CARDIAC OUTPUT AND RELATED HAEMODYNAMICS DURING PREGNANCY: A SERIES OF META-ANALYSES

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Abstract

OBJECTIVE: Cardiac output, a fundamental parameter of cardiovascular function, has consistently been shown to increase across healthy pregnancy; however the time course and magnitude of adaptation remains equivocal within published literature. The aim of the present meta-analyses was to comprehensively describe the pattern of change in cardiac output during healthy pregnancy.

METHOD: A series of meta-analyses of previously published cardiac output data during healthy, singleton pregnancies was completed. PubMed and Scopus databases were searched for studies published between 1996 and 2014. Included studies reported absolute values during a predetermined gestational age (non-pregnant, late first trimester, early and late second trimester, early and late third trimester, early and late postpartum). Cardiac output was measured through echocardiography, impedance cardiography or inert gas rebreathing. Observational data was meta-analysed at each gestational age using a random-effects model. If reported, related haemodynamic variables were evaluated.

RESULTS: In total, 39 studies were eligible for inclusion, with pooled sample sizes ranging from 259 to 748. Cardiac output increased during pregnancy reaching its peak in the early third trimester, 1.5 $L \cdot min^{-1}$ (31%) above non-pregnant values. The observed results from this study indicated a non-linear rise to this point. In the early postpartum, cardiac output had returned to non-pregnant values.

CONCLUSIONS: The present results suggest that cardiac output peaks in the early third trimester, following a non-linear pattern of adaptation, however this must be confirmed using longitudinal studies. The findings provide new insight into the normal progression of cardiac output during pregnancy.

Key Questions

What is already known about the subject?

During pregnancy, maternal cardiac output adapts to accommodate the demands of the developing foetus. There is a lack of consensus within the literature regarding the progression of cardiac output across healthy pregnancy, thus impairing the understanding of pregnancy-related cardiovascular complications.

What does this study add?

This series of meta-analyses comprehensively characterises the healthy maternal cardiac output response to pregnancy.

How might this impact on clinical practice?

These meta-analyses provide new insight into the expected timing and magnitude of adaptation in maternal cardiac output during healthy gestation. In clinical practice, the normative values derived from the present analyses could be used to identify maternal maladaptation during pregnancy.

Introduction

During pregnancy, progressive adaptation of the maternal cardiovascular system is necessary for foetal development and growth. As part of the many physiological adaptations occurring during pregnancy the maternal heart undergoes major structural and functional changes. These changes occur to ensure adequate oxygen and nutrient delivery to the foetus. It is known that changes in cardiac function typically precede structural remodelling, and therefore, may be early markers of adaptation during pregnancy[1, 2]. Cardiac output ($\dot{Q}$), a fundamental functional parameter, reflects the total demand placed on the maternal cardiovascular system. During pregnancy, this is increased due to the additional requirement for blood flow to the uterus / placenta, kidneys, breasts, skin and the heart itself[1, 2, 3].

Despite a wealth of literature describing $\dot{Q}$ during healthy gestation, there is a lack of consensus in published literature regarding the time course of adaptation[1, 2, 4, 5, 6, 7, 8, 9, 10, 11]. Previous reviews agree that $\dot{Q}$ increases across pregnancy, however, there are discrepancies regarding the magnitude and pattern of change after the second trimester[2, 11, 12, 13]. Specifically, $\dot{Q}$ has been reported to follow three different patterns of change throughout pregnancy, namely: (i) a continued increase until term[1, 4, 5]; (ii) a continued increase to peak in the latter half of pregnancy, after which $\dot{Q}$ decreases towards term[6, 7]; (iii) a continued increase to peak in the latter half of pregnancy, after which $\dot{Q}$ plateaus until term[8, 9, 10]. The contribution of the determinants of $\dot{Q}$ to the pregnancy-related adaptation also remains unclear[11]. The adaptation of $\dot{Q}$ may be driven by increases in blood volume and heart rate (HR), altered regulation of the autonomic nervous system or as a result of changes within the peripheral vasculature[1, 4, 5, 6, 7, 8, 9, 10, 11, 14, 15, 16].

Presently, the lack of certainty in the haemodynamic adaptation during healthy pregnancy impairs the understanding, and therefore the early diagnosis, of pregnancy-

related cardiovascular complications, such as preeclampsia and gestational hypertension. To improve the current understanding of normal cardiac adaption to pregnancy, insight from larger cohorts with greater statistical power than typically possible within pregnancy research is required[17]. Therefore, the aim of this study was to perform a series of meta-analyses to determine the time course of adaptation in $\dot{Q}$ and related haemodynamics in response to healthy pregnancy.

Methods

Ethical approval and search strategy

This study received ethical approval from the Cardiff Metropolitan University ethics board. A comprehensive literature search of the PubMed and Scopus databases for peer-reviewed publications examining the maternal cardiovascular responses to pregnancy was conducted. The pre-set search engine criteria, both on PubMed and Scopus, were restricted to studies using humans, females and publications written in the English language. Reviews, editorials, case reports and unpublished data were excluded. The keywords and phrases used in the online search included combinations of the words *cardiac output, maternal, cardiovascular, pregnancy, haemodynamic/hemodynamic, normotensive, and healthy,* referring to uncomplicated gestation. As the last review on cardiac output during pregnancy[2] was published in 1996, the search was limited to studies published between 1st January 1996 and 31st December 2014. There was no overlap of included studies between the last review and the current analyses.

Study Selection Criteria

Studies were eligible for inclusion in the meta-analyses if they met the following criteria;

(i) Examined uncomplicated, healthy, singleton pregnancies;

(ii) Recruited females aged 19-35 years who conceived naturally;

(iii) Tested participants during one or more of the following gestational ages; first trimester (6-13 weeks); early second trimester (14-20 weeks); late second trimester (21-27 weeks); early third trimester (28-34 weeks), late third trimester (34 weeks-term); during the early (4-12 weeks) or late (13-52 weeks) postpartum period;

(iv) Provided the mean ($L \cdot min^{-1}$) and standard deviation of $\dot{Q}$;

(v) Assessed $\dot{Q}$ using one of the following methods: magnetic resonance imaging (MRI), echocardiography, impedance cardiography or inert gas re-breathing. A brief description of each method is included within the legend of Table S1 in the supplementary material.

Studies of longitudinal and cross sectional design were eligible to be included within the meta-analyses.

Patient involvement

There was no patient or public involvement in the design of this study.

Outcome variables

The primary variable, $\dot{Q}$, was assessed across healthy pregnancy. Secondary variables were related haemodynamic variables, namely heart rate (HR), stroke volume (SV), mean arterial pressure (MAP), systemic vascular resistance (SVR) and left ventricular (LV) mass.

Study Process

The lead author (VM) independently screened and reviewed the titles and abstracts of all identified publications. Full text articles were retrieved for each study that was considered relevant from the initial evaluation. Full text articles were independently assessed by two reviewers (VM and EJS) through completion of a predesigned

eligibility form. Inclusion into the final dataset was based on the *a priori* selection criteria described. Consensus was sought on the final set of articles to be included and disagreements were resolved through discussion. Some issues could not be resolved according to the inclusion criteria set *a priori*. In studies where conception was not explicitly described, it was assumed that participants conceived naturally and not through use of reproductive therapies. Where $\dot{Q}$ was only included in a graphical format or not reported in $L \cdot min^{-1}$ as a mean and SD, the corresponding authors of the original publications were contacted by email and asked to provide the required data. Suitable data provided by authors of original publications were included in the analyses. When data was not provided, the publications were excluded.

Data Extraction

The lead author extracted all relevant data from the full-text articles to be included in the meta-analyses. The mean ± SD for $\dot{Q}$ for each study was transferred into a predesigned form along with the sample sizes (Excel 2010, Microsoft Corp). Where reported, HR, SV, MAP, SVR and LV mass (mean ± SD, and sample size) were also extracted from the same studies.

Statistical Analyses

As all parameters were continuous variables, sample size and mean ± SD were input into the analysis software (Comprehensive Meta-analysis software version 2.0, Biostat, Englewood, NJ, USA). Separate random-effects meta-analyses were applied to all primary and secondary outcome variables for each gestational stage (non-pregnant, first trimester, early and late second trimester, early and late third trimester, early and late postpartum). As the meta-analyses were based upon observational data obtained from populations which would unlikely have a common variance, a random-effects model was used. True effects would inherently vary from study to study due to different effect sizes, and the random-effects model allows for variation between studies. Use of

a random-effects model also allows for generalisation to similar studies that may be conducted in the future, allowing this dataset to serve as a potential reference point. For each analysis, a weighted mean, standard error, variance, upper and lower limits were computed through the DerSimonian and Laird method[18]. The homogeneity of the reported data for each parameter was assessed, with no indication of skewness. Publication bias was evaluated through a funnel plot and, if present, was corrected through use of Duval and Tweedie's trim and fill method. Forest plots were created for each individual meta-analysis[19] and presented as a compiled figure for each variable at each time point of analyses (Excel 2010, Microsoft Corp).

Results

Search Results

The search process, as illustrated in Figure 1, resulted in the inclusion of observational data from a total of 39 articles sourced from both the original database and reference list searches. Originally, only 32 articles were eligible as the numerical data were not reported as per requirement for inclusion, however, following email contact other data was obtained for seven studies[5, 20, 21, 22, 23, 24, 25].

Four studies reported multiple data sets within one of the predetermined gestational age ranges e.g. data at week eight and week ten, both eligible to be included for first trimester (6 to 13 weeks) analyses[4, 6, 9, 26]. In all cases, the data was not included within the meta-analysis for that predetermined gestational age in order to avoid statistical bias that would arise from inclusion of multiple data sets from an individual study.

Following the review process, observational data from 39 studies were included within the final analyses however the number of studies included in the individual meta-analyses conducted for each of the eight time points ranged from 9 to 19, as shown in

Figure 1. The non-pregnant data was collected from eligible studies that reported data for a non-pregnant control or preconception group[4, 5, 9, 25, 27, 28, 29, 30, 31]. Details of the 39 included studies are reported in Table 1. More detailed information about the methodology of each study is included in the supplementary material (Table S1).

Search Outcomes

For the 39 included studies, the total sample size included within the analyses of $\dot{Q}$ was 1479, with numbers ranging from 259 – 748 in the individual analyses (Figure 1). Within the analyses of the additional haemodynamic variables, the required data were not consistently reported; therefore, total sample sizes were, in some cases, much reduced in the analyses of additional parameters (included as supplementary material Table S2).

Publication bias

Examination of funnel plots indicated publication bias in two of the 8 time points within the meta-analyses for $\dot{Q}$. Original outputs were adjusted to reflect the presence of bias and these values were reported as the final results. Within the forest plot of $\dot{Q}$ (Figure 2), the original outputs prior to any adjustment for bias are shown. Similarly, publication bias was also identified within some of the meta-analyses of HR, SV, MAP, SVR and LV mass and all analyses were corrected accordingly. The original outputs prior to any adjustment for bias are also shown within the forest plots for each parameter (supplementary material – Figures S1-S5).

Analyses results

A composite figure of forest plots for $\dot{Q}$ at each time point of analyses is shown in Figure 2. Forest plots for each associated variable are included as supplementary material (Figures S1 – S5). The summary effect, or weighted mean, and 95%

confidence intervals for $\dot{Q}$ and related haemodynamics at each gestational age are provided in Table 2 and presented in Figure 3. Observations of the results are discussed below; no statistical tests have been performed to infer differences between gestational ages.

During the first trimester, $\dot{Q}$ was 0·74 L·min^{-1} (15%) higher than non-pregnant values. The peak value of 6·48 L·min^{-1} for $\dot{Q}$ was observed in the early third trimester; representing a 1·5 L·min^{-1} (31%) increase above non-pregnant values. $\dot{Q}$ did not increase linearly until peak, observed by a small drop of 0.11 L·min^{-1} (2%) from the early second to late second trimester. After the observed peak in the early third trimester, $\dot{Q}$ was lower by 0·41 L·min^{-1} (6%) in the late third trimester. In the early postpartum period, $\dot{Q}$ returned to non-pregnant values, after which, there was a subsequent modest increase in the late postpartum period by 0·63 L·min^{-1} (12%).

HR rose progressively over the course of gestation, reaching its highest value in the late third trimester 16 beats·min^{-1} (24%) above non-pregnant values. Following birth, HR returned to non-pregnant values and remained stable across the early and late postpartum period. From non-pregnant values, SV increased by 6 ml (8%) in the first trimester. The peak adaptation occurred in the early second trimester where a 10 ml (13%) difference from non-pregnant values was identified.

MAP remained relatively stable throughout pregnancy and did not exceed non-pregnant values at any gestational age. The greatest reduction from non-pregnant values occurred during the second trimester with an average decrease of 8 mm Hg (9%). SVR progressively decreased over the course of pregnancy, with the lowest value 396 dyne·s·cm^{-6} (30%) below non-pregnant values occurring during the early third trimester. As expected with the limited changes in MAP, SVR followed a similar pattern to that observed in $\dot{Q}$. Following birth, SVR returned to non-pregnant values.

The greatest difference in LV mass was observed during the early third trimester with an increase of 40 g (34%) above non-pregnant values. Despite returning to non-pregnant levels in the early postpartum period, LV mass remained elevated by 9 g (8%) in the late postpartum period.

Discussion

The aim of the present study was to determine the time course of adaptation in $\dot{Q}$ and related haemodynamics in response to healthy pregnancy from previously published observational data. The results from the present meta-analyses show that $\dot{Q}$ increases during healthy pregnancy, however the pattern of change may not be linear up until the point of peak adaptation. These findings may have important implications in identifying healthy *vs.* abnormal adaptation of the maternal cardiovascular system during gestation.

Cardiac output changes in the first trimester

During healthy pregnancy, $\dot{Q}$ is known to increase above non-pregnant levels; however the magnitude and time course of change remains unclear within the published literature. Discrepancies in the reported adaptation of $\dot{Q}$ early in pregnancy exist and it is not well understood if the changes occur as a result of increases in SV, HR or a combination of both contributing factors[2, 11]. Increased SV, as a result of an increased blood volume, was previously believed to be the main determinant of the increase in $\dot{Q}$ in the first trimester[4, 8, 32]. However, the present results showed only a small contribution of SV to the observed increase in $\dot{Q}$[6, 9]. This may be result of substantial vasodilation of the renal and systemic circulation combined with an increased capacity and filling state of the venous compartment accommodating the increased blood volume[33, 34]. Supported by previous longitudinal data[27], the

present study shows a reduction in SVR from pre-pregnancy to early first trimester indicating a reduction in afterload, which in turn, will stimulate the sympathetic nervous system, and increase HR. Thus, the results from the present analyses indicated that increased $\dot{Q}$ early in pregnancy may be largely the result of a reduced afterload.

Peak cardiac output in the early third trimester

As discussed within previous reviews[2, 11], the third trimester has been associated with significant discrepancies in the pattern of $\dot{Q}$ adaptation; with either a continual increase, decrease, or plateau within the final weeks of gestation. Supporting some of the previous data[6, 7], this study shows peak $\dot{Q}$ is achieved in the early third trimester, followed by a decrease towards term. One explanation for this pattern could be that compression of the inferior vena cava as a result of considerable and progressive foetal growth occurring during the third trimester affects venous return[2]. In addition, blood flow to the uteroplacental circulation is at its peak (approximately 12% of total $\dot{Q}$) during the late third trimester in order to meet foetal metabolic demands[35, 36]. Both factors could contribute to a reduced cardiac preload and therefore $\dot{Q}$ during the late third trimester. The progressive increase in HR throughout pregnancy peaking in the late third trimester, identified previously[5, 13, 27] and confirmed here, likely offsets the decrease in cardiac preload, thus maintaining $\dot{Q}$ at a functional level until delivery. The alterations in HR, SVR and LV mass reflect increased sympathetic activation, decreased vascular tone, and structural remodelling of the maternal heart, all of which may be secondary to hormonal surges and an increased physiological demand of gestation. In line with the decrease from peak $\dot{Q}$ in the late third trimester, the results from the present analyses also show that LV mass declines prior to delivery. Whilst this finding has not been observed previously with the literature, the consistent confidence intervals in these meta-analyses suggest that this is a physiological phenomenon. Speculatively, this decline may be as a result of changes in LV wall stress[37] and/or

reductions in hormonal concentrations in late third trimester, such as placental growth factor[38], but future investigations are warranted.

Non-linear increase of $\dot{Q}$ during pregnancy

The results of this study demonstrate the increase in $\dot{Q}$ until peak during pregnancy may not be linear. From the non-pregnant state to term, a steady and progressive rise in $\dot{Q}$ is interrupted by small reductions in the late second trimester and late third trimester, with the peak value achieved between these points in the early third trimester. As shown in supplementary Figure S6(a), this finding may not have been observed in previous literature due to the simple collation of data by trimester. As discussed previously, the reduction in $\dot{Q}$ in the late third trimester is supported by previous literature and likely occurs as a result of a reduction in cardiac preload. However, the small reduction in $\dot{Q}$ during the late second trimester has not previously been observed and may also be attributed to changes in cardiac preload. Maternal-foetal circulation within the placenta is only achieved after 14 weeks gestation yet uteroplacental blood flow remains stable until 20 weeks gestation[39], after which it increases rapidly as a result of foetal growth and metabolic demand. Blood volume remains relatively unchanged during the second trimester which, when combined with a progressively increasing uteroplacental blood flow, may cause the drop in venous return and hence SV during the late second trimester[40]. Appropriately powered longitudinal studies with assessments at regular intervals across gestation should be used to statistically confirm these findings.

Postpartum regression of adaptation

As discussed in a previous review[2], $\dot{Q}$ is considerably reduced after delivery in the early postpartum period returning to non-pregnant values. The rapid decline in $\dot{Q}$ following birth is likely a consequence of reduced maternal cardiovascular demand and

hormonal drive following delivery[41]. Within the extended postpartum period, $\dot{Q}$ increases modestly above non-pregnant values[11]. Previous studies have reported prolonged effects on cardiovascular function following gestation, including increased arterial compliance[42]. In the late postpartum, SVR is reduced below non-pregnant and early postpartum levels. Favourable peripheral adaptations post-pregnancy may contribute to the increased $\dot{Q}$ at this time point. In addition, many factors likely influence maternal $\dot{Q}$ in the postpartum period. Breastfeeding and/or a return to physical activity after birth may also explain the variability in the regression of cardiac structure and function observed.

Clinical implications

The understanding of pregnancy-related cardiovascular complications, such as pre-eclampsia and gestational hypertension, is limited by the incomplete understanding of healthy cardiovascular adaptation to pregnancy. Whilst it is generally accepted that $\dot{Q}$ increases during healthy pregnancy, the time course of adaptation, as determined in this study, provides new insight into the expected timing and magnitude of responses. These meta-analyses have suitable power from a pooled observational dataset to provide a representative 'norm' of adaptations to $\dot{Q}$ and related haemodynamics during uncomplicated gestation. The findings represent the healthy cardiac adaptation to pregnancy.

Limitations and future directions

Whilst the present meta-analyses offer new insight into the course of cardiovascular adaptation to healthy pregnancy, limitations of this study must be acknowledged. Despite the pooled sample sizes being greater than most pregnancy research studies, it must be highlighted that within each of the meta-analyses for $\dot{Q}$, the sample size ranged between 258 and 748 (data presented in Figure 1 and supplementary data -

Table S2). The reductions in the sample size within analyses for additional haemodynamic parameters must also be considered. Careful interpretation of results from analyses with a low sample size is required (Table S2). Inclusion in the meta-analyses was based on the mean gestational age at assessment fitting within a predefined time frame, and took no consideration of the range or SD of this mean, thus, overlap between gestational ages may be present within the analyses. Statistical significance was not analysed between the meta-analyses of each gestational age for each parameter so all reported results are observations of trends and must be interpreted carefully.

There are limitations to each methodology included within these analyses that should be considered. The determination of $\dot{Q}$ by inert gas rebreathing relies upon correct alveolar gas mixing and a constant oxygen saturation during measurement[43] which cannot be confirmed without invasive procedures. The calculation of $\dot{Q}$ from impedance cardiography is based upon assumptions that may not be appropriate during pregnancy as a result of the developing foetal unit[44]. In echocardiography, the upward shift of the diaphragm may interfere with the image acquisition[45] which may alter the reliability of measurement. However, echocardiography is the preferred method for cardiac imaging during pregnancy[46]. To identify if the results of these analyses were altered due to the inclusion of varying methodologies, the analyses were completed with studies using echocardiography only (n = 29). Only minor differences between the two outputs were noted (see supplementary Figures S6(b)). The values derived from incorporation of the differing techniques in these analyses may allow a wider application within clinical practice and research.

The left lateral position has been shown to be a preferable position for $\dot{Q}$ measurement in pregnant women in order to avoid inferior vena cava compression[47]. Accordingly,

the meta-analyses were re-run on studies that collected data in the left lateral position only (n = 29). Comparison of these analyses to the total dataset suggested limited impact of maternal position (see supplementary Figure S6(c)).

An influence of parity, ethnicity, pre-pregnancy BMI, and gestational weight gain have previously been observed[2, 11]. The impact of breast feeding on postpartum regression has also not been addressed within this study. These analyses were limited in control of these factors due to the inherent use of previously published data. Future studies should be conducted with consideration for maternal factors and should investigate their impact on the course of cardiovascular adaptation during and after healthy pregnancy.

Conclusions

Through use of meta-analyses based on observational data, this study shows that $\dot{Q}$ is increased above non-pregnant levels as early as the first trimester, reaching its peak in the early third trimester. Importantly, the present results indicate that changes in $\dot{Q}$ may not increase linearly to this peak; however these observations require confirmation from robust longitudinal studies. The results of this study may serve as a reference point for cardiovascular adaptation to healthy pregnancy and therefore, could enable the identification of a maladaptive maternal response.

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Data sharing statement: The full set of data from included studies in these meta-analyses is available upon request from the corresponding author at vimeah@cardiffmet.ac.uk.

Transparency: The lead author (VLM) affirms that the manuscript is an honest, accurate and transparent account of the study being reported. No important aspect of the study has been omitted. No discrepancies are withheld.

References

1 Desai DK, Moodley J, Naidoo DP. Echocardiographic assessment of cardiovascular hemodynamics in normal pregnancy. *Obstet Gynecol* 2004;**104**:20-9.

2 van Oppen AC, Stigter RH, Bruinse HW. Cardiac output in normal pregnancy: a critical review. *Obstet Gynecol* 1996;**87**:310-8.

3 Wallenburg HC. Maternal haemodynamics in pregnancy. *Fetal and Maternal Medicine Review* 1990;**2**:45 - 66.

4 Clapp JF, 3rd, Capeless E. Cardiovascular function before, during, and after the first and subsequent pregnancies. *Am J Cardiol* 1997;**80**:1469-73.

5 Savu O, Jurcut R, Giusca S, et al. Morphological and functional adaptation of the maternal heart during pregnancy. *Circ Cardiovasc Imaging* 2012;**5**:289-97.

6 Mone SM, Sanders SP, Colan SD. Control mechanisms for physiological hypertrophy of pregnancy. *Circulation* 1996;**94**:667-72.

7 Easterling TR, Benedetti TJ, Schmucker BC, et al. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. *Obstet Gynecol* 1990;**76**:1061-9.

8 Robson SC, Hunter S, Boys RJ, et al. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989;**256**:H1060-5.

9 Ogueh O, Brookes C, Johnson MR. A longitudinal study of the maternal cardiovascular adaptation to spontaneous and assisted conception pregnancies. *Hypertens Pregnancy* 2009;**28**:273-89.

10 Estensen ME, Beitnes JO, Grindheim G, et al. Altered maternal left ventricular contractility and function during normal pregnancy. *Ultrasound Obstet Gynecol* 2013;**41**:659-66.

11 Melchiorre K, Sharma R, Thilaganathan B. Cardiac structure and function in normal pregnancy. *Curr Opin Obstet Gynecol* 2012;**24**:413-21.

12 May L. Cardiac Physiology of Pregnancy. *Compr Physiol* 2015;**5**:1325-44.

13 Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. *Circulation* 2014;**130**:1003-8.

14 Mesa A, Jessurun C, Hernandez A, et al. Left ventricular diastolic function in normal human pregnancy. *Circulation* 1999;**99**:511-7.

15 Fok WY, Chan LY, Wong JT, et al. Left ventricular diastolic function during normal pregnancy: assessment by spectral tissue Doppler imaging. *Ultrasound Obstet Gynecol* 2006;**28**:789-93.

16 Geva T, Mauer MB, Striker L, et al. Effects of physiologic load of pregnancy on left ventricular contractility and remodeling. *Am Heart J* 1997;**133**:53-9.

17 Dennis AT, Castro J, Carr C, et al. Haemodynamics in women with untreated pre-eclampsia. *Anaesthesia* 2012;**67**:1105-18.

18 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177-88.

19 Neyeloff JL, Fuchs SC, Moreira LB. Meta-analyses and Forest plots using a microsoft excel spreadsheet: step-by-step guide focusing on descriptive data analysis. *BMC Res Notes* 2012;**5**:52.

20 Tamas P, Szilagyi A, Jeges S, et al. Effects of maternal central hemodynamics on fetal heart rate patterns. *Acta Obstet Gynecol Scand* 2007;**86**:711-4.

21 Armstrong S, Fernando R, Columb M, et al. Cardiac index in term pregnant women in the sitting, lateral, and supine positions: an observational, crossover study. *Anesth Analg* 2011;**113**:318-22.

22 Cornette J, Duvekot JJ, Roos-Hesselink JW, et al. Maternal and fetal haemodynamic effects of nifedipine in normotensive pregnant women. *BJOG* 2011;**118**:510-40.

23 Gyselaers W, Tomsin K, Staelens A, et al. Maternal venous hemodynamics in gestational hypertension and preeclampsia. *BMC Pregnancy Childbirth* 2014;**14**:212.
24 D'Silva LA, Davies RE, Emery SJ, et al. Influence of somatic state on cardiovascular measurements in pregnancy. *Physiol Meas* 2014;**35**:15-29.
25 Vartun A, Flo K, Acharya G. Effect of passive leg raising on systemic hemodynamics of pregnant women: a dynamic assessment of maternal cardiovascular function at 22-24 weeks of gestation. *PLoS One* 2014;**9**:e94629.
26 Moertl MG, Schlembach D, Papousek I, et al. Hemodynamic evaluation in pregnancy: limitations of impedance cardiography. *Physiol Meas* 2012;**33**:1015-26.
27 Mahendru AA, Everett TR, Wilkinson IB, et al. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. *J Hypertens* 2014;**32**:849-56.
28 Borghi C, Esposti DD, Immordino V, et al. Relationship of systemic hemodynamics, left ventricular structure and function, and plasma natriuretic peptide concentrations during pregnancy complicated by preeclampsia. *Am J Obstet Gynecol* 2000;**183**:140-7.
29 Lof M, Olausson H, Bostrom K, et al. Changes in basal metabolic rate during pregnancy in relation to changes in body weight and composition, cardiac output, insulin-like growth factor I, and thyroid hormones and in relation to fetal growth. *Am J Clin Nutr* 2005;**81**:678-85.
30 Schannwell CM, Zimmermann T, Schneppenheim M, et al. Left ventricular hypertrophy and diastolic dysfunction in healthy pregnant women. *Cardiology* 2002;**97**:73-8.
31 Yosefy C, Shenhav S, Feldman V, et al. Left atrial function during pregnancy: a three-dimensional echocardiographic study. *Echocardiography* 2012;**29**:1096-101.
32 Flo K, Wilsgaard T, Vartun A, et al. A longitudinal study of the relationship between maternal cardiac output measured by impedance cardiography and uterine artery blood flow in the second half of pregnancy. *BJOG* 2010;**117**:837-44.
33 Reynolds LP, Borowicz PP, Caton JS, et al. Uteroplacental vascular development and placental function: an update. *Int J Dev Biol* 2010;**54**:355-66.
34 Thornburg KL, Louey S. Uteroplacental circulation and fetal vascular function and development. *Curr Vasc Pharmacol* 2013;**11**:748-57.
35 Dowell RT, Kauer CD. Maternal hemodynamics and uteroplacental blood flow throughout gestation in conscious rats. *Methods Find Exp Clin Pharmacol* 1997;**19**:613-25.
36 Thaler I, Manor D, Itskovitz J, et al. Changes in uterine blood flow during human pregnancy. *Am J Obstet Gynecol* 1990;**162**:121-5.
37 Opie LH, Commerford PJ, Gersh BJ, et al. Controversies in ventricular remodelling. *Lancet* 2006;**367**:356-67.
38 Aasa KL, Zavan B, Luna RL, et al. Placental growth factor influences maternal cardiovascular adaptation to pregnancy in mice. *Biol Reprod* 2015;**92**:44.
39 Coppens M, Loquet P, Kollen M, et al. Longitudinal evaluation of uteroplacental and umbilical blood flow changes in normal early pregnancy. *Ultrasound Obstet Gynecol* 1996;**7**:114-21.
40 Chapman AB, Abraham WT, Zamudio S, et al. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney Int* 1998;**54**:2056-63.
41 Soldin OP, Guo T, Weiderpass E, et al. Steroid hormone levels in pregnancy and 1 year postpartum using isotope dilution tandem mass spectrometry. *Fertil Steril* 2005;**84**:701-10.
42 Morris EA, Hale SA, Badger GJ, et al. Pregnancy induces persistent changes in vascular compliance in primiparous women. *Am J Obstet Gynecol* 2015;**212**:633 e1-6.
43 Farina S, Teruzzi G, Cattadori G, et al. Noninvasive cardiac output measurement by inert gas rebreathing in suspected pulmonary hypertension. *Am J Cardiol* 2014;**113**:546-51.

519 44 McIntyre JP, Ellyett KM, Mitchell EA, et al. Validation of thoracic impedance
520 cardiography by echocardiography in healthy late pregnancy. *BMC Pregnancy Childbirth*
521 2015;**15**:70.
522 45 Rang S, de Pablo Lapiedra B, van Montfrans GA, et al. Modelflow: a new method for
523 noninvasive assessment of cardiac output in pregnant women. *Am J Obstet Gynecol*
524 2007;**196**:235 e1-8.
525 46 Waksmonski CA. Cardiac imaging and functional assessment in pregnancy. *Semin*
526 *Perinatol* 2014;**38**:240-4.
527 47 Bamber JH, Dresner M. Aortocaval compression in pregnancy: the effect of changing
528 the degree and direction of lateral tilt on maternal cardiac output. *Anesth Analg* 2003;**97**:256-
529 8, table of contents.
530 48 Bamfo JE, Kametas NA, Nicolaides KH, et al. Maternal left ventricular diastolic and
531 systolic long-axis function during normal pregnancy. *Eur J Echocardiogr* 2007;**8**:360-8.
532 49 Estensen ME, Grindheim G, Remme EW, et al. Systemic arterial response and
533 ventriculo-arterial interaction during normal pregnancy. *Am J Hypertens* 2012;**25**:672-7.
534 50 Gilson GJ, Samaan S, Crawford MH, et al. Changes in hemodynamics, ventricular
535 remodeling, and ventricular contractility during normal pregnancy: a longitudinal study. *Obstet*
536 *Gynecol* 1997;**89**:957-62.
537 51 Hennessy TG, MacDonald D, Hennessy MS, et al. Serial changes in cardiac output
538 during normal pregnancy: a Doppler ultrasound study. *Eur J Obstet Gynecol Reprod Biol*
539 1996;**70**:117-22.
540 52 Jia RZ, Liu XM, Wang X, et al. Relationship between cardiovascular function and fetal
541 growth restriction in women with pre-eclampsia. *Int J Gynaecol Obstet* 2010;**110**:61-3.
542 53 Kuleva M, Youssef A, Maroni E, et al. Maternal cardiac function in normal twin
543 pregnancy: a longitudinal study. *Ultrasound Obstet Gynecol* 2011;**38**:575-80.
544 54 Novelli GP, Vasapollo B, Gagliardi G, et al. Left ventricular midwall mechanics at 24
545 weeks' gestation in high-risk normotensive pregnant women: relationship to placenta-related
546 complications of pregnancy. *Ultrasound Obstet Gynecol* 2012;**39**:430-7.
547 55 Pandey AK, Banerjee AK, Das A, et al. Evaluation of maternal myocardial performance
548 during normal pregnancy and post partum. *Indian Heart J* 2010;**62**:64-7.
549 56 Poppas A, Shroff SG, Korcarz CE, et al. Serial assessment of the cardiovascular system
550 in normal pregnancy. Role of arterial compliance and pulsatile arterial load. *Circulation*
551 1997;**95**:2407-15.
552 57 San-Frutos LM, Fernandez R, Almagro J, et al. Measure of hemodynamic patterns by
553 thoracic electrical bioimpedance in normal pregnancy and in preeclampsia. *Eur J Obstet*
554 *Gynecol Reprod Biol* 2005;**121**:149-53.
555 58 Tyldum EV, Backe B, Stoylen A, et al. Maternal left ventricular and endothelial
556 functions in preeclampsia. *Acta Obstet Gynecol Scand* 2012;**91**:566-73.
557 59 Valensise H, Novelli GP, Vasapollo B, et al. Maternal cardiac systolic and diastolic
558 function: relationship with uteroplacental resistances. A Doppler and echocardiographic
559 longitudinal study. *Ultrasound Obstet Gynecol* 2000;**15**:487-97.
560 60 Valensise H, Novelli GP, Vasapollo B, et al. Maternal diastolic dysfunction and left
561 ventricular geometry in gestational hypertension. *Hypertension* 2001;**37**:1209-15.
562 61 Valensise H, Vasapollo B, Novelli GP, et al. Maternal total vascular resistance and
563 concentric geometry: a key to identify uncomplicated gestational hypertension. *BJOG*
564 2006;**113**:1044-52.
565 62 van der Graaf AM, Zeeman GG, Groen H, et al. Non-invasive assessment of maternal
566 hemodynamics in early pregnancy. *Pregnancy Hypertens* 2013;**3**:261-9.

567 63 Vasapollo B, Valensise H, Novelli GP, et al. Abnormal maternal cardiac function and
568 morphology in pregnancies complicated by intrauterine fetal growth restriction. *Ultrasound*
569 *Obstet Gynecol* 2002;**20**:452-7.
570 64 Vlahovic-Stipac A, Stankic V, Popovic ZB, et al. Left ventricular function in gestational
571 hypertension: serial echocardiographic study. *Am J Hypertens* 2010;**23**:85-91.
572 65 Wolfe LA, Preston RJ, Burggraf GW, et al. Effects of pregnancy and chronic exercise on
573 maternal cardiac structure and function. *Can J Physiol Pharmacol* 1999;**77**:909-17.
574 66 Yuan L, Duan Y, Cao T. Echocardiographic study of cardiac morphological and
575 functional changes before and after parturition in pregnancy-induced hypertension.
576 *Echocardiography* 2006;**23**:177-82.

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Table 1. Details of included studies.

Study	Design	*n*	Parity	Method	Body position
Armstrong *et al.,* 2011[21]	Cross-sectional	25	NP & MP	Suprasternal Doppler	Left lateral
Bamfo *et al.,* 2007[48]	Cross-sectional	17	NP & MP	Echocardiography	Left lateral
Borghi *et al.*, 2000[28]	Cross-sectional	10 - 35	NP & MP	Echocardiography	Left lateral
Clapp and Capeless, 1997[4]	Longitudinal	30	NP & MP	Echocardiography	Left lateral
Cornette *et al.,* 2011[22]	Cross-sectional	15	DNR	Echocardiography	Left lateral
Desai *et al.,* 2004[1]	Longitudinal	6 - 33	NP & MP	Echocardiography	Left lateral
D'Silva *et al.*, 2014[24]	Longitudinal	28	DNR	Impedance cardiography	Supine
Estensen *et al.,* 2012[49]	Longitudinal	61 - 65	NP & MP	Echocardiography	Left lateral
Geva *et al.,* 1997[16]	Longitudinal	34	NP & MP	Echocardiography	Left lateral
Gilson *et al.,* 1997[50]	Longitudinal	76	NP	Echocardiography	Left lateral
Gyselaers *et al.,* 2014[23]	Cross-sectional	13	NP & MP	Impedance cardiography	Supine/standing
Hennessy *et al*., 1996[51]	Longitudinal	26	DNR	Echocardiography	Left lateral
Jia *et al.,* 2010[52]	Cross-sectional	103	DNR	Impedance cardiography	Left lateral
Kuleva *et al*., 2011[53]	Longitudinal	10	NP & MP	Echocardiography	Left lateral
Lof *et al*., 2005[29]	Longitudinal	22	DNR	Echocardiography	Left lateral
Mahendru *et al.,* 2014[27]	Longitudinal	54	NP & MP	Inert gas re-breathing	Left lateral
Mesa *et al*., 1999[14]	Longitudinal	8 - 35	DNR	Echocardiography	Left lateral
Moertl *et al*., 2012[26]	Longitudinal	48	DNR	Impedance cardiography	Left lateral
Mone *et al*., 2006[6]	Longitudinal	33	NP & MP	Echocardiography	Left lateral
Novelli *et al.,* 2012[54]	Longitudinal	54	NP	Echocardiography	Supine
Ogueh *et al.,* 2009[9]	Longitudinal	10 - 13	NP & MP	Echocardiography	Left lateral
Pandey *et al.,* 2010[55]	Longitudinal	22	DNR	Echocardiography	DNR
Poppas *et al*., 2007[56]	Longitudinal	14	NP & MP	Echocardiography	Left lateral
Rang *et al*., 2007[45]	Longitudinal	16	NP	Echocardiography	Left lateral
San-Frutos *et al.,* 2005[57]	Longitudinal	18	DNR	Impedance cardiography	Left lateral
Savu *et al.,* 2012[5]	Longitudinal	10 - 50	DNR	Echocardiography	Left lateral
Schannwell *et al*., 2002[30]	Longitudinal	46	NP	Echocardiography	DNR
Tamas *et al.,* 2007[20]	Cross-sectional	100	NP & MP	Impedance cardiography	Left lateral
Tyldum *et al.,* 2012[58]	Longitudinal	19	NP & MP	Echocardiography	Left lateral
Valensise *et al*., 2000[59]	Longitudinal	43	NP	Echocardiography	Left lateral
Valensise *et al*., 2001[60]	Cross-sectional	21	DNR	Echocardiography	Left lateral
Valensise *et al.,* 2006[61]	Longitudinal	41	NP & MP	Echocardiography	Supine
Van der Graaf *et al*., 2013[62]	Cross-sectional	116	NP & MP	Suprasternal Doppler	DNR
Vartun *et al*., 2014[25]	Cross-sectional	54 - 108	NP & MP	Impedance cardiography	Supine
Vasapollo *et al*., 2002[63]	Cross-sectional	21	NP	Echocardiography	DNR
Vlahovic-Spipac *et al.,* 2010[64]	Longitudinal	12	DNR	Echocardiography	DNR
Wolfe *et al*., 1999[65]	Longitudinal	19	NP & MP	Echocardiography	Left lateral
Yosefy *et al*., 2012[31]	Cross-sectional	20	DNR	Echocardiography	Left lateral
Yuan *et al.,* 2006[66]	Cross-sectional	24	DNR	Echocardiography	Left lateral

NP, nulliparous; *MP*, multiparous; *DNR*, data not reported.
Further data on methodology is available in supplementary material Table S1.

Table 2. Weighted mean and 95% confidence intervals for cardiac output and related haemodynamics during pregnancy.

	Non-pregnant	First trimester	Early second trimester	Late second trimester	Early third trimester	Late third trimester	Early postpartum	Late postpartum
$\dot{Q}$ (L·min^{-1})	4·96 (4·64 – 5·28)	5·70 (5·23 – 6·18)	6·38 (5·71 – 7·04)	6·27 (5·93 – 6·61)	6·48 (6·21 – 6·76)	6·07 (5·75 – 6·40)	4·91 (4·43 – 5·40)	5·54 (4·99 – 6·10)
HR (beats·min^{-1})	66 (62 – 71)	72 (67 – 77)	73 (70 – 76)	79 (75 – 83)	81 (77 – 85)	83 (80 – 85)	69 (64 – 73)	69 (66 – 72)
SV (ml)	74 (68 – 81)	80 (71 – 90)	84 (73 – 95)	72 (65 – 79)	80 (75 – 86)	77 (70 – 85)	71 (59 – 83)	75 (69 – 80)
MAP (mm Hg)	82 (80 – 84)	80 (77 – 82)	75 (67 – 82)	74 (69 – 80)	78 (77 – 80)	79 (73 – 86)	80 (77 – 82)	81 (77 – 86)
SVR (dyne·s·cm^{-6})	1331 (1226 – 1435)	1170 (1069 – 1270)	974 (912 – 1036)	1027 (985 – 1070)	934 (880 – 989)	981 (935 – 1027)	1325 (1228 – 1423)	1156 (912 – 1401)
LV mass (g)	117 (105 – 130)	125 (114 – 136)	129 (124 – 133)	137 (128 – 149)	157 (146 – 169)	138 (132 – 143)	117 (113 – 122)	126 (118 – 135)

$\dot{Q}$, cardiac output; *HR*, heart rate; *SV*, stroke volume; *MAP*, mean arterial pressure; *SVR*, systemic vascular resistance; *LV,* left ventricular

Figure Legends

Figure 1. Flow diagram of study inclusion and exclusion process.
$\dot{Q}$, cardiac output; *SD*, standard deviation.

Figure 2. Individual forest plots for each meta-analyses of cardiac output at different gestational ages.

Filled grey squares represent study outputs (■). Filled black diamonds (◆) represent the weighted mean as a result of the analyses. Unfilled diamonds (◇) represent outputs from biased analyses that were corrected for using Duval and Tweedie's trim and fill method. Dotted line represents non-pregnant weighted mean on all figures. Black solid line represents weighted mean for that individual gestational age.

† Non-pregnant weighted mean at same value as weighted mean for early postpartum (4.96 vs. 4.91 $L \cdot min^{-1}$).

Figure 3. Compiled weighted mean and 95% confidence intervals derived from meta-analyses for cardiac output, heart rate (HR), stroke volume (SV), mean arterial pressure (MAP), systemic vascular resistance (SVR) and left ventricular (LV) mass at each gestational age.
Coloured bars represent the first, second and third trimester of gestation.
NP, non-pregnant; *T1,* trimester one; *T2,* trimester two; *T3,* trimester three; *PP,* postpartum.