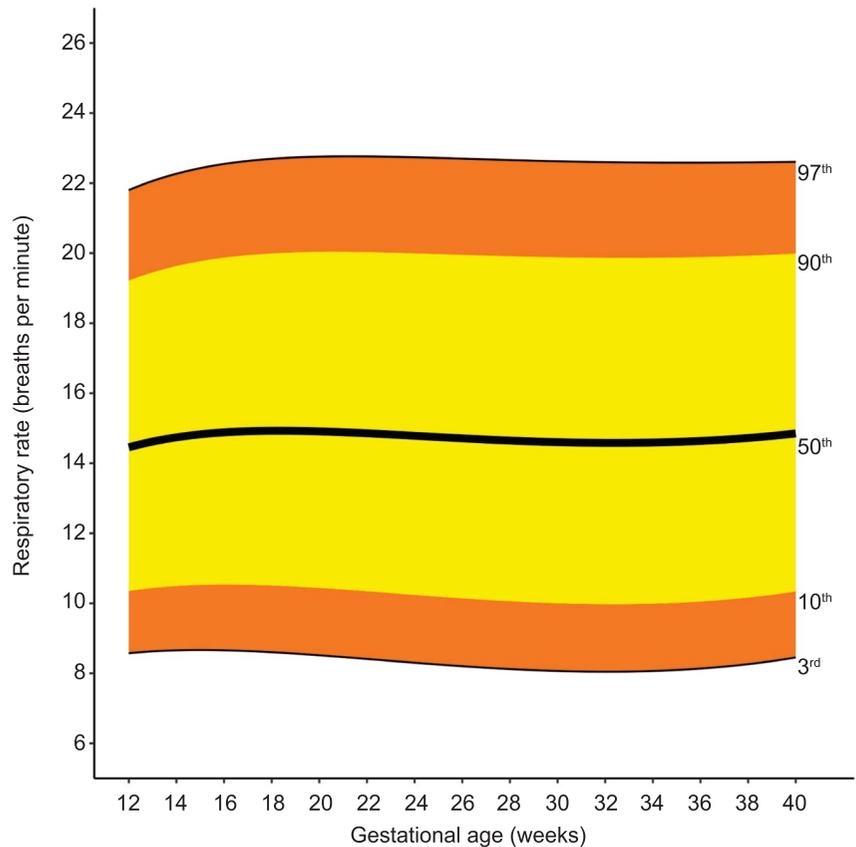


Fig. 4. Smoothed centiles for respiratory rate from tapping technique. Green. *Vital Sign Reference Ranges for Pregnancy. Obstet Gynecol 2020.*

(3rd–97th centile) 78 (62–95) mm Hg at 40 weeks, a difference (95% CI) of 9 (8–10) mm Hg from minimum to maximum diastolic BP. Figure 2 represents smoothed gestation-specific centiles for systolic and diastolic BP for the 3rd, 10th, 50th, 90th, and 97th centiles.

The median (3rd–97th centile) heart rate was lowest at 12 weeks of gestation—82 (63–105) beats per minute (bpm). Median (3rd–97th centile) heart rate rose progressively until 34.1 weeks of gestation to a maximum of 91 (68–115) bpm, a difference (95% CI) of 9 (8–10) bpm. Heart rate then decreased slightly to a median (3rd–97th centile) of 89 (65–114) at 40 weeks, a difference (95% CI) of –2 (–3 to 0) bpm (Fig. 3).

There was no significant change in respiratory rate with gestation irrespective of the method used. Using the tapping technique, the median (3rd–97th centile) respiratory rate at 12 weeks of gestation was 15 (9–22) breaths per minute and 15 (9–23) breaths per minute at 40 weeks (Fig. 4). Figures and gestation-specific values for respiratory rate from manual counting are in Appendix 4, available online at <http://links.lww.com/AOG/B749>.

SpO₂ decreased from 12 weeks of gestation: median (3rd–97th centile) 98% (94–99%) to reach a minimum of 97% (93–99%) at 40 weeks, a change (95% CI) of –1.0 (–1 to –1)% (Fig. 5).

Temperature measurements with both Fora and Genius devices were recorded at 2,990 visits. The Bland-Altman plot showed wide limits of agreement, around 2°C (Appendix 5, available online at <http://links.lww.com/AOG/B750>). Therefore, it was not appropriate to pool data from the two thermometers. For the Genius device, median (3rd–97th centile) temperature decreased from its maximum at 12 weeks of gestation of 36.7 (35.6–37.5)°C to a minimum of 36.5 (35.3–37.3)°C at 33.4 weeks, a change (95% CI) of only –0.2 (–0.2 to –0.1)°C. Temperature subsequently plateaued until 40 weeks of gestation: median (3rd–97th centile) 36.6 (35.4–37.4)°C at 40 weeks (Fig. 6). Results for the Fora device are shown in Appendix 4 (<http://links.lww.com/AOG/B749>).

For each vital sign measured, gestation-specific values for the smoothed centiles and a smoothed gestation-specific centile plot with associated 95% CI can be found in Appendix 4 (<http://links.lww.com/AOG/B749>). Duplicate measurements were

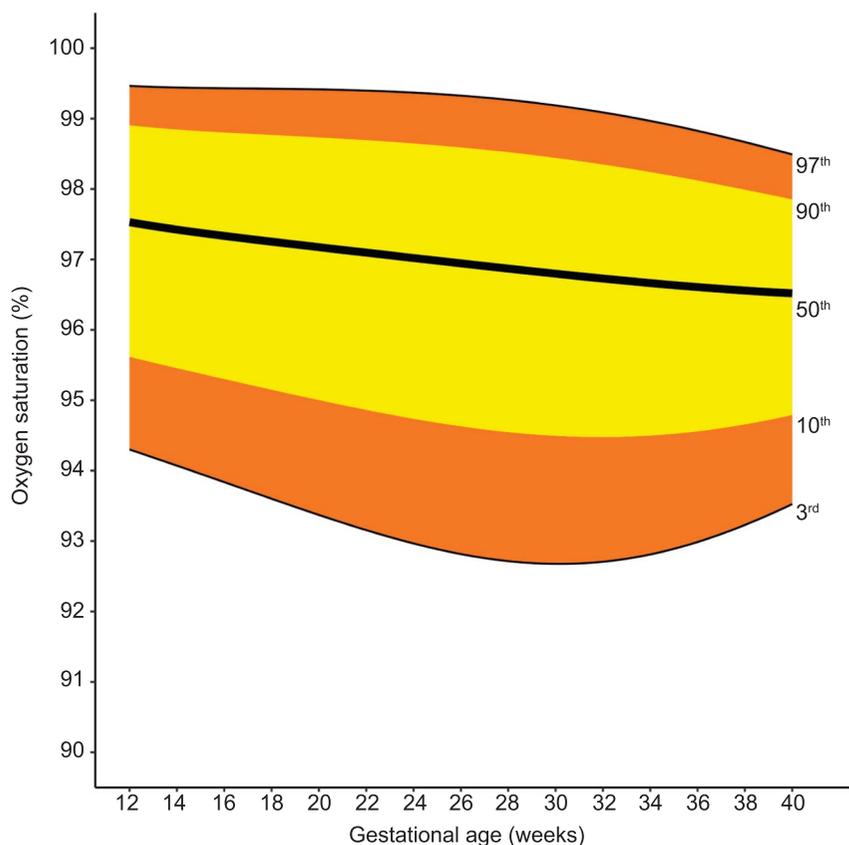


Fig. 5. Smoothed centiles for oxygen saturation in percentage.

Green. *Vital Sign Reference Ranges for Pregnancy*. *Obstet Gynecol* 2020.

recorded for a subset of 273 participant visits (4.6%). There were no clinically meaningful differences between first and second measures of vital signs in pregnancy, so duplicate readings were not continued (Appendix 6, available online at <http://links.lww.com/AOG/B751>). We found no evidence of systematic sensor performance alteration over time (see Appendix 7, available online at <http://links.lww.com/AOG/B752>).

Applying the “restrictive” population definitions reduced the cohort to 595/1,041 women (Appendix 8, available online at <http://links.lww.com/AOG/B753>). Although systolic and diastolic BP centiles were numerically slightly lower in the restrictive cohort (higher BPs having been excluded) the relatively narrow CIs mainly overlapped. Centiles for other vital signs were similar to the “pragmatic” cohort.

Blood pressures from 460 nulliparous women were slightly higher than those from the 581 parous women (Appendix 9, available online at <http://links.lww.com/AOG/B754>). Excluding women who delivered before 37 weeks of gestation did not change the shape of the heart rate centiles (Appendix 10, available online at <http://links.lww.com/AOG/B755>).

DISCUSSION

Our multicenter study includes longitudinal data from more than 1,041 women. From these data we produced evidence-based, gestation-specific centiles for vital signs during pregnancy. Our findings refute a large drop in BP during pregnancy after week 12, when women are usually first measured. Textbooks suggest a 10–15-mm Hg drop in diastolic BP^{39–41} during pregnancy. Evidence supporting this BP drop came from small single center studies^{6,42–45} or larger birth cohorts from one geographical region^{46,47} commonly using routinely collected,^{6,44} nonstandardized measurements^{42,45} with equipment not ratified for use in pregnancy.^{6,42–44,46–48} Our study concurs with recent publications, including a recently published systematic review^{7,25,49} that challenge this teaching, and strongly supports the resulting call to abandon this notion.⁵⁰ Several studies suggest a drop occurs from prepregnancy levels in the first few weeks of pregnancy.^{8,48,51,52} However, preconception BPs are not normally available in clinical practice. Our findings allow clinicians to recognize that relative hypotension from the first BP in pregnancy may warrant

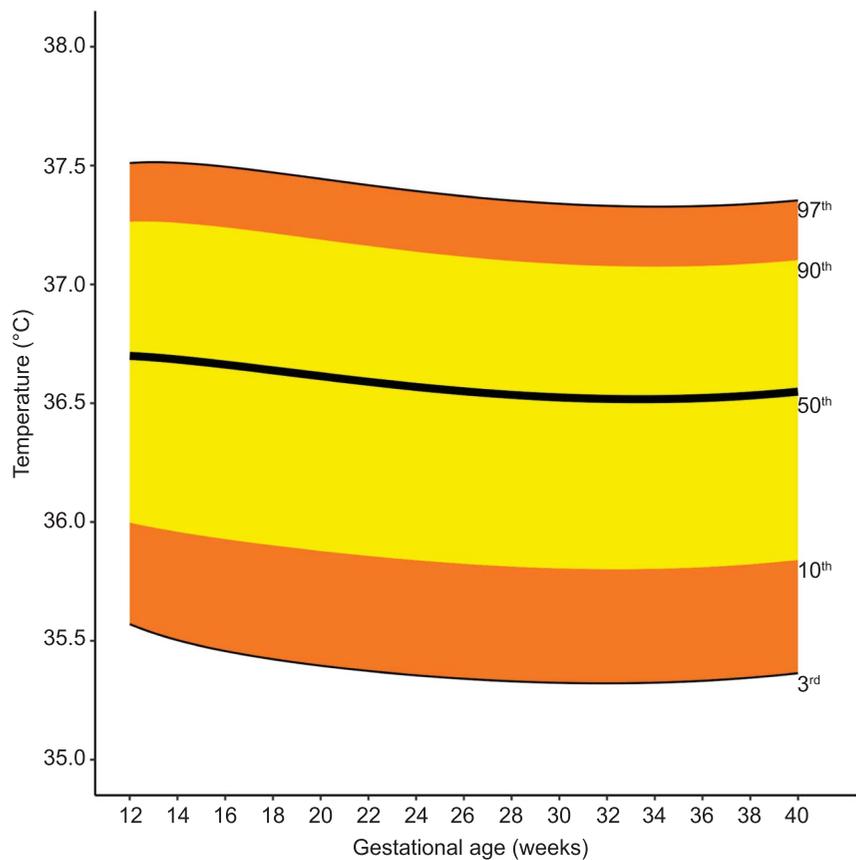


Fig. 6. Smoothed centiles for temperature (°C) from a tympanic thermometer.

Green. *Vital Sign Reference Ranges for Pregnancy. Obstet Gynecol* 2020.

investigation. The third centile for systolic BP was never less than 94 mm Hg and was greater than 96 mm Hg after 30 weeks of gestation in all groups. These thresholds are above the less than 90 mm Hg used to recognize sepsis in pregnancy^{53,54} and modified obstetric early warning score charts trigger for escalation.^{1,17,18,55} The BP rise toward the end of pregnancy suggests gestational threshold adjustment could improve detection of deteriorating mothers.

Before our study, the best evidence for longitudinal reference ranges for BP in normal pregnancy probably came from the Avon Longitudinal Study of Parents and Children, a large, single-center cohort study using data from 20 years ago.⁵ The Avon Longitudinal Study of Parents and Children reported a small (1.7 mm Hg) nadir of systolic BP at 17–18 weeks of gestation, similar to the 1-mm Hg drop at 18.6 weeks of gestation in our multicenter cohort. The subtle nadir in diastolic BP was also similar in both studies. The Avon Longitudinal Study of Parents and Children relied on BPs documented in women's routine obstetric records, rather than measuring BP with validated equipment following a standard operating procedure. Despite this, the median and ranges of

our systolic BPs are similar, providing reassurance that our BP ranges will be valid in routine clinical practice.

It is commonly taught that heart rate increases by 10–15 bpm from the first trimester onward.^{40,56} An increase in heart rate of 20–25% is reported by studies which compare heart rate in pregnancy to prepregnancy baseline.^{8,51,57} However, prepregnancy vital sign data are not usually available. We demonstrated a smaller increase in heart rate of 9 bpm between 12 weeks of gestation and the third trimester. This is consistent with our recent systematic review, that also highlighted that the outer centiles of heart rate in pregnancy have not been demonstrated in large modern studies.²⁵ From 18 weeks of gestation, heart rates of more than 100 bpm (more than 105 bpm from 28 weeks of gestation) occurred in more than 10% of observations taken in healthy pregnancy. However the 97th centile for heart rate increased from 105 bpm at 12 weeks of gestation to 115 at 36 weeks, suggesting that a 120 bpm threshold for the high-risk threshold for modified obstetric early warning score escalation^{1,17,55} may be too high.

Centiles for respiratory rate in pregnancy have not been determined in a large modern cohort,

though our finding that respiratory rate does not change with gestation is supported by a longitudinal study of 20 women.¹⁴ Our work shows that a respiratory rate of more than 22 breaths per minute (as used in the quick Sepsis Related Organ Failure Assessment tool⁵⁸) occurs in fewer than 3% of observations in normal pregnancy, suggesting this threshold could translate from other medical practice. Current moderate and high-risk thresholds for respiratory rate of 21–24 and 25 breaths per minute or more (as advocated by the UK Sepsis Trust,⁵⁴ the Irish Maternity Early Warning System¹⁷ and the Scottish Patient Safety Programme⁵⁵) may more accurately detect women at risk of sepsis than moderate¹ and high-risk^{1,18} thresholds of more than 21–30 and more than 30 breaths per minute.

We identified a small drop in SpO₂ during pregnancy. Previous small studies suggest a modest reduction in SpO₂ between the second and third trimester⁵⁹ and oxygen partial pressure (PaO₂) across gestation.¹⁴ The lower thresholds of oxygen saturation have not been determined at scale. We showed that SpO₂ less than 93% is an abnormal finding in pregnancy. However, from 16 weeks of gestation onward, SpO₂ of 94% is within the normal range. These findings suggest that a lower alerting threshold of less than 95%^{1,17,18,55} may be too high.

Longitudinal temperature studies during pregnancy providing data on outer centiles are lacking, with only small previous studies.¹³ We found a clinically insignificant drop in temperature from 12 to 40 weeks of gestation (less than 0.2°C). Many modified obstetric early warning score systems use a high-risk escalation threshold of 38°C or higher.^{1,17,55} However, temperatures of 37.5°C were uncommon (fewer than 3% of observations), suggesting this may be an appropriate threshold to further investigate women.

Although higher BPs were excluded from the restrictive cohort, BP differences from the pragmatic cohort were marginal. In the nulliparous group, BPs were higher than in the parous cohort, particularly at 40 weeks of gestation. All other vital sign centiles were similar between subgroups.

In our systematic literature review^{25,60} we could not identify a study using World Health Organization recommended centiles developed from longitudinal vital sign data to provide reliable data for clinicians in clinical practice. By adopting a prescriptive approach to gestational age calculation and using standardized, pregnancy-specific equipment to collect data prospectively from three sites, we are confident our reference ranges are robust. Our study population is of similar age to the U.K. national average for pregnancy⁶¹ and of

similar BMI to previous U.K. findings.⁶² Women were predominantly of Caucasian ethnicity (85.2%), equivalent to the most recent England and Wales census data (86%).⁶³ Our population therefore appears representative and applicable to clinical practice. Extending to an international population would improve external validity for other settings.

We present widely relevant, gestation-specific reference ranges for systolic and diastolic BP, heart rate, respiratory rate, oxygen saturation and temperature. Our findings refute the idea that a clinically significant first-to-mid trimester drop in BP is normal and suggest evidence-based ranges for other vital signs. These reference ranges can be used to facilitate early recognition of unwell pregnant women. The differences from current accepted values used to detect deterioration in pregnant women emphasize the need for robustly derived ranges for a modified obstetric early warning score system.

REFERENCES

1. Lewis G, editor. Saving Mothers' Lives. Reviewing maternal deaths to make motherhood safer—2003–2005: the seventh report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. Available at: <https://www.publichealth.hscni.net/sites/default/files/Saving%20Mothers%27%20Lives%202003-05%20.pdf>. Retrieved October 7, 2019.
2. Lewis G, editor. Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006–2008. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011;118:1–203.
3. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk J. Saving Lives, Improving Mothers' Care—lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–2012. Available at: <https://www.npeu.ox.ac.uk/downloads/files/mbrace-uk/reports/Saving Lives Improving Mothers Care report 2014 Full.pdf>. Retrieved October 7, 2019.
4. Knight M, Nair M, Tuffnell D, Shakespeare J, Kenyon S, Kurinczuk J, editors. Saving Lives, Improving Mothers' Care. Lessons learned to inform future maternity care from the UK and Ireland. Confidential Enquiries into Maternal Deaths and Morbidity, 2013–2015. Available at: <https://www.npeu.ox.ac.uk/downloads/files/mbrace-uk/reports/MBRACE-UK Maternal Report 2017 - Web.pdf>. Retrieved October 7, 2019.
5. Macdonald-Wallis C, Silverwood RJ, Fraser A, Nelson SM, Tilling K, Lawlor DA, et al. Gestational-age-specific reference ranges for blood pressure in pregnancy. *J Hypertens* 2015;33:96–105.
6. Ishikuro M, Obara T, Metoki H, Ohkubo T, Yamamoto M, Akutsu K, et al. Blood pressure measured in the clinic and at home during pregnancy among nulliparous and multiparous women: the BOSHI study. *Am J Hypertens* 2013;26:141–8.
7. Andreas M, Kuessel L, Kastl SP, Wirth S, Gruber K, Rhomberg F, et al. Bioimpedance cardiography in pregnancy: a longitudinal cohort study on hemodynamic pattern and outcome. *BMC Pregnancy Childbirth* 2016;16:1–9.
8. Mahendru AA, Everett TR, Wilkinson IB, Lees CC, McEniery CM. A longitudinal study of maternal cardiovascular function

- from preconception to the postpartum period. *J Hypertens* 2014;32:849–56.
9. Grindheim G, Estensen ME, Langesaeter E, Rosseland LA, Toska K. Changes in blood pressure during healthy pregnancy: a longitudinal cohort study. *J Hypertens* 2012;30:342–50.
 10. Gu H, Zhang S, Qiao Y, Luo Z, Zeng Y, Wang Q. A study of maternal hemodynamic change during healthy pregnancy and women with gestation hypertension. *Biomed Mater Eng* 1991; 16:77–82.
 11. Van Oppen ACC, Van Der Tweel I, Alsbach GPJ, Heethaar RM, Bruinse HW. A longitudinal study of maternal hemodynamics during normal pregnancy. *Obstet Gynecol* 1996;88:40–6.
 12. Tuffnell DJ, Buchan PC, Albert D, Tyndale-Biscoe S. Fetal heart rate responses to maternal exercise, increased maternal temperature and maternal circadian variation. *J Obstet Gynaecol* 1990;10:387–91.
 13. Hartgill TW, Bergersen TK, Pirhonen J. Core body temperature and the thermoneutral zone: a longitudinal study of normal human pregnancy. *Acta Physiol* 2011;201:467–74.
 14. Templeton A, Kelman GR. Maternal blood-gases, (PAO₂-PaO₂), physiological shunt and VD/VT in normal pregnancy. *Br J Anaesth* 1976;48:1001–4.
 15. Ekholm EMK, Erkkola RU, Piha SJ, Jalonen JO, Metsälä TH, Antila KJ. Changes in autonomic cardiovascular control in mid-pregnancy. *Clin Physiol* 1992;12:527–36.
 16. Deckardt R, Fembacher PM, Schneider KT, Graeff H. Maternal arterial oxygen saturation during labor and delivery: pain-dependent alterations and effects on the newborn. *Obstet Gynecol* 1987;70:21–5.
 17. Department of Health. Irish Maternity Early Warning System (IMEWS) V2 (NCEC National Clinical Guideline No. 4 Version 2). Available at: <https://www.gov.ie/en/collection/517f60-irish-maternity-early-warning-system-imews-version-2/>. Retrieved October 8, 2019.
 18. Mhyre JM, D’Oria R, Hameed AB, Lappen JR, Holley SL, Hunter SK, et al. The maternal early warning criteria: a proposal from the national partnership for maternal safety. *Obstet Gynecol* 2014;124:782–6.
 19. Smith GB, Isaacs R, Andrews L, Wee MYK, van Teijlingen E, Bick DE, et al. Vital signs and other observations used to detect deterioration in pregnant women: an analysis of vital sign charts in consultant-led UK maternity units. *Obstetric vital signs charts*. *Int J Obstet Anesth* 2017;30:44–51.
 20. 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;69:687–92.
 21. McGlennan AP, Sherratt K. Charting change on the labour ward. *Anaesthesia* 2013;68:338–41.
 22. Friedman AM. Maternal early warning systems. *Obstet Gynecol Clin North Am* 2015;42:289–98.
 23. Tarassenko L, Clifton DA, Pinsky MR, Hravnak MT, Woods JR, Watkinson PJ. Centile-based early warning scores derived from statistical distributions of vital signs. *Resuscitation* 2011;82:1013–8.
 24. Watkinson PJ, Pimentel MAF, Clifton DA, Tarassenko L. Manual centile-based early warning scores derived from statistical distributions of observational vital-sign data. *Resuscitation* 2018;129:55–60.
 25. Loerup L, Pullon RM, Birks J, Fleming S, Mackillop LH, Gerry S, et al. Trends of blood pressure and heart rate in normal pregnancies: a systematic review and meta-analysis. *BMC Med* 2019;17:167.
 26. Kumar F, Kemp J, Edwards C, Pullon RM, Loerup L, Triantafyllidis A, et al. Pregnancy physiology pattern prediction study (4P study): protocol of an observational cohort study collecting vital sign information to inform the development of an accurate centile-based obstetric early warning score. *BMJ Open* 2017;7: e016034.
 27. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370: 1453–7.
 28. The INTERBIO-21st Consortium. INTERBIO-21st study protocol. Available at: www.interbio21.org.uk. Retrieved October 8, 2019.
 29. Stirnemann J, Villar J, Salomon LJ, Ohuma E, Ruyan P, Altman DG, et al. International estimated fetal weight standards of the INTERGROWTH-21st project. *Ultrasound Obstet Gynecol* 2017;49:478–86.
 30. American Society of Anesthesiologists. ASA physical status classification system. Available at: <https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system>. Retrieved November 24, 2018.
 31. Villar J, Altman DG, Purwar M, Noble JA, Knight HE, Ruyan P, et al. The objectives, design and implementation of the INTERGROWTH-21st Project. *BJOG* 2013;120(suppl 2):9–26.
 32. De Onis M. WHO child growth standards based on length/height, weight and age. *Acta Paediatr Int J Paediatr* 2006;95(suppl 450): 1–101.
 33. WHO Multicentre Growth Reference Study Group, de Onis M, Onyango A, Borghi E, Siyam A, Pinol A. WHO child growth standards: growth velocity based on weight, length and head circumference: methods and development. Available at: <https://apps.who.int/iris/handle/10665/44026>. Retrieved October 15, 2019.
 34. Papageorghiou AT, Kennedy SH, Salomon LJ, Ohuma EO, Ismail LC, Barros FC, et al. International standards for early fetal size and pregnancy dating based on ultrasound measurement of crown-rump length in the first trimester of pregnancy. *Ultrasound Obstet Gynecol* 2014;44:641–8.
 35. Altman DG, Ohuma EO. Statistical considerations for the development of prescriptive fetal and newborn growth standards in the INTERGROWTH-21st Project. *BJOG* 2013; 120(suppl 2):71–6.
 36. Ohuma EO, Altman DG; The INTERGROWTH-21st Project. Statistical methodology for constructing gestational age-related charts using cross-sectional and longitudinal data: the INTERGROWTH-21st project as a case study. Available at: <https://onlinelibrary.wiley.com/doi/epdf/10.1002/sim.8018>. Retrieved October 8, 2019.
 37. Ohuma EO, Altman DG; The INTERGROWTH-21st Project. Design and other methodological considerations for the construction of human fetal and neonatal size and growth charts. Available at: <https://onlinelibrary.wiley.com/doi/epdf/10.1002/sim.8000>. Retrieved October 8, 2019.
 38. Villar J, Papageorghiou AT, Pang R, Ohuma EO, Ismail LC, Barros FC, et al. The likeness of fetal growth and newborn size across non-isolated populations in the INTERGROWTH-21st project: the fetal growth longitudinal study and newborn cross-sectional study. *Lancet Diabetes Endocrinol* 2014;2:781–92.
 39. Khalil A. Physiology of pregnancy. In: Fiander A, Thilaganathan B, editors. *Your essential revision guide: MRCOG part one: the official companion to the Royal College of Obstetricians and Gynaecologists revision course*. 1st ed. Cambridge, UK: Cambridge University Press; 2016. p. 538.

40. O'Donoghue K. Physiological changes in pregnancy. In: Baker P, Kenny L, editors. *Obstetrics by ten teachers*. 19th ed. London, UK: Hodder Arnold; 2011. p. 319.
41. Blackburn S Cardiovascular system. In: *Maternal, fetal, & neonatal physiology: a clinical perspective*. 4th ed. Philadelphia, PA: Elsevier Saunders; 2013. p. 719.
42. Wilson M, Morganti AA, Zervoudakis I, Letcher RL, Romney BM, Von Oeyon P, et al. Blood pressure, the renin-aldosterone system and sex steroids throughout normal pregnancy. *Am J Med* 1980;68:97–104.
43. Hermida RC, Ayala DE, Mojón A, Fernández JR, Alonso I, Silva I, et al. Blood pressure patterns in normal pregnancy, gestational hypertension, and preeclampsia. *Hypertension* 2000;36:149–58.
44. Strevens H, Wide-Svensson D, Ingemarsson I. Blood pressure during pregnancy in a Swedish population; impact of parity. *Acta Obstet Gynecol Scand* 2001;80:824–9.
45. MacGillivray I, Rose G, Rowe B. Blood pressure survey in pregnancy. *Clin Sci* 1969;37:395–407.
46. Bakker R, Steegers EA, Mackenbach JP, Hofman A, Jaddoe VW. Maternal smoking and blood pressure in different trimesters of pregnancy: the Generation R Study. *J Hypertens* 2010;28:2210–8.
47. Timmermans S, Steegers-Theunissen RPM, Vujkovic M, Bakker R, Den Breeijen H, Raat H, et al. Major dietary patterns and blood pressure patterns during pregnancy: the Generation R Study. *Am J Obstet Gynecol* 2011;205:337.e1–12.
48. Shen M, Tan H, Zhou S, Smith GN, Walker MC, Wen SW. Trajectory of blood pressure change during pregnancy and the role of pre-gravid blood pressure: a functional data analysis approach. *Sci Rep* 2017;7:1–6.
49. Nama V, Antonios TF, Onwude J, Manyonda IT. Mid-trimester blood pressure drop in normal pregnancy: myth or reality? *J Hypertens* 2011;29:763–8.
50. Tranquilli AL. Mid-trimester blood pressure in pregnancy. Blood pressure fall or fall of a myth? *J Hypertens* 2011;29:658–9.
51. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. *Circulation* 2014;130:1003–8.
52. Foo FL, Collins A, McEniery CM, Bennett PR, Wilkinson IB, Lees CC. Preconception and early pregnancy maternal haemodynamic changes in healthy women in relation to pregnancy viability. *Hum Reprod* 2017;32:985–92.
53. Acosta CD, Kurinczuk JJ, Lucas DN, Tuffnell DJ, Sellers S, Knight M. Severe maternal sepsis in the UK, 2011–2012: a national case-control study. *PLoS Med* 2014;11:2011–2.
54. UK Sepsis Trust. Inpatient maternal sepsis tool. Available at: <https://sepsistrust.org/professional-resources/clinical/>. Retrieved October 8, 2019.
55. Scottish patient safety programme, maternity and children quality improvement collaborative. Scottish maternity early warning score (MEWS) chart. Available at: https://ihub.scot/media/5308/national-mews-chart_web.pdf. Retrieved October 8, 2019.
56. De Swiet M. Chapter 2, The Cardiovascular System. In: Chamberlain G, Broughton Pipkin F, editors. *Clinical physiology in obstetrics*. 3rd ed. Oxford, UK: Blackwell Science; 1998.
57. Carruth JE, Mirvis SB, Brogan DR, Wenger NK. The electrocardiogram in normal pregnancy. *Am Heart J* 1981;102:1074–5.
58. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis 3). *JAMA* 2016;315:801–10.
59. Van Hook JW, Harvey CJ, Anderson GD. Effect of pregnancy on maternal oxygen saturation values: use of reflectance pulse oximetry during pregnancy. *South Med J* 1996;89:1188–92.
60. Loerup L, Pullon RM, Birks J, Fleming S, Mackillop LH, Watkinson PJ. Trends of vital signs with gestational age in normal pregnancies: a systematic review protocol. *BMJ Open* 2016;6:1–5.
61. Office for National Statistics. Statistical bulletin. Births by parents' characteristics in England and Wales: 2016. Available at: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsbyparent-characteristicsinenglandandwales/2016>. Retrieved October 8, 2019.
62. Knight M, Kurinczuk JJ, Spark P, Brocklehurst P. Extreme obesity in pregnancy in the United Kingdom. *Obstet Gynecol* 2010;115:989–997.
63. Office for National Statistics. Ethnicity and national identity in England and Wales: 2011. Available at: <https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicityandnationalidentityinenglandandwales/2012-12-11>. Retrieved October 8, 2019.

Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? **Yes.**

What data in particular will be shared? *Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).*

What other documents will be available? *Study protocol, case report forms, standard operating procedures, consent form.*

When will data be available (start and end dates)? *Data will be available between 3 and 36 months after publication.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Researchers who present a sound analysis plan for any valid research will apply by contacting the corresponding author. Proposals considered valid by the Kadoorie Critical Care Research Group Data Access Committee (which comprises independent researchers, clinicians, patient and public representatives). Data will be provided using the group's current compliant system.*

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