Effects of slow and deep breathing on reducing obstetric intervention in women with pregnancy-induced hypertension: A feasibility study protocol

Felton, M.[a*], Hundley, V.A.[a], Grigsby, S.[ab] and McConnell, A.K.[c]

[a] Bournemouth University, Bournemouth, United Kingdom; [b] St Mary's Maternity Unit, Poole Hospital NHS Foundation Trust, Poole, United Kingdom; [c] Auckland Road, Christchurch, United Kingdom

*Corresponding author e-mail address: mfelton@bournemouth.ac.uk

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Abstract

Objective: To evaluate whether a slow and deep breathing (SDB) intervention is acceptable to pregnant women. *Methods:* The trial aims to recruit 67 pregnant women who have developed pregnancy-induced hypertension (clinicaltrials.gov: NCT04059822). SDB will be undertaken daily for 10-minutes using a video aid and women will self-monitor blood pressure (BP) daily. At 36-weeks gestation women will complete an online questionnaire. Adherence, recruitment rates and acceptance of the intervention will be evaluated. *Conclusion:* The findings from this trial will evaluate if women accept SDB as a treatment method. Initial analysis will evaluate if BP and/or obstetric interventions reduce following SDB intervention.

Keywords: Pregnancy-induced hypertension; gestational hypertension; slow and deep breathing; protocol; women-centered care

Introduction

Hypertension is the most common medical disorder during pregnancy and up to 10% of pregnancies are complicated by hypertension, increasing mortality and morbidity of both mother and baby [1,2]. Hypertensive disorders during pregnancy are the most common cause of mortality in both low and high income countries accounting for 14% of maternal deaths worldwide [3]. Furthermore, there is an increased risk for obstetric complications during all categories of hypertensive pregnancies [4]. Despite the known consequences, there remains no definitive, effective treatment [5].

Controversy surrounding the use of anti-hypertensive medications during pregnancy stems from, i) unclear evidence in relation to maternal benefits; ii) similar uncertainty regarding fetal risks [5]; and iii) reticence of many women to take medication during pregnancy [6]. Therefore, there is an urgent need for new and different methods of treating hypertension during pregnancy; in particular, non-pharmacological options.

A promising lifestyle-related method of reducing blood pressure (BP) in primary hypertension has emerged over the past decade; slow and deep breathing (SDB) encourages users to practice daily bouts of slower than normal breathing (<10 breaths per minute). Whilst some studies have demonstrated clinically meaningful chronic antihypertensive effects of SDB, others have not, and a 2016 Summary Evidence Review [7] concluded that SDB is currently a promising, but unproven treatment for primary hypertension [8]. Nonetheless, a recent meta-analysis found an overall reduction in systolic blood pressure of 5.6 mmHg and 3.0 mmHg in diastolic blood pressure following daily SDB [9].

However, when examining pregnancy-induced hypertension (PIH; hypertension that develops during pregnancy and was not present <20 weeks gestation [10]) there are indications that the condition may be more amenable to treatment using SDB than primary hypertension. The most compellingly of these is that the etiology of PIH has been linked to dysfunctional breathing [11], in particular, high breathing frequencies [12], which may be underpinned by the increase in intra-abdominal mass [13], as caused by pregnancy. A second reason that PIH might be amenable to SDB is that pregnant women with PIH are usually otherwise healthy, minimizing potential confounders, as well as the influence of certain medications upon responsiveness to SDB, e.g., medications affecting the peripheral vasculature. These are important factors that may explain the inter-study variation of BP effect size following SDB in primary hypertension. Finally, there are a number of characteristics that make women with PIH an excellent population in which to evaluate SDB:

- They are the only group of service users to undergo routine monitoring of arterial BP;
- Most pregnant women have an aversion to medication [14];
- Therefore they have high levels of engagement and are highly motivated to comply with non-pharmacological interventions [15].

A number of studies using interventions that include SDB as a component have demonstrated significant reductions in BP in pregnant women post-intervention [16-18]. Additionally, daily practice of SDB improves pregnancy outcomes in women who have PIH, such as birth weight and gestational age at birth [19]. Yoga, which emphasizes slow breath control, has also been shown to improve pregnancy and fetal outcomes, including lowering the incidence of PIH [20,21].

The pathophysiology for PIH and other hypertensive disorders of pregnancy is not fully understood and there are multiple potential pathways and mechanisms that lead to the development of high blood pressure [22]. However, it is generally accepted that PIH is characterized by sympathetic overactivity [23] and there is evidence that yoga and SDB decrease sympathetic dominance and increase parasympathetic activity [24,25]. SDB has also been shown to reduce total peripheral resistance [26], combating the increase in total peripheral resistance associated with PIH [27].

Unfortunately, studies to date are scarce, and have employed non-specific breathing interventions, such as SDB during mindfulness and yoga. These types of breathing exercises require extensive tuition and/or monitoring to ensure that the required breathing frequencies are met; in contrast, guided SDB can be undertaken independently and remotely. A recent-meta analysis of randomized control trials (RCTs) found that SDB interventions where the breathing was guided by an outside source/aid, produced similar reductions in BP as non-guided (pranayama/yoga type) breathing exercises [9]. Therefore, a guided SDB intervention could produce similar reductions in BP, but using

a cheaper, more convenient and robust method that is potentially easier for women to adhere to the optimal breathing frequency.

During the worldwide challenge of coronavirus, at-home interventions that require little interaction with health professionals are of growing importance. Pregnant women have been categorized as 'high-risk' in many countries and there is a need to treat underlying health conditions. SDB interventions could reduce visits to hospital and therefore the burden on the healthcare system.

Additionally, recent studies have found that using at-home BP monitoring during pregnancy can help women feel reassured and empowered by taking control of their condition [28]. It is feasible that SDB may produce similar feelings in pregnant women by giving them control over the intervention and therefore the condition; this has been found in studies of other non-pharmacological treatments [15]. Few trials using digital interventions aimed at pregnant women have conducted in-depth acceptability testing [29]. This study aims to address this gap in knowledge through a rigorously designed feasibility trial of SDB with women who have developed PIH. The study will allow piloting of the study design and provide an understanding of how best to undertake a later, adequately powered RCT.

Methods

Research design

The protocol outlined will assess the feasibility of using SDB, guided by a video pacing aid, to lower BP and reduce obstetric intervention with women who have been diagnosed with PIH. Participants will use a video aid to undertake SDB for 10 minutes daily, in addition to completing daily at-home BP measurements. Clear information will be provided regarding PIH and only BP monitors validated for use with pregnant women will be used. This addresses concerns raised by NHS staff in a previous study [30]. The womens' normal care pathways will be unaffected by trial participation.

Patient and Public Involvement is an ongoing process in the development of the protocol; specifically, a group of pregnant women provided feedback on potential SDB breathing frequencies. The women completed 5 minutes of breathing at 4, 6 and 8 breaths per minute in a randomised order and reported that 6 breaths per minute was the breathing frequency at which they felt most comfortable and would choose to use if they were asked to complete SDB daily.

The study will recruit women from an Antenatal Day Assessment Unit (ANDA) at a single NHS Foundation Trust in England. The enrolment session will be conducted at university premises, and the intervention performed at-home by the women. Ethical approval was granted on 19th December 2019 by Hampshire B Research Ethics Committee and study approval by the Health Research Authority. The study is registered on clinicaltrials.gov (NCT04059822).

Participants and recruitment

Eligible pregnant women are those who have been diagnosed with PIH in accordance with the NICE definition of "new hypertension presenting after 20 weeks of pregnancy without significant proteinuria" [10] or diagnosed as one-off high BP but at risk of developing PIH. This criterion will be verified by midwives and/or obstetricians within ANDA. Potential participants will be assessed against the inclusion and exclusion criteria (Table 1).

[Table 1 near here]

Eligible women will be identified by members of the research team within ANDA, which will include midwives, research midwives and obstetricians. They will be provided with a participant information sheet (PIS) and will opt-in to the study by contacting the lead researcher directly. Women will also be informed of the study by trial posters and leaflets in the ANDA waiting room and on social media.

Thus, women may also self-identify by asking a midwife for a PIS, or by contacting the lead researcher.

There will be at least 24 hours between receiving the PIS and attending the enrolment session. Written consent will be received at the enrolment session, after the women have the opportunity to ask questions. They will then practice using the SDB video aid and receive training in using the automated BP monitor. They will also undertake a short protocol to investigate the immediate cardiovascular responses to SDB with the aim of examining differences between the responses of pregnant women with PIH to existing data from normotensive pregnant and non-pregnant women. The acute responses may also help evaluate differences in the responsiveness of BP to the SDB intervention. The acute responses protocol will involve breathing at different frequencies while cardiovascular responses (including heart rate and BP) are continuously recorded (see online supplement for more details).

Sample size

Sample size was calculated pragmatically given the feasibility nature of the study. ANDA receives between 17-45 women referred for high BP each month. With an average of 28 women per month this is equivalent to 140 over the proposed 6-month recruitment period. It is anticipated that ~25% will be referred immediately for obstetric-led care (leaving 105) and allowing for 20% to be excluded using the exclusion criteria, 84 women will be eligible for this study. Previous recruitment within ANDA suggest ~80% of women undergoing midwife-led care will volunteer (based on previous research), calculating a sample size of n = 67. A sample size of 67 will allow the proportion of women completing at least 57% of their SDB sessions to be estimated with a precision of ±10% (see data collection section for justification of 57% sessions). Precision of this estimate will be based on the width of 95% confidence interval. This assumes that ~80% of women will adhere to the SDB (at least 4 days a week) and that adherence data is available for ~90% of women.

This estimation of sample size is in accordance with the current guidance in the literature for feasibility studies of this nature. Teare et al. [31] suggest between 60-100 participants for a single group feasibility study, while Sim and Lewis [32] recommend at least 50 participants. Although this sample size is optimistic, successful recruitment at this rate is feasible as women are more likely to change their health behaviour during pregnancy [33]. It is also important to note that one of the main aims of this study is to allow a realistic and achievable sample size to be calculated for a future RCT and therefore this study will provide a basis for these calculations.

The SDB intervention

The women will be asked to complete a 10-minute breathing exercise daily to produce a state of SDB. The 10-minute duration is in accordance with previous SDB studies that have used a device to guide breathing (rather than in person guiding such as yoga) in the general population [9] and reflects the duration of yoga-style breathing performed with pregnant women [34]. The breathing exercise will be guided by a video aid, which is accessed via a dedicated webpage. The women will breathe in time with the moving graphic in the video aid; a dome graphic that rises and falls, where participants breathe in when the dome rises and breathe out when the dome falls (Figure 1). By breathing in time with the video aid the women's breathing rate will be reduced to 6 breaths per minute.

[Figure 1 near here]

The video aid can be accessed on any device with an internet connection. Where women don't have access to a stable internet connection, they will be able to download a local copy of the video. The SDB exercise can be completed at any time of day and will be undertaken daily from enrolment until birth. The duration of intervention for individual women will depend on the timing of their diagnosis

and therefore enrolment into the study. Women can be enrolled from 20-weeks gestation and therefore could complete a maximum of 20 weeks SDB if they give birth at 40-weeks.

The women will also self-monitor BP at home using an automated BP monitor (Omron M3 Comfort, Intelli Wrap Cuff). This model has been validated for use by pregnant women with high BP [35]. They will be asked to take 1 measurement daily at a similar time of day, following 5 minutes of rest. To encourage adherence, it will be emphasised that occasional missed readings/sessions are OK, and to continue when they can re-start. This follows findings by Band et al. [29] who found that a barrier to long-term adherence of self-monitoring BP was guilt over missed readings, which stopped women re-engaging with the intervention following missed sessions.

All women will undertake the SDB daily exercises, without a control group, and therefore blinding will not be possible. However, as the primary outcomes for the study are adherence and recruitment rates it is anticipated this will not have an impact on the research findings regarding acceptability in this population group.

Outcomes

Due to the feasibility nature of this study the primary outcome is the proportion of women adhering to the intervention, using proportion of days SDB completed. Reminders won't be conducted in this study to allow a true measure of adherence without interference by investigators. Several secondary outcomes will also be measured (Table 2). The data generated from this trial will provide evidence as to whether a future, larger trial, would be feasible and valuable for accurately measuring clinical outcomes including change in BP and obstetric intervention. The clinical outcomes in this study will only provide preliminary supporting data.

[Table 2 near here]

Data collection

Recruitment rates will be monitored using the number of women screened in ANDA for PIH, those eligible to receive a PIS, and those who are subsequently recruited.

Adherence to the SDB intervention will be monitored using the webpage hosting the video aid. Time of day and time spent watching the video are recorded for each view. As some women may use a downloaded copy of the video aid (webpage data not available) and as the platform hosting the video is untested, women will also complete a daily record detailing their adherence. The daily record can be accessed online, using Online Surveys, or using a paper copy, which will be submitted to researchers. The rates of paper vs. online usage will be monitored to plan for future trials. Women will also use the daily record to record their BP measurements and any difficulties or problems they experienced. The daily record will allow submission of changes in midwife/obstetrician care, medication and after they give birth, the women will record their delivery date and mode of birth.

At 36-weeks gestation the women will be invited to participate in an online questionnaire (Online Surveys). Gestation of 36-weeks was chosen, rather than at the end of the intervention, to reduce the burden on participants after they give birth and reduce the percentage of women who may give birth before 40-weeks. NICE guidelines advise not to offer planned early birth before 37 weeks to women with PIH [10] and therefore most women should not have given birth prior to receiving the questionnaire. However, if a woman does give birth before 36-weeks gestation, she will be sent the questionnaire within 3 weeks. Women experiencing an intrauterine death or stillbirth will not be expected to complete the questionnaire. The questionnaire will gather data on the acceptability of the intervention, asking for the women's thoughts of participating in the intervention and any reasons or barriers for non-adherence. The women will submit feedback on the protocols used in the study and give their opinion on possible options for future trials, such as if they would be willing to

be randomised and if they would have preferred to receive reminders and/or follow up contact from investigators.

Data analysis

For the primary outcome analysis, adherence to the breathing exercises will be assessed in two ways, 1) a pooled estimate of adherence for the whole group calculated by dividing the number of times SDB was completed by the number of times it should have been completed, and (2) the proportion (with 95% confidence interval) of women who completed at least 57% of their SDB sessions. The proportion of 57% adherence was chosen based on the existing guidance to complete at least 40 minutes of SDB per week for treatment of high BP (total time if completed daily = 70-minutes per week [7 days x 10 min]. 40-minutes per week = 57% of 70 min). The same analysis will be completed for adherence to the self-measurement of BP.

The proportion of women who are referred to obstetric-led care will be calculated (with 95% confidence interval) using the number of women who participated in the study against the number who were referred to obstetric-care. The time between consent to referral will be examined using Kaplan-Meier survival analysis. This is potentially a more sensitive measure and takes into account the fact that women will be recruited at, and will give birth at, a variety of gestational ages and therefore be "at risk" of referral for differing lengths of time. A varied duration of enrolment has been used previously in studies with pregnant women who had a inclusion criteria of 24 – 36 weeks [19] and we analyse any differences in relation to duration of participation.

Acceptability measures will be examined using questionnaire responses to assess the acceptability of the intervention and will be analysed in conjunction with adherence rates. The questionnaire data will also provide evidence to support the planning of a future RCT, ensuring that womens' views guide protocol development.

Discussion

This study addresses an important gap in current knowledge regarding SDB, i.e. the anti-hypertensive effects of SDB with women who develop hypertension during pregnancy. It will provide feasibility data on whether SDB is an acceptable treatment for PIH, and therefore provide evidence to support a future RCT. The data will allow accurate estimation of sample size, support for specific protocol design elements, such as reminders, and add to the growing evidence of the benefits of self-monitoring BP during pregnancy. It is important to ensure maternity studies use a women-based approach, which helps promote engagement and adherence [29], and allowing the women to provide feedback in the questionnaire will help shape future protocols based on their experiences. Providing women with a greater feeling of control during pregnancy is important in a world where coronavirus provides an added risk to pregnancy. The SDB at-home intervention could reduce the need for prolonged monitoring in hospital and provide a more 'normal' pregnancy experience for women.

Additionally, although at-home BP monitoring is used by approximately one third of people in the UK who have hypertension [36], few studies have examined the acceptability for pregnant women [28]. This study will quantify adherence to at-home BP monitoring during PIH and provide qualitative feedback.

Limitations

Enrolment into this study uses the 'opt-in' method, which leads to a particular group of people participating. However, pregnant women are very supportive of research and we feel this will appeal to women and should not cause recruitment problems. The study also places additional demands on ANDA midwives to provide the PIS to potential participants, but this is the best way to reach the women.

Although the main outcomes are related to adherence and recruitment rates, secondary clinical outcomes may be influenced by a placebo effect. There may be a beneficial effect of 10-minutes daily relaxation, as opposed to the SDB itself. However, if adherence suggest that the SDB intervention is accepted, our aim is to undertake a follow-up RCT, which would include a placebo breathing protocol. The placebo protocol would replicate the breathing exercise video aid but would not produce a reduced breathing rate when followed by the user.

Overall, this study is the first step in a project to expand the potential benefits of using SDB as a non-pharmacological treatment for PIH. The relatively inexpensive method could easily be transferred for use in low income countries and there is potential to expand the research to investigate the use of SDB with women who are at risk but have not yet developed PIH. Women who subsequently develop PIH have sympathetic overactivity that develops prior to diagnosis during the first trimester [37]; therefore, if SDB can maintain autonomic balance early in pregnancy, sympathetic overactivity could be stopped before it fully develops into PIH. This intervention is especially important while coronavirus is active and underlying health conditions must be monitored and treated.

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Table 1 Participant inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Diagnosed with pregnancy-induced hypertension (PIH) **OR** diagnosed as having one-off high blood pressure but at risk of developing PIH	Referred immediately to obstetric-led care after PIH diagnosis for immediate intervention, with systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg
Over 20 weeks gestation	Carrying a multiple pregnancy
18 years old or older	Current smoker (including vaping)
Capable of giving informed consent	Current diagnosis of respiratory diseases*; asthma, COPD (Chronic Obstructive Pulmonary Disease), bronchitis

** A previous occurrence or diagnosis that has not been present for longer than 1 year does not exclude women, i.e. childhood asthma.*

Table 2 Study Outcomes

Outcome Measures	
Adherence outcomes	Proportion of women undertaking the daily slow and deep breathing intervention *(proportion of days breathing exercise completed)*
	Proportion of women recording blood pressure readings daily *(proportion of days blood pressure measured)*
Recruitment outcomes	Proportion of women meeting eligibility criteria at ANDA
	Proportion of women participating in the study
	Proportion of women not contributing data due to premature delivery, drop-out or worsening high blood pressure
Clinical outcomes	Proportion of women referred to obstetric-led care*
	Changes in blood pressure during intervention period
Other outcomes	Proportion of women who would be willing to be randomised in future trials
	Practicality and acceptance of the protocol in delivering slow and deep breathing as an intervention during pregnancy
	Cardiovascular responses to different slow and deep breathing frequencies *(short-term protocol; see online supplement)*

**Referral to obstetric-led care will be on the grounds of a test result of 30 mg/mmol^{-1} in a spot urinary protein, symptom exacerbation and/or increase in systolic and/or diastolic blood pressure.*

Figure 1:

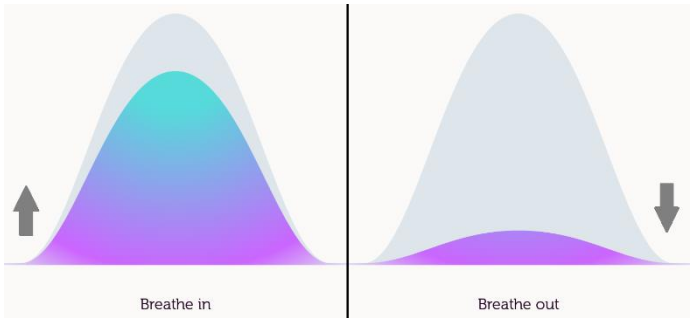

Figure captions:

Figure 1 Screenshots of video aid

N.B: Arrows do not appear on video but are shown here to display the direction of graphic movement.