Efficacy of advice from healthcare professionals to pregnant women on avoiding the wearing of constrictive clothes around the trunk: a study protocol for a randomized, controlled trial

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<td>Protocol</td>
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<td>Date Submitted by the Author:</td>
<td>24-Mar-2015</td>
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| <b>Primary Subject Heading</b>: | Nursing |
| Secondary Subject Heading: | Obstetrics and gynaecology, Nursing |
| Keywords: | Maternal medicine < OBSTETRICS, EPIDEMIOLOGY, PREVENTIVE MEDICINE |
Title page

Title: Efficacy of advice from healthcare professionals to pregnant women on avoiding the wearing of constrictive clothes around the trunk: a study protocol for a randomized, controlled trial

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Keywords:
premature birth, quality of life, randomized controlled trial, midwifery, prenatal care

Word count: 4,019 words (including abstract, acknowledgement, author’s contribution, funding statement, ethics approval, and competing interest.)
ABSTRACT

Introduction:

As a component of midwife care, eliminating clothing that constricts the trunk has been shown to markedly elevate the uterine fundus, soften the uterus and abdomen, and reduce abdominal wall tension in women admitted to hospital due to the risk of miscarriage or premature delivery. However, no prospective study has conclusively verified the efficacy of avoiding the wearing of constrictive clothes around the trunk in pregnant women. We aim to verify the efficacy of instructing pregnant women to wear loose clothing that does not constrict the trunk.

Methods and analysis:

This study will be a randomized controlled trial of pregnant women scheduled to deliver at the National Center for Child Health and Development in Tokyo, Japan. A total of 616 pregnant women from whom written informed consent has been obtained will be allocated randomly to an intervention group or a control group. Women in the control group will be provided with anemia prevention leaflets at 20 weeks and skin-care leaflets at 30 weeks’ gestation. Women in the intervention group will be provided with the same leaflets and will also receive health advice by health professionals to avoid wearing tight clothing that constricts the trunk. The primary outcome will be a difference between these groups in the frequency of any one of the following category variables: (1) cervical length <30 mm up to 28 weeks’ gestation, (2) hospital admission for threatened premature delivery, or (3) premature delivery. Secondary outcomes will include quality of life during pregnancy, maternal state of health, and status of fetal development.

Ethics and dissemination:

This study has been approved by the Institutional Review Board and Ethics Committee of the
National Center for Child Health and Development in Japan. The findings of this study will be disseminated widely through conference presentations and peer-reviewed publications.

Trial registration: UMIN000016853

ARTICLE SUMMARY

Strengths and limitations of this study:

- In this study, healthcare professionals will develop an advice program for pregnant women on suitable types of clothing to wear and how to wear clothing comfortably during pregnancy. The study will verify the program’s efficacy in reducing the risk of premature birth and improving QOL during pregnancy.

- Compared with current premature delivery prevention programs, this program will be noninvasive, economical, and easily provided without the need for special equipment.

- There is limited information on similar interventions in previous studies, and the evidence used for parameters such as sample size calculations may be inadequate.

- Members of the study staff who will implement the intervention, as well as participants, cannot be blinded.

INTRODUCTION

Preventing premature delivery and improving women’s quality of life (QOL) both before and after childbirth are important issues in perinatal medicine. With the incidence of premature delivery at 7.5% in developed countries and 9.6% worldwide,¹ the development of interventional methods that may prevent premature delivery is much needed. Randomized controlled trials (RCTs) and meta-analyses of these methods have already been performed and have demonstrated the
effectiveness of preventive interventions such as therapy with magnesium and other supplements, drug therapy with medications such as terbutaline (a sympathetic β2-receptor agonist), cervical cerclage, bed rest, and relaxation. Thus far, no study has demonstrated the effectiveness of advice from healthcare professionals to pregnant women regarding the avoidance of wearing tight clothing that constricts the trunk area during pregnancy.

Previous studies on the effect of clothing on health in ordinary adults have found that clothing-induced constriction may increase the time taken for feces to pass through the intestines and decrease the amount of feces, increase the incidence of vaginitis, worsen autonomic nervous system function, worsen food digestive function, decrease trunk musculature activity, and increase the risk of lumbar problems. Constipation is one of the most common minor problems experienced by pregnant women, and vaginitis is a known risk factor for premature delivery. Thus, a physiological association between the pressure of clothing on the trunk and premature delivery and reduced QOL during pregnancy is certainly feasible. It has also been suggested that hiesho ("sensitivity to the cold") —a concept widely accepted in Japan and elsewhere in Asia—may be a risk factor for premature delivery, and advice from healthcare professionals on using clothing to prevent feeling cold or chilled has been found to be effective. These previous studies suggest that a focus on clothing during pregnancy may be extremely important. However, previous studies on the types of clothing suitable for pregnant women and ways of wearing clothes comfortably during pregnancy have been limited, and have mostly focused on aspects such as the effectiveness of thigh-length support stockings to improve hemodynamic response. In addition, previous research has shown that the effectiveness of abdominal decompression on normal pregnant women is unclear. Overall, available evidence on the effect of clothing and abdominal compression during pregnancy is currently inadequate.

Between April 2011 and March 2013, we conducted a trial program for pregnant women admitted
to the National Center for Child Health and Development for threatened miscarriage or premature
birth, wherein they were advised by healthcare professionals to reduce the pressure of their clothing
around the trunk area. We then performed a retrospective study by using data from the medical
records of 208 women. We found that after adjustment for age, pre-pregnancy body mass index
(BMI), delivery history, history of threatened miscarriage or premature birth, year of hospitalization,
and prescription medications, the incidence of premature birth at <34 weeks’ gestation was
significantly lower in the intervention group (adjusted odds ratio 0.16, 95% CI: 0.04–0.60). There
was no association, however, with premature birth at <37 weeks’ gestation, for which the adjusted
odds ratio was 0.72 (95% CI: 0.30–1.72). The results of this preliminary study provided important
evidence to support the implementation of a clinical trial of an advice program by healthcare
professionals, however the preliminary study had some limitations.

In the present study, we aim to verify the effectiveness of advice from healthcare professionals to
pregnant women to avoid wearing trunk-constricting clothing in order to reduce the risk of
premature birth and improve QOL during pregnancy.

**METHODS**

**Study design**

This study will be a single blinded, randomized, controlled trial. Figure 1 shows the study design in
detail. It will be implemented at the National Center for Child Health and Development in Japan.

**Participants and recruitment**

The participants of this study will be pregnant women scheduled to give birth at the facility where
the study will be implemented and to whom none of the following 11 exclusion criteria apply: (1)
individuals who undergo their first prenatal checkup after 20 weeks’ gestation or later; (2)
individuals with psychiatric conditions; (3) individuals with uterine deformity; (4) individuals with previous uterine surgery (conization/radical trachelectomy for cervical cancer); (5) individuals who have undergone circumferential suture of the cervix; (6) individuals with fetal diseases; (7) individuals with suspected recurrent pregnancy loss; (8) individuals whose cervical length is already <30 mm before the start of intervention; (9) individuals who are already hospitalized; (10) individuals whose participation has been judged by a doctor as undesirable, and (11) individuals who have difficulty reading, writing, or conversing in Japanese.

For participant recruitment, the study staff will first view information from the medical records of pregnant women scheduled to give birth at the National Center for Child Health and Development after they have undergone a prenatal checkup at approximately 8–10 weeks’ gestation, to ensure that none of the 11 exclusion criteria apply. Participants to whom none of the exclusion criteria apply will be informed of the purpose of the study and its overall outline from the study staff after their prenatal checkup at approximately 12–14 weeks’ gestation. At this checkup, the staff will explain that non-participation in the study will not negatively affect the reception of medical services or midwife care, and that even after they have given consent, they may still withdraw their consent. They will also be informed, however, that it may not be possible for their data to be deleted at their request under certain circumstances, such as after data analysis has been completed. Participants who agree to participate in the study will sign a consent form, which they may either give directly to the study staff or subsequently send to the researchers by mail. Recruitment will continue until the required number of participants has been reached.

**Randomization and blinding**

The RAND function in Microsoft Excel will be used to perform the permuted block method that will allocate participants to the two groups. Doctors and clinical nursing staff in the hospital who
evaluate primary outcomes of this study will be blinded to the results of this allocation. Participants cannot be blinded because the intervention programs vary depending on the group. Participants will also be asked to avoid talking to other pregnant women about the content of the intervention program as much as possible to prevent contamination. The study staff will be responsible for distributing and collecting questionnaires from participants and for performing a number of measurements. We will determine fixed procedures in advance and request that the study staff implement these in order to control performance bias.

**Intervention**

Anemia prevention and skin-care leaflets

Leaflets on anemia prevention and skin care will be distributed to participants in both the intervention and control groups. The participants will receive the anemia prevention leaflet at 20 weeks' gestation and the skin-care leaflet at 30 weeks' gestation from study staff in a private room designated for study participants. After receiving the leaflets, participants will have the opportunity to ask members of the study staff questions regarding the contents of the leaflets. The time required for implementation of the intervention program is approximately 5 minutes. The main content of the anemia prevention leaflet will consist of basic knowledge of anemia, the impact of anemia on maternal and fetal health, and ways to prevent the condition. The skin-care leaflet will cover basic knowledge of skin conditions during pregnancy, including faster growth of facial and body hair, an increase in freckles, and ways to prevent itching and stretch marks.

Constriction Elimination Program

Healthcare professionals will provide this program only to participants in the intervention group after the anemia prevention and skin-care leaflets are distributed. The study staff will explain the
content of the program orally aided by illustrations and demonstrations, and will answer questions from participants. The time required for implementation of the program is approximately 10–15 minutes. The main content of the program will consist of (1) physical changes during pregnancy; (2) potential risks that result from constricting the trunk; (3) types of clothing and how to wear them so as not to constrict the trunk; and (4) how to wear a seatbelt when traveling by car.

During pregnancy, hormonal effects cause the ligaments to loosen, and the shape of the pelvis and chest in particular change to support the uterus as it increases in size. Wearing clothing that constricts the trunk during pregnancy hinders these physical changes from progressing and can cause physical discomfort. Constriction above the uterus causes the uterus to be pressed against the backbone, while constriction in the chest region makes breathing more difficult and prevents the chest from expanding. It is therefore important to avoid clothing that constricts the trunk at any stage of pregnancy, so as not to inhibit natural changes in body shape.

In terms of practical clothing choices and how they should be worn, participants will be instructed to wear loose clothing overall, both as underwear and outer clothing. Clothing tied with ribbons around the chest, as well as tops with built-in brassieres and tank tops, may become tight and cause constriction. Participants will be encouraged to practice caution with these garments. They will be told to avoid brassieres that feel tight and to take preventative measures, such as hooking the fastener of their bra one hook less than usual in order to give a looser fit. Even if briefs or outer clothing do not feel tight, if the elastic or other material leaves a pressure mark on the skin, they should be considered constrictive. Participants will also be told that even the design of underwear and outer clothing sold as maternity wear should be carefully regarded, and that they must be careful when purchasing clothing as some such items are structured to compress the trunk more than necessary. To keep their trunks warm, participants will be encouraged to use non-constricting belly bands, rather than adjusting their underwear or clothing.
Ligaments throughout the body become looser during pregnancy; however, loosening of the pelvis, in particular, causes a range of uncomfortable symptoms. To address these symptoms, participants will be advised to ensure that the elastic of pants and briefs does not come up to the abdomen, but sits above the pubic bone at the hipline, thus supporting excessive loosening.

Advice on how to wear a seatbelt when traveling by car during pregnancy will be provided based on the guidelines for obstetrical practice published by the Japan Society of Obstetrics and Gynecology. In practical terms, this means always wearing both the shoulder and lap belts and ensuring that they do not cut across the bump of the pregnant uterus.

**Outcome measurements**

**Primary outcome**

The primary outcome of this study will be whether any of the following category variables has been met: (1) cervical length <30 mm up to 28 weeks’ gestation, (2) admission to hospital for threatened premature delivery, or (3) premature delivery (gestational age <37 weeks). Data from all 3 categories will be collected from medical records by a blinded gynecologist. A cervical length of <30 mm or <26 mm is associated with a 3.8-fold or 6.2-fold relative risk of premature birth, respectively. The negative predictive values of a cervical length of ≥30 mm at 24 weeks and 28 weeks’ gestation are 97% and 98%, respectively. Considering this gynecological evidence, the criterion of whether or not the cervical length is <30 mm at up to 28 weeks’ gestation is considered to be valid for investigating the efficacy of advice by healthcare professionals for pregnant women.

**Secondary outcomes**

The secondary outcomes of this study comprise data collected for the following 10 items associated with the QOL and state of health of pregnant women: (1) tension and hardness of the abdominal muscles, (2) amount of weight gained, (3) degree of constipation, (4) degree of urinary frequency, (5) degree of leg edema, (6) degree of fatigue, (7) degree of anxiety, (8) degree of depression, (9) degree of difficulty in sleep, and (10) degree of difficulty in daily activities.
wall; (2) temperature of the extremities and trunk region; (3) stress; (4) urinary incontinence; (5) QOL; (6) location of fetal activity; (7) bowel evacuation problems; (8) gynecological complications; (9) velocity of the umbilical artery; and (10) birth weight.

Tension and hardness of the abdominal wall will be measured with a muscle hardness meter at 2 predetermined locations in the abdominal region, and the means of 3 separate measurements will be calculated in each case. Temperature of the extremities and the trunk will be measured by thermography. Stress will be measured using salivary amylase. Urinary incontinence will be assessed using the Japanese version of the International Consultation on Incontinence Questionnaire – Short Form (ICIQ-SF). The QOL will be evaluated using the Japanese version of the SF-8. The location of fetal activity and frequency of bowel evacuation will be ascertained from the answers to questions on subjective frequency and status in a self-administered questionnaire. Data on these 7 items will be collected by the study staff between 20 and 30 weeks’ gestation. Data on the other 3 items (gynecological complications, velocity of the umbilical artery, and birth weight) will be transcribed by study staff from electronic medical records after delivery.

Sample size calculation

When calculating the sample size, the level of significance (α) will be set at 0.05 and the power (1 – β) at 0.8. The previous study on data from medical records included pregnant women who were admitted to hospital for threatened premature birth, unlike the pregnant women of the present study. Nevertheless, the study found an 8.5% difference in the incidence of premature birth at ≤34 weeks’ gestation, with rates of 8.7% in the intervention group and 17.2% in the nonintervention group. In practice, we anticipate the incidence of threatened premature birth at ≤34 weeks’ gestation to be lower than this value, given that the participants of this study will comprise a lower risk population; however, the incidence between groups will indicate the difference made by the intervention.
A survey of all 181 women who gave birth at the National Center for Child Health and Development in Japan in June 2014 found that the exclusion criteria applied to 25 women. Of the remaining 156 women, at least 1 of the 3 items that constituted the primary outcome was found to apply to 22 (14.1%). As the study is currently in the preparatory phase, health professionals are not currently providing advice on constriction of the trunk, suggesting that this 14.1% is from a subject population that has experienced almost no intervention and can be assumed to represent the proportion of outcomes likely to occur in the control group. We used STATA12 to calculate the sample size based on this assumption and the assumption that the 8.5% difference in incidence based on medical record observations from a previous study will be obtained. If the incidence in the intervention group is assumed to be 8.1% (6% difference in incidence), the sample size of a single group should be 462 pregnant women. For an incidence of 7.1% (7% difference in incidence), the sample size should be 331 women, and for an incidence of 6.1% (8% difference in incidence) it should be 246 women. In this study, we expect to achieve an effect close to the 8.5% found in the previous study, and estimate that 246 members in each group will be required to obtain a total sample of 492 women. This will correspond to the 6.1% incidence of the primary outcome in the control group. As we envisage a drop-out rate of 20% of participants between the beginning and end of the study, we calculate that 616 participants (308 in each group) will be required for this study.

Handling of adverse events

In the event of the occurrence or suspected occurrence of any serious adverse events in association with this study, in accordance with the guidelines set out by the researchers’ institution, these events shall immediately be reported in writing to the Chair of the Ethics Committee and the director of the institution concerned. These members will issue advice on whether or not the study will be permitted to proceed. The level of physical invasiveness in this study is extremely low as the intervention
consists of reducing clothing compression around the trunk, and data measurements will consist only of the transcription of data from self-administered questionnaires and electronic medical records, muscle hardness meter and salivary component measurements, and temperature measurement by thermography. Therefore, we believe that there is a low probability that this intervention will directly cause markedly severe adverse events among participants.

Data management

All data collected in this study will be entered and saved on a computer that is isolated from the Internet. All data will be backed up on a password-protected device, and this device will be stringently managed. Only designated members will be able to access the study data. Paper-based documentation, such as consent forms collected during recruitment and questionnaires, will be stored until March 31, 2017 (the end of the study period), after which they will be shredded and disposed of. Electronic data from which individuals can be identified will similarly be deleted on March 31, 2017, but anonymized data sets will be stored long-term and used for generating research results.

Statistical analysis

Data analyses will be performed according to the intention-to-treat approach. Baseline data at 20 weeks of pregnancy will be compared between the intervention and control groups to assess the validity of the randomization process. We will use the Chi-squared test for binary valuables including primary outcomes regarding preterm birth and Student’s t-test or the Mann-Whitney U-test for continuous valuables to evaluate the difference between the 2 groups, with a significance level of 0.05. To perform multivariate analysis, we will use multiple logistic regressions for binary outcomes and multiple linear regressions for continuous outcomes. The regression analyses in this study will be adjusted for any baseline differences and other relevant covariates. The data will be analyzed
using STATA version 12.0 (Stata Corporation, College Station, TX, USA) and SPSS statistics V19.0 (IBM SPSS Statistics for Windows, IBM Corp, Armonk, New York).

As previous studies are not sufficient to calculate the sample size of this study accurately, we will conduct an interim analysis when 100 participants from each group finish this trial. This analysis will estimate the proportion of primary and secondary outcomes in each group and calculate the sample size of this study. However, if the results of the interim analysis show no difference in any outcomes in both groups, we will consider the discontinuation of this study.

ETHICS AND DISSEMINATION

This study is of minimal risk for pregnant women because the intervention programs regarding health advice and leaflets are not invasive. Study staff will explain the objectives and schedule of this study to all participants at recruitment. Participants who do not meet the study criteria or do not give informed written consent will not be enrolled in this study. This study has been approved by the Institutional Review Board and Ethics Committee of the National Center for Child Health and Development in Japan (Approval Number 814). Written consent to participate in this study will be obtained from all eligible participants. The findings of this study will be disseminated widely through peer-reviewed publications and presented at national and international conferences.

DISCUSSION

This study is designed to verify the effect of a unique intervention program, that is, advice by healthcare professionals to pregnant women about types of clothing and how to wear them to reduce the risk of premature birth and improve QOL during pregnancy. This program’s advantages over other premature birth prevention programs include a low level of invasiveness and easy, cost-effective provision, without the need for special equipment. This program could thus be adopted
not only in developed countries but also in developing countries and in rural areas with few medical resources. In addition to demonstrating the effectiveness of such advice by healthcare professionals, the implementation of this randomized comparative study may further highlight suitable types of clothing and wearing styles for pregnant women, thus potentially improving their state of health.

Previous studies on types of clothing for pregnant women and how clothing should be worn have been inadequate, and the possibility that the calculated sample size may not be appropriate cannot, therefore, be ruled out. However, based on the results of a previous retrospective study of data from medical records as well as inferences about physiological causal relationships used in other previous studies, we consider that sufficient evidence is present to indicate that constriction of the trunk has an adverse effect on health.

ACKNOWLEDGEMENTS

The authors appreciate the help received from Dr. Noriyoshi Watanabe, who contributed greatly to the preliminary retrospective study of medical records and the development and design of the current study. The authors also acknowledge the advice and support from medical staff and pregnant women who participated in pilot tests in this center. We also appreciate the editorial support of Emma Barber of the Department of Education for Clinical Research at the National Center for Child Health and Development, for editing this manuscript.

AUTHORS’ CONTRIBUTIONS

SK developed the intervention programs in this study. KT, SK, CN, AS and JSC conducted the preliminary retrospective study using medical records and analyzed the data. KT, SK, AS, JSC, NK, CN, HS, YN, TA, EI and YI participated in the design of this study. KT, SK, NK, HS, YN, TA and YI constructed the logistics of this study. KT and SK mainly wrote the first draft of the manuscript, and
all authors reviewed and revised the manuscript and gave final approval for publication of this protocol.

FUNDING STATEMENT

This work was supported by The Grant of National Center for Child Health and Development (Grant Number: 26-8).

ETHICS APPROVAL

The study protocol has been approved by the Institutional Review Board and Ethics Committee of the National Center for Child Health and Development in Japan (Approval Number 814).

COMPETING INTERESTS

We declare that we have no conflicts of interest.

REFERENCES


Selection of participants based on data from electronic medical records

Recruitment and data collection
Collection of data on basic characteristics

Random allocation

Intervention group

Baseline survey
1. Data collection
2. Provision of anemia prevention leaflet
3. Advice from a healthcare professional on eliminating constriction by clothing in the trunk area

Confirmation of how well participants are implementing the advice given
(Preventing or eliminating constriction)

Control group

Baseline survey
1. Data collection
2. Provision of anemia prevention leaflet

Follow-up survey
1. Data collection
2. Provision of skin-care leaflet

Follow-up survey
1. Data collection
2. Provision of skin-care leaflet

Data collection from medical records

Figure 1  Summary of the study design
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ABSTRACT

Introduction:

As a component of midwife care, eliminating clothing that constricts the trunk has been shown to markedly elevate the uterine fundus, soften the uterus and abdomen, and reduce abdominal wall tension in women admitted to hospital due to the risk of miscarriage or premature delivery. However, no prospective study has conclusively verified the efficacy of avoiding constrictive clothes around the trunk in pregnant women. We aim to verify the efficacy of instructing pregnant women to wear loose clothing that does not constrict the trunk to reduce the risk of premature birth and improve QOL during pregnancy.

Methods and analysis:

We will conduct a randomized controlled trial of pregnant women scheduled to deliver at the National Center for Child Health and Development in Tokyo, Japan. A total of 616 pregnant women, from whom written informed consent will be obtained, will be allocated randomly to an intervention group or a control group. Women in the control group will be provided with anemia prevention leaflets at 20 weeks’ and skin-care leaflets at 30 weeks’ gestation. Women in the intervention group will be provided with the same leaflets and will also receive health advice from health professionals to avoid constrictive clothing around the trunk. The primary outcome will be a difference between these groups in the frequency of any one of the following category variables: (1) cervical length <30 mm up to 28 weeks’ gestation, (2) hospital admission for threatened premature delivery, or (3) premature delivery. Secondary outcomes will include quality of life during pregnancy, maternal state of health, and status of fetal development.

Ethics and dissemination:
The Institutional Review Board and Ethics Committee at the National Center for Child Health and Development, Japan, has approved this study. Our findings will be widely disseminated through conference presentations and peer-reviewed publications.

Trial registration: UMIN000016853

ARTICLE SUMMARY

Strengths and limitations of this study:

- In this study, healthcare professionals will develop an advice program for pregnant women on suitable types of clothing to wear and how to wear clothing comfortably during pregnancy. The study will verify the program’s efficacy in reducing the risk of premature birth and improving quality of life during pregnancy.
- Compared with current premature delivery prevention programs, this program will be noninvasive, economical, and easily provided without the need for special equipment.
- There is limited information on similar interventions in previous studies, and the evidence used for parameters such as sample size calculations may be inadequate.
- Members of the study staff who will implement the intervention, as well as participants, cannot be blinded.

INTRODUCTION

Preventing premature delivery and improving women’s quality of life (QOL) both before and after childbirth are important issues in perinatal medicine. With the incidence of premature delivery at 7.5% in developed countries and 9.6% worldwide, the cultivation of interventional methods to prevent premature delivery is much needed. Randomized controlled trials (RCTs) and meta-analyses...
of these methods have already been performed and have demonstrated the effectiveness of preventive interventions such as therapy with magnesium and other supplements,\(^2\) drug therapy with medications such as terbutaline (a sympathetic β2-receptor agonist),\(^3\) cervical cerclage,\(^4\) bed rest,\(^5\) and relaxation.\(^6\) Thus far, no study has demonstrated the effectiveness of advice from healthcare professionals to pregnant women regarding the avoidance of wearing tight clothing that constricts the trunk area during pregnancy.

Women’s bodies undergo many changes during pregnancy to support the uterus due to hormonal effects. Hormonal activity loosens up ligaments, and increases the capacity of the chest and abdominal cavity. The wearing of tight clothes can therefore interfere with these physical changes and cause discomfort. According to some midwives and obstetricians at our hospital, many pregnant Japanese women tend to choose tighter, more fashionable clothes over looser, more comfortable options. Women may be unaware that tight clothing can constrict their growing body. Even maternity wear, such as maternity pants, belly bands, brassieres, and abdominal support, if tightly fitted may constrict a pregnant woman’s changing shape. Previous studies on the effect of clothing on health in ordinary adults have found that clothing-induced constriction may increase the time taken for feces to pass through the intestines and decrease the amount of feces,\(^7\) worsen autonomic nervous system function,\(^8\) worsen food digestive function,\(^9\) decrease trunk musculature activity, and increase the risk of lumbar problems.\(^10\) Constipation is one of the most common minor problems experienced by pregnant women,\(^11\) and tight clothing may further aggravate this condition.\(^7\)

It has also been suggested that \textit{hiesho} (“sensitivity to the cold”)\(^12\)—a concept widely accepted in Japan and elsewhere in Asia—is a risk factor for premature delivery. Previous studies have shown that pregnant women with \textit{hiesho} have a 3.4–3.5 times higher risk for premature delivery compared to pregnant women without \textit{hiesho}.\(^13,14\) Advice from healthcare professionals on wearing clothes to prevent feeling cold has been found to be effective.\(^15\) Constriction from tight clothes may lead to
hiesho due to restricted blood circulation. Thus, a physiological association of the pressure from
clothing around the trunk with premature delivery and reduced QOL during pregnancy is certainly
feasible.

The above studies suggest that a focus on clothing during pregnancy may be extremely important.
However, previous studies on the types of clothing suitable for pregnant women and ways of
wearing clothes comfortably during pregnancy have been limited, and have mostly focused on
aspects such as the effectiveness of thigh-length support stockings to improve hemodynamic
response. In addition, previous research has shown that the effectiveness of abdominal
decompression on normal pregnant women is unclear. Overall, available evidence on the effect
of clothing and abdominal compression during pregnancy is currently inadequate.

Between April 2011 and March 2013, we conducted a trial program for pregnant women admitted
to the National Center for Child Health and Development for threatened miscarriage or premature
birth, wherein they were advised by healthcare professionals to reduce the pressure of their clothing
around the trunk area. We then performed a retrospective study using data from the medical records
of 208 women. We found that after adjustment for age, pre-pregnancy body mass index (BMI),
delivery history, history of threatened miscarriage or premature birth, year of hospitalization, and
prescription medications, the incidence of premature birth at <34 weeks’ gestation was significantly
lower in the intervention group (adjusted odds ratio 0.16, 95% CI: 0.04–0.60). There was no
association, however, with premature birth at <37 weeks’ gestation, for which the adjusted odds ratio
was 0.72 (95% CI: 0.30–1.72). The results of this preliminary study provided important evidence
to support the implementation of a clinical trial of an advice program by healthcare professionals;
however, the preliminary study had some limitations.

In the present study, we aim to verify the effectiveness of advice from healthcare professionals to
pregnant women to avoid wearing trunk-constricting clothing in order to reduce the risk of
premature birth and improve QOL during pregnancy.

METHODS

Study design

This study will be a single-blinded, randomized controlled trial. Figure 1 shows the study design in detail. It will be implemented at the National Center for Child Health and Development in Japan.

Participants and recruitment

The participants of this study will be pregnant women scheduled to give birth at the facility where the study will be implemented, and to whom none of the following 11 exclusion criteria apply: (1) individuals who undergo their first prenatal checkup after 20 weeks’ gestation or later; (2) individuals with psychiatric conditions; (3) individuals with uterine deformity; (4) individuals with previous uterine surgery (conization/radical trachelectomy for cervical cancer); (5) individuals who have undergone circumferential suture of the cervix; (6) individuals with fetal diseases; (7) individuals with suspected recurrent pregnancy loss; (8) individuals whose cervical length is already <30 mm before the start of the intervention; (9) individuals who are already hospitalized; (10) individuals whose participation has been judged by a doctor as undesirable, and (11) individuals who have difficulty reading, writing, or conversing in Japanese.

For participant recruitment, the study staff will first view information from the medical records of pregnant women scheduled to give birth at the National Center for Child Health and Development after they have undergone a prenatal checkup at approximately 8–10 weeks’ gestation, to ensure that none of the 11 exclusion criteria apply. Participants to whom none of the exclusion criteria apply will be informed of the purpose of the study and its overall outline from the study staff after their prenatal checkup at approximately 12–14 weeks’ gestation. At this checkup, staff will explain that
non-participation in the study will not negatively affect the reception of medical services or midwife care, and that even after they have given consent, they may still withdraw their consent. Participants who agree to participate in the study will sign a consent form, which they may either give directly to the study staff or subsequently send to the researchers by mail. Recruitment will continue until the required number of participants has been reached.

**Randomization and blinding**

The RAND function in Microsoft Excel will be used to perform the permuted block method that will allocate participants to the two groups. Doctors and clinical nursing staff in the hospital who evaluate primary outcomes of this study will be blinded to the results of this allocation. Participants cannot be blinded because the intervention programs vary depending on the group. Participants will also be asked to avoid talking to other pregnant women about the content of the intervention program as much as possible to prevent contamination. The study staff will be responsible for distributing and collecting questionnaires from participants and for performing a number of measurements. We will determine fixed procedures in advance and request that the study staff implement these in order to control performance bias.

**Intervention**

*Anemia prevention and skin-care leaflets*

Leaflets on anemia prevention and skin care will be distributed to participants in both the intervention and control groups. The participants will receive the anemia prevention leaflet at 20 weeks’ gestation and the skin-care leaflet at 30 weeks’ gestation from study staff in a private room designated for study participants. After receiving the leaflets, participants will have the opportunity to ask members of the study staff questions regarding the contents of the leaflets. The time required
for implementation of the intervention program is approximately 5 minutes. The main content of the anemia prevention leaflet will consist of basic knowledge of anemia, the impact of anemia on maternal and fetal health, and ways to prevent the condition. The skin-care leaflet will cover basic knowledge of skin conditions during pregnancy, including faster growth of facial and body hair, an increase in freckles, and ways to prevent itching and stretch marks.

Constriction Elimination Program

Healthcare professionals will provide this program only to participants in the intervention group after the anemia prevention and skin-care leaflets are distributed. The study staff will explain the content of the program orally aided by illustrations and demonstrations, and will answer questions from participants. The time required for implementation of the program is approximately 10–15 minutes. The main content of the program will consist of (1) physical changes during pregnancy; (2) potential risks that result from constricting the trunk; (3) types of clothing and how to wear them so as not to constrict the trunk; and (4) how to wear a seatbelt when traveling by car.

Women will be given the following information in detail. During pregnancy, hormonal effects cause the ligaments to loosen, and the shape of the pelvis and chest in particular change to support the uterus as it increases in size. Wearing clothing that constricts the trunk during pregnancy hinders these physical changes from progressing and can cause physical discomfort. Constriction above the uterus causes the uterus to be pressed against the backbone, while constriction in the chest region makes breathing more difficult and prevents the chest from expanding. It is therefore important to avoid clothing that constricts the trunk at any stage of pregnancy, so as not to inhibit natural changes in body shape.

In terms of practical clothing choices and how they should be worn, participants will be instructed to wear loose clothing overall, both as underwear and outer clothing. Clothing tied with
ribbons around the trunk, as well as tops with built-in brassieres and tank tops, may become tight and cause constriction. Participants will be encouraged to practice caution with these garments. They will be told to avoid brassieres that feel tight and to take preventative measures, such as hooking the fastener of their bra one hook less than usual in order to give a looser fit. Even if briefs or outer clothing do not feel tight, if the elastic or other material leaves a pressure mark on the skin, they should be considered constrictive. Participants will also be told that even the design of underwear and outer clothing sold as maternity wear should be carefully regarded, and that they must be careful when purchasing clothing as some such items are structured to compress the trunk more than necessary. To keep their trunks warm, participants will be encouraged to use non-constricting belly bands, rather than adjusting their underwear or clothing.

Ligaments throughout the body become looser during pregnancy; however, loosening of the pelvis, in particular, causes a range of uncomfortable symptoms. To address these symptoms, participants will be advised to ensure that the elastic of pants and briefs does not come up to the abdomen, but sits above the pubic bone at the hipline, thus supporting excessive loosening.

Advice on how to wear a seatbelt when traveling by car during pregnancy will be provided based on the guidelines for obstetrical practice published by the Japan Society of Obstetrics and Gynecology. In practical terms, this means always wearing both the shoulder and lap belts and ensuring that they do not cut across the bump of the pregnant uterus.

Outcome measurements

Primary outcome

The primary outcome of this study will be whether any of the following category variables has been met: (1) cervical length < 30 mm up to 28 weeks’ gestation, (2) admission to hospital for threatened premature delivery, or (3) premature delivery (gestational age < 37 weeks). Data from all three
categories will be collected from medical records by a blinded gynecologist. A cervical length of <30 mm or <26 mm is associated with a 3.8-fold or 6.2-fold relative risk of premature birth, respectively.\textsuperscript{19} The negative predictive values of a cervical length of \至少 \geq 30 mm at 24 weeks and 28 weeks’ gestation are 97% and 98%, respectively.\textsuperscript{21} Adjusted odds ratios and a 95% confidence interval of 0.95 (0.92-0.98) and 0.94 (0.92-0.97) were used for cervical length at 24–26 weeks and 30–31 weeks for premature delivery.\textsuperscript{22} Considering this gynecological evidence, the criterion of whether or not cervical length is <30 mm at up to 28 weeks’ gestation is considered to be valid for investigating the efficacy of advice from healthcare professionals for pregnant women.

**Secondary outcomes**

The secondary outcomes of this study comprise data collected for the following ten items associated with the QOL and state of health of pregnant women: (1) tension and hardness of the abdominal wall; (2) temperature of the extremities and trunk region; (3) stress; (4) urinary incontinence; (5) QOL; (6) location of fetal activity; (7) bowel evacuation problems; (8) gynecological complications; (9) velocity of the umbilical artery; and (10) birth weight.

Tension and hardness of the abdominal wall will be measured with a muscle hardness meter at two predetermined locations in the abdominal region, and the means of three separate measurements will be calculated in each case. Temperature of the extremities and the trunk will be measured by thermography. Stress will be measured using salivary amylase. Urinary incontinence will be assessed using the Japanese version of the International Consultation on Incontinence Questionnaire – Short Form (ICIQ - SF).\textsuperscript{23} The QOL will be evaluated using the Japanese version of the SF-8.\textsuperscript{24} The location of fetal activity and frequency of bowel evacuation will be ascertained from the answers to questions on subjective frequency and status in a self-administered questionnaire. Data on these seven items will be collected by the study staff between 20 and 30 weeks’ gestation. Data on the
other three items (gynecological complications, velocity of the umbilical artery, and birth weight) will be transcribed by study staff from electronic medical records after delivery.

Sample size calculation

When calculating the sample size, the level of significance ($\alpha$) will be set at 0.05 and the power (1 – $\beta$) at 0.8. Our previous retrospective study based on data from medical records included pregnant women who were admitted to hospital for threatened premature birth, unlike the pregnant women of the present study. Nevertheless, the study found an 8.5% difference in the incidence of premature birth at $\leq$34 weeks’ gestation, with rates of 8.7% in the intervention group and 17.2% in the nonintervention group. In practice, we anticipate the incidence of threatened premature birth at $\leq$34 weeks’ gestation to be lower than this value, given that the participants of this study will comprise a lower risk population; however, the incidence between groups will indicate the difference made by the intervention.

We used STATA12 to calculate the sample size based on this assumption, as well as the assumption that the 8.5% difference in incidence based on medical record observations from our previous retrospective study will be obtained. If the incidence in the intervention group is assumed to be 8.1% (6% difference in incidence), the sample size of a single group should be 462 pregnant women. For an incidence of 7.1% (7% difference in incidence), the sample size should be 331 women, and for an incidence of 6.1% (8% difference in incidence) it should be 246 women. In this study, we expect to achieve an effect close to the 8.5% found in our previous study, and estimate that 246 members in each group will be required to obtain a total sample of 492 women. This will correspond to the 6.1% incidence of the primary outcome in the control group. As we envisage a drop-out rate of 20% of participants between the beginning and end of the study, we calculate that 616 participants (308 in each group) will be required for this study.
Handling of adverse events

In the event of the occurrence or suspected occurrence of any serious adverse events in association with this study, in accordance with the guidelines set out by the researchers’ institution, these events shall immediately be reported in writing to the Chair of the Ethics Committee and the director of the institution concerned. These members will issue advice on whether or not the study will be permitted to proceed. The level of physical invasiveness in this study is extremely low as the intervention consists of reducing clothing compression around the trunk, and data measurements will consist only of the transcription of data from self-administered questionnaires and electronic medical records, muscle hardness meter and salivary component measurements, and temperature measurement by thermography. Therefore, we believe that there is a low probability that this intervention will directly cause markedly severe adverse events among participants.

Data management

All data collected in this study will be entered and saved on a computer that is isolated from the Internet. All data will be backed up on a password-protected device, and this device will be stringently managed. Only designated members will be able to access the study data. Paper-based documentation, such as consent forms collected during recruitment and questionnaires, will be stored until March 31, 2017 (the end of the study period), after which they will be shredded and disposed of. Electronic data from which individuals can be identified will similarly be deleted on March 31, 2017, but anonymized data sets will be stored long-term and used for generating research results.

Statistical analysis

Data analyses will be performed according to the intention-to-treat approach. Baseline data at 20
weeks of pregnancy will be compared between the intervention and control groups to assess the
validity of the randomization process. We will use the Chi-squared test for binary valuables,
including primary outcomes regarding preterm birth, and Student’s \( t \)-test or the Mann-Whitney
U-test for continuous valuables to evaluate the difference between the two groups, with a
significance level of 0.05. To perform multivariate analysis, we will use multiple logistic regressions
for binary outcomes and multiple linear regressions for continuous outcomes. The regression
analyses in this study will be adjusted for any baseline differences and other relevant covariates. The
data will be analyzed using STATA version 12.0 (Stata Corporation, College Station, TX, USA) and
SPSS statistics V19.0 (IBM SPSS Statistics for Windows, IBM Corp, Armonk, New York).

As previous studies are not sufficient to calculate the sample size of this study accurately, we will
conduct an interim analysis when 100 participants from each group finish this trial. This analysis
will estimate the proportion of primary and secondary outcomes in each group and calculate the
sample size of this study. However, if the results of the interim analysis show no difference in any
outcomes in both groups, we will consider the discontinuation of this study.

**Monitoring**

A Data Monitoring Board is not needed because the intervention program of this study produces
minimal risk to participants. We will conduct an interim analysis when the number of participants in
both groups reaches 100 women. However, the aim of this interim analysis is not for early stopping
but to redesign the sample size.

**ETHICS AND DISSEMINATION**

This study is of minimal risk for pregnant women because the intervention programs regarding
health advice and leaflets are not invasive. Study staff will explain the objectives and schedule of
participants at recruitment. Participants who do not meet the study criteria or do not give informed written consent will not be enrolled in this study. This study has been approved by the Institutional Review Board and Ethics Committee of the National Center for Child Health and Development in Japan (Approval Number 814). Written consent to participate in this study will be obtained from all eligible participants. The findings of this study will be disseminated widely through peer-reviewed publications and presented at national and international conferences.

**DISCUSSION**

As described above, previous research remains limited on types of clothing for pregnant women and how clothing should be worn. This study is designed to verify the effect of a unique intervention program, that is, advice from healthcare professionals to pregnant women about types of clothing and how to wear them to reduce the risk of premature birth and improve QOL during pregnancy. This program’s advantages over other premature birth prevention programs include a low level of invasiveness and easy, cost-effective provision, without the need for special equipment. This program could thus be adopted not only in developed countries but also in developing countries and in rural areas with few medical resources. In addition to demonstrating the effectiveness of such advice from healthcare professionals, the implementation of this randomized comparative study may further highlight suitable types of clothing and wearing styles for pregnant women, thus potentially improving their state of health.

Previous studies on types of clothing for pregnant women and how clothing should be worn have been inadequate, and the possibility that the calculated sample size may not be appropriate cannot, therefore, be ruled out. However, based on the results of a previous retrospective study of data from medical records as well as inferences about physiological causal relationships used in other previous studies, we consider that sufficient evidence is present to indicate that constriction of the trunk has
an adverse effect on health.

ACKNOWLEDGEMENTS

The authors appreciate the help received from Dr. Noriyoshi Watanabe, who contributed greatly to the preliminary retrospective study of medical records and the development and design of the current study. The authors also acknowledge the advice and support from medical staff and pregnant women who participated in pilot tests in this center. We also appreciate the editorial support of Emma Barber of the Department of Education for Clinical Research at the National Center for Child Health and Development, Tokyo, Japan.

AUTHORS’ CONTRIBUTIONS

SK developed the intervention programs in this study. KT, SK, CN, AS and JSC conducted the preliminary retrospective study using medical records and analyzed the data. KT, SK, AS, JSC, NK, CN, HS, YN, TA, EI and YI participated in the design of this study. KT, SK, NK, HS, YN, TA and YI constructed the logistics of this study. KT and SK mainly wrote the first draft of the manuscript, and all authors reviewed and revised the manuscript and gave final approval for publication of this protocol. All contributors will have the right to access the final dataset of this study.

FUNDING STATEMENT

This work was supported by a grant from the National Center for Child Health and Development, Tokyo, Japan (Grant Number: 26-8).

ETHICS APPROVAL

The study protocol has been approved by the Institutional Review Board and Ethics Committee of...
the National Center for Child Health and Development in Japan (Approval Number 814).

COMPETING INTERESTS

We declare that we have no conflicts of interest.

REFERENCES


Figure 1 Summary of the study design

210x297mm (200 x 200 DPI)
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

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<th>Section/item</th>
<th>Item No</th>
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<td>Administrative information</td>
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<tr>
<td>Title</td>
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<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
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<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
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<td>All items from the World Health Organization Trial Registration Data Set</td>
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<td>Date and version identifier</td>
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<td>Sources and types of financial, material, and other support</td>
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<td>Roles and responsibilities</td>
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<td>Names, affiliations, and roles of protocol contributors</td>
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<td></td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
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<td>5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
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<td>5d</td>
<td>Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)</td>
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</table>
Introduction

Background and rationale
6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

2-5

6b Explanation for choice of comparators


Objectives
7 Specific objectives or hypotheses

5

Trial design
8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, no inferiority, exploratory)

5

Methods: Participants, interventions, and outcomes

Study setting
9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

5

Eligibility criteria
10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

5-6

Interventions
11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

7-9

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)


11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)


11d Relevant concomitant care and interventions that are permitted or prohibited during the trial


Outcomes
12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

9-10

Participant timeline
13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

6,10
Sample size 14  Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment 15  Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation 16a  Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism 16b  Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Implementation 16c  Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions

Blinding (masking) 17a  Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how

17b  If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods 18a  Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

18b  Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
<table>
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<tr>
<td>Data management</td>
<td>Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol</td>
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<tr>
<td>Statistical methods</td>
<td>Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol</td>
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<td>Methods: Monitoring</td>
<td>Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed</td>
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<td>Harms</td>
<td>Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct</td>
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<tr>
<td>Auditing</td>
<td>Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor</td>
</tr>
<tr>
<td>Ethics and dissemination</td>
<td>Plans for seeking research ethics committee/institutional review board (REC/IRB) approval</td>
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<tr>
<td>Protocol amendments</td>
<td>Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)</td>
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<td>Consent or assent</td>
<td>26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)</td>
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<tr>
<td>Consent or assent</td>
<td>26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable</td>
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<td>Confidentiality</td>
<td>27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial</td>
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<td>Declaration of interests</td>
<td>28 Financial and other competing interests for principal investigators for the overall trial and each study site</td>
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<tr>
<td>Access to data</td>
<td>29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators</td>
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<tr>
<td>Ancillary and post-trial care</td>
<td>30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation</td>
</tr>
<tr>
<td>Dissemination policy</td>
<td>31a Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions</td>
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<tr>
<td>Dissemination policy</td>
<td>31b Authorship eligibility guidelines and any intended use of professional writers</td>
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<tr>
<td>Dissemination policy</td>
<td>31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code</td>
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**Appendices**

- **Informed consent materials**
  - 32 Model consent form and other related documentation given to participants and authorised surrogates

- **Biological specimens**
  - 33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.*
Efficacy of advice from healthcare professionals to pregnant women on avoiding constrictive clothing around the trunk: a study protocol for a randomized controlled trial

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<td>Complete List of Authors:</td>
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<td>Obstetrics and gynaecology, Nursing</td>
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<td>Keywords:</td>
<td>Maternal medicine &lt; OBSTETRICS, EPIDEMIOLOGY, PREVENTIVE MEDICINE</td>
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Title page

Title: Efficacy of advice from healthcare professionals to pregnant women on avoiding constrictive clothing around the trunk: a study protocol for a randomized controlled trial

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Keywords:

premature birth, quality of life, randomized controlled trial, midwifery, prenatal care

Word count: 4,146 words (including abstract, acknowledgement, author’s contribution, funding statement, ethics approval, and competing interest.)
ABSTRACT

Introduction:

As a component of midwife care, eliminating clothing that constricts the trunk has been shown to markedly elevate the uterine fundus, soften the uterus and abdomen, and reduce abdominal wall tension in women admitted to hospital due to the risk of miscarriage or premature delivery. However, no prospective study has conclusively verified the efficacy of avoiding constrictive clothes around the trunk in pregnant women. We aim to verify the efficacy of instructing pregnant women to wear loose clothing that does not constrict the trunk to reduce the risk of premature birth and improve QOL during pregnancy.

Methods and analysis:

We will conduct a randomized controlled trial of pregnant women scheduled to deliver at the National Center for Child Health and Development in Tokyo, Japan. A total of 616 pregnant women, from whom written informed consent will be obtained, will be allocated randomly to an intervention group or a control group. Women in the control group will be provided with anemia prevention leaflets at 20 weeks’ and skin-care leaflets at 30 weeks’ gestation. Women in the intervention group will be provided with the same leaflets and will also receive health advice from health professionals to avoid constrictive clothing around the trunk. The primary outcome will be a difference between these groups in the frequency of any one of the following category variables: (1) cervical length < 30 mm up to 28 weeks’ gestation, (2) hospital admission for threatened premature delivery, or (3) premature delivery. Secondary outcomes will include quality of life during pregnancy, maternal state of health, and status of fetal development.

Ethics and dissemination:
The Institutional Review Board and Ethics Committee at the National Center for Child Health and Development, Japan, has approved this study. Our findings will be widely disseminated through conference presentations and peer-reviewed publications.

Trial registration: UMIN000016853

ARTICLE SUMMARY

Strengths and limitations of this study:

- In this study, healthcare professionals will develop an advice program for pregnant women on suitable types of clothing to wear and how to wear clothing comfortably during pregnancy. The study will verify the program’s efficacy in reducing the risk of premature birth and improving quality of life during pregnancy.
- Compared with current premature delivery prevention programs, this program will be noninvasive, economical, and easily provided without the need for special equipment.
- There is limited information on similar interventions in previous studies, and the evidence used for parameters such as sample size calculations may be inadequate.
- Members of the study staff who will implement the intervention, as well as participants, cannot be blinded.

INTRODUCTION

Preventing premature delivery and improving women’s quality of life (QOL) both before and after childbirth are important issues in perinatal medicine. With the incidence of premature delivery at 7.5% in developed countries and 9.6% worldwide, the cultivation of interventional methods to prevent premature delivery is much needed. Randomized controlled trials (RCTs) and meta-analyses
of these methods have already been performed and have demonstrated the effectiveness of preventive interventions such as therapy with magnesium and other supplements,\(^2\) drug therapy with medications such as terbutaline (a sympathetic β2-receptor agonist),\(^3\) cervical cerclage,\(^4\) bed rest,\(^5\) and relaxation.\(^6\) Thus far, no study has demonstrated the effectiveness of advice from healthcare professionals to pregnant women regarding the avoidance of wearing tight clothing that constricts the trunk area during pregnancy.

Women’s bodies undergo many changes during pregnancy to support the uterus due to hormonal effects. Hormonal activity loosens up ligaments, and increases the capacity of the chest and abdominal cavity. The wearing of tight clothes can therefore interfere with these physical changes and cause discomfort. According to some midwives and obstetricians at our hospital, many pregnant Japanese women tend to choose tighter, more fashionable clothes over looser, more comfortable options. Women may be unaware that tight clothing can constrict their growing body. Even maternity wear, such as maternity pants, belly bands, brassieres, and abdominal support, if tightly fitted may constrict a pregnant woman’s changing shape. Previous studies on the effect of clothing on health in ordinary adults have found that clothing-induced constriction may increase the time taken for feces to pass through the intestines and decrease the amount of feces,\(^7\) worsen autonomic nervous system function,\(^8\) worsen food digestive function,\(^9\) decrease trunk musculature activity, and increase the risk of lumbar problems.\(^10\) Constipation is one of the most common minor problems experienced by pregnant women,\(^11\) and tight clothing may further aggravate this condition.\(^7\)

It has also been suggested that hiesho (‘sensitivity to the cold’)\(^12\)—a concept widely accepted in Japan and elsewhere in Asia—is a risk factor for premature delivery. Previous studies have shown that pregnant women with hiesho have a 3.4–3.5 times higher risk for premature delivery compared to pregnant women without hiesho.\(^13, 14\) Advice from healthcare professionals on wearing clothes to prevent feeling cold has been found to be effective.\(^15\) Constriction from tight clothes may lead to
hiesho due to restricted blood circulation. Thus, a physiological association of the pressure from clothing around the trunk with premature delivery and reduced QOL during pregnancy is certainly feasible.

The above studies suggest that a focus on clothing during pregnancy may be extremely important. However, previous studies on the types of clothing suitable for pregnant women and ways of wearing clothes comfortably during pregnancy have been limited, and have mostly focused on aspects such as the effectiveness of thigh-length support stockings to improve hemodynamic response.\textsuperscript{16} In addition, previous research has shown that the effectiveness of abdominal decompression on normal pregnant women is unclear.\textsuperscript{17,18} Overall, available evidence on the effect of clothing and abdominal compression during pregnancy is currently inadequate.

Between April 2011 and March 2013, we conducted a trial program for pregnant women admitted to the National Center for Child Health and Development for threatened miscarriage or premature birth, wherein they were advised by healthcare professionals to reduce the pressure of their clothing around the trunk area. We then performed a retrospective study using data from the medical records of 208 women.\textsuperscript{19} We found that after adjustment for age, pre-pregnancy body mass index (BMI), delivery history, history of threatened miscarriage or premature birth, year of hospitalization, and prescription medications, the incidence of premature birth at <34 weeks’ gestation was significantly lower in the intervention group (adjusted odds ratio 0.16, 95% CI: 0.04–0.60). There was no association, however, with premature birth at <37 weeks’ gestation, for which the adjusted odds ratio was 0.72 (95% CI: 0.30–1.72).\textsuperscript{19} The results of this preliminary study provided important evidence to support the implementation of a clinical trial of an advice program by healthcare professionals; however, the preliminary study had some limitations.

In the present study, we aim to verify the effectiveness of advice from healthcare professionals to pregnant women to avoid wearing trunk-constricting clothing in order to reduce the risk of
premature birth and improve QOL during pregnancy.

METHODS

Study design

This study will be a single-blinded, randomized controlled trial. Figure 1 shows the study design in detail. It will be implemented at the National Center for Child Health and Development in Japan.

Participants and recruitment

The participants of this study will be pregnant women scheduled to give birth at the facility where the study will be implemented, and to whom none of the following 11 exclusion criteria apply: (1) individuals who undergo their first prenatal checkup after 20 weeks’ gestation or later; (2) individuals with psychiatric conditions; (3) individuals with uterine deformity; (4) individuals with previous uterine surgery (conization/radical trachelectomy for cervical cancer); (5) individuals who have undergone circumferential suture of the cervix; (6) individuals with fetal diseases; (7) individuals with suspected recurrent pregnancy loss; (8) individuals whose cervical length is already <30 mm before the start of the intervention; (9) individuals who are already hospitalized; (10) individuals whose participation has been judged by a doctor as undesirable, and (11) individuals who have difficulty reading, writing, or conversing in Japanese.

For participant recruitment, the study staff will first view information from the medical records of pregnant women scheduled to give birth at the National Center for Child Health and Development after they have undergone a prenatal checkup at approximately 8–10 weeks’ gestation, to ensure that none of the 11 exclusion criteria apply. Participants to whom none of the exclusion criteria apply will be informed of the purpose of the study and its overall outline from the study staff after their prenatal checkup at approximately 12–14 weeks’ gestation. At this checkup, staff will explain that
non-participation in the study will not negatively affect the reception of medical services or midwife care, and that even after they have given consent, they may still withdraw their consent. Participants who agree to participate in the study will sign a consent form, which they may either give directly to the study staff or subsequently send to the researchers by mail. Recruitment will continue until the required number of participants has been reached.

Randomization and blinding

The RAND function in Microsoft Excel will be used to perform the permuted block method that will allocate participants to the two groups. Doctors and clinical nursing staff in the hospital who evaluate primary outcomes of this study will be blinded to the results of this allocation. Participants cannot be blinded because the intervention programs vary depending on the group. Participants will also be asked to avoid talking to other pregnant women about the content of the intervention program as much as possible to prevent contamination. The study staff will be responsible for distributing and collecting questionnaires from participants and for performing a number of measurements. We will determine fixed procedures in advance and request that the study staff implement these in order to control performance bias.

Intervention

Anemia prevention and skin-care leaflets

Leaflets on anemia prevention and skin care will be distributed to participants in both the intervention and control groups. The participants will receive the anemia prevention leaflet at 20 weeks’ gestation and the skin-care leaflet at 30 weeks’ gestation from study staff in a private room designated for study participants. After receiving the leaflets, participants will have the opportunity to ask members of the study staff questions regarding the contents of the leaflets. The time required
for implementation of the intervention program is approximately 5 minutes. The main content of the anemia prevention leaflet will consist of basic knowledge of anemia, the impact of anemia on maternal and fetal health, and ways to prevent the condition. The skin-care leaflet will cover basic knowledge of skin conditions during pregnancy, including faster growth of facial and body hair, an increase in freckles, and ways to prevent itching and stretch marks.

Constriction Elimination Program

Healthcare professionals will provide this program only to participants in the intervention group after the anemia prevention is distributed at 20 weeks’ gestation. The study staff will explain the content of the program orally aided by illustrations and demonstrations, and will answer questions from participants. The time required for implementation of the program is approximately 10–15 minutes. The main content of the program will consist of (1) physical changes during pregnancy; (2) potential risks that result from constricting the trunk; (3) types of clothing and how to wear them so as not to constrict the trunk; and (4) how to wear a seatbelt when traveling by car. At 24 and 30 weeks’ gestation, healthcare professionals will assess intervention-group participants in order to check their trunk for pressure marks on the skin and abdominal tension and to assess whether women have experienced any discomfort due to restrictive clothing. Healthcare professionals will also ask participants at 30 weeks’ gestation to complete an open-ended questionnaire about their experience of this program.

Women will be given the following information in detail. During pregnancy, hormonal effects cause the ligaments to loosen, and the shape of the pelvis and chest in particular change to support the uterus as it increases in size. Wearing clothing that constricts the trunk during pregnancy hinders these physical changes from progressing and can cause physical discomfort. Constriction above the uterus causes the uterus to be pressed against the backbone, while constriction in the chest region
makes breathing more difficult and prevents the chest from expanding. It is therefore important to
avoid clothing that constricts the trunk at any stage of pregnancy, so as not to inhibit natural changes
in body shape.

In terms of practical clothing choices and how they should be worn, participants will be
instructed to wear loose clothing overall, both as underwear and outer clothing. We will define
constrictive clothing as clothing that feels tight and uncomfortable to wear, leaves pressure marks on
the skin, and clothing that when removed makes the woman feel more comfortable. For example,
clothing tied with ribbons around the trunk, as well as tops with built-in brassieres and tank tops,
may become tight and cause constriction. Participants will be encouraged to practice caution with
these garments. They will be told to avoid brassieres that feel tight and to take preventative measures,
such as hooking the fastener of their bra one hook less than usual in order to give a looser fit. Even if
briefs or outer clothing do not feel tight, if the elastic or other material leaves a pressure mark on the
skin, they should be considered constrictive. Participants will also be told that even the design of
underwear and outer clothing sold as maternity wear should be carefully regarded, and that they
must be careful when purchasing clothing as some such items are structured to compress the trunk
more than necessary. To keep their trunks warm, participants will be encouraged to use
non-constricting belly bands, rather than adjusting their underwear or clothing.

Ligaments throughout the body become looser during pregnancy; however, loosening of the pelvis,
in particular, causes a range of uncomfortable symptoms. To address these symptoms, participants
will be advised to ensure that the elastic of pants and briefs does not come up to the abdomen, but
sits above the pubic bone at the hipline, thus supporting excessive loosening.

Advice on how to wear a seatbelt when traveling by car during pregnancy will be provided based
on the guidelines for obstetrical practice published by the Japan Society of Obstetrics and
Gynecology. In practical terms, this means always wearing both the shoulder and lap belts and
ensuring that they do not cut across the bump of the pregnant uterus.

Outcome measurements

Primary outcome

The primary outcome of this study will be whether any of the following category variables has been met: (1) cervical length $< 30$ mm up to 28 weeks’ gestation, (2) admission to hospital for threatened premature delivery, or (3) premature delivery (gestational age $< 37$ weeks). Data from all three categories will be collected from medical records by a blinded gynecologist. A cervical length of $< 30$ mm or $< 26$ mm is associated with a 3.8-fold or 6.2-fold relative risk of premature birth, respectively. The negative predictive values of a cervical length of $\geq 30$ mm at 24 weeks and 28 weeks’ gestation are 97% and 98%, respectively. Adjusted odds ratios and a 95% confidence interval of 0.95 (0.92-0.98) and 0.94 (0.92-0.97) were used for cervical length at 24–26 weeks and 30–31 weeks for premature delivery. Considering this gynecological evidence, the criterion of whether or not cervical length is $< 30$ mm at up to 28 weeks’ gestation is considered to be valid for investigating the efficacy of advice from healthcare professionals for pregnant women.

Secondary outcomes

The secondary outcomes of this study comprise data collected for the following ten items associated with the QOL and state of health of pregnant women: (1) tension and hardness of the abdominal wall; (2) temperature of the extremities and trunk region; (3) stress; (4) urinary incontinence; (5) QOL; (6) location of fetal activity; (7) bowel evacuation problems; (8) gynecological complications; (9) velocity of the umbilical artery; and (10) birth weight.

Tension and hardness of the abdominal wall will be measured with a muscle hardness meter at two predetermined locations in the abdominal region, and the means of three separate measurements will
be calculated in each case. Temperature of the extremities and the trunk will be measured by thermography. Stress will be measured using salivary amylase. Urinary incontinence will be assessed using the Japanese version of the International Consultation on Incontinence Questionnaire – Short Form (ICIQ - SF). The QOL will be evaluated using the Japanese version of the SF-8. The location of fetal activity and frequency of bowel evacuation will be ascertained from the answers to questions on subjective frequency and status in a self-administered questionnaire. Data on these seven items will be collected by the study staff between 20 and 30 weeks’ gestation. Data on the other three items (gynecological complications, velocity of the umbilical artery, and birth weight) will be transcribed by study staff from electronic medical records after delivery.

**Sample size calculation**

When calculating the sample size, the level of significance (α) will be set at 0.05 and the power (1 – β) at 0.8. Our previous retrospective study based on data from medical records included pregnant women who were admitted to hospital for threatened premature birth, unlike the pregnant women of the present study. Nevertheless, the study found an 8.5% difference in the incidence of premature birth at ≤34 weeks’ gestation, with rates of 8.7% in the intervention group and 17.2% in the nonintervention group. In practice, we anticipate the incidence of threatened premature birth at ≤34 weeks’ gestation to be lower than this value, given that the participants of this study will comprise a lower risk population; however, the incidence between groups will indicate the difference made by the intervention.

We used STATA12 to calculate the sample size based on this assumption, as well as the assumption that the 8.5% difference in incidence based on medical record observations from our previous retrospective study will be obtained. If the incidence in the intervention group is assumed to be 8.1% (6% difference in incidence), the sample size of a single group should be 462 pregnant
women. For an incidence of 7.1% (7% difference in incidence), the sample size should be 331 women, and for an incidence of 6.1% (8% difference in incidence) it should be 246 women. In this study, we expect to achieve an effect close to the 8.5% found in our previous study, and estimate that 246 members in each group will be required to obtain a total sample of 492 women. This will correspond to the 6.1% incidence of the primary outcome in the control group. As we envisage a drop-out rate of 20% of participants between the beginning and end of the study, we calculate that 616 participants (308 in each group) will be required for this study.

Handling of adverse events

In the event of the occurrence or suspected occurrence of any serious adverse events in association with this study, in accordance with the guidelines set out by the researchers’ institution, these events shall immediately be reported in writing to the Chair of the Ethics Committee and the director of the institution concerned. These members will issue advice on whether or not the study will be permitted to proceed. The level of physical invasiveness in this study is extremely low as the intervention consists of reducing clothing compression around the trunk, and data measurements will consist only of the transcription of data from self-administered questionnaires and electronic medical records, muscle hardness meter and salivary component measurements, and temperature measurement by thermography. Therefore, we believe that there is a low probability that this intervention will directly cause markedly severe adverse events among participants.

Data management

All data collected in this study will be entered and saved on a computer that is isolated from the Internet. All data will be backed up on a password-protected device, and this device will be stringently managed. Only designated members will be able to access the study data. Paper-based
documentation, such as consent forms collected during recruitment and questionnaires, will be stored
until March 31, 2017 (the end of the study period), after which they will be shredded and disposed of.
Electronic data from which individuals can be identified will similarly be deleted on March 31, 2017,
but anonymized data sets will be stored long-term and used for generating research results.

**Statistical analysis**

Data analyses will be performed according to the intention-to-treat approach. Baseline data at 20
weeks of pregnancy will be compared between the intervention and control groups to assess the
validity of the randomization process. We will use the Chi-squared test for binary valuables,
including primary outcomes regarding preterm birth, and Student’s t-test or the Mann-Whitney
U-test for continuous valuables to evaluate the difference between the two groups, with a
significance level of 0.05. To perform multivariate analysis, we will use multiple logistic regressions
for binary outcomes and multiple linear regressions for continuous outcomes. The regression
analyses in this study will be adjusted for any baseline differences and other relevant covariates. The
data will be analyzed using STATA version 12.0 (Stata Corporation, College Station, TX, USA) and
SPSS statistics V19.0 (IBM SPSS Statistics for Windows, IBM Corp, Armonk, New York).

As previous studies are not sufficient to calculate the sample size of this study accurately, we will
conduct an interim analysis when 100 participants from each group finish this trial. This analysis
will estimate the proportion of primary and secondary outcomes in each group and calculate the
sample size of this study. However, if the results of the interim analysis show no difference in any
outcomes in both groups, we will consider the discontinuation of this study.

**Monitoring**

A Data Monitoring Board is not needed because the intervention program of this study produces
minimal risk to participants. We will conduct an interim analysis when the number of participants in both groups reaches 100 women. However, the aim of this interim analysis is not for early stopping but to redesign the sample size.

ETHICS AND DISSEMINATION
This study is of minimal risk for pregnant women because the intervention programs regarding health advice and leaflets are not invasive. Study staff will explain the objectives and schedule of this study to all participants at recruitment. Participants who do not meet the study criteria or do not give informed written consent will not be enrolled in this study. This study has been approved by the Institutional Review Board and Ethics Committee of the National Center for Child Health and Development in Japan (Approval Number 814). Written consent to participate in this study will be obtained from all eligible participants. The findings of this study will be disseminated widely through peer-reviewed publications and presented at national and international conferences.

DISCUSSION
As described above, previous research remains limited on types of clothing for pregnant women and how clothing should be worn.\textsuperscript{7-10, 15, 16, 19} This study is designed to verify the effect of a unique intervention program, that is, advice from healthcare professionals to pregnant women about types of clothing and how to wear them to reduce the risk of premature birth and improve QOL during pregnancy. This program’s advantages over other premature birth prevention programs include a low level of invasiveness and easy, cost-effective provision, without the need for special equipment. This program could thus be adopted into clinical practice not only in developed countries but also in developing countries and in rural areas with few medical resources. In addition to demonstrating the effectiveness of such advice from healthcare professionals, the implementation of this randomized
comparative study may further highlight suitable types of clothing and wearing styles for pregnant women, thus potentially improving their state of health.

Previous studies on types of clothing for pregnant women and how clothing should be worn have been inadequate, and the possibility that the calculated sample size may not be appropriate cannot, therefore, be ruled out. However, based on the results of a previous retrospective study of data from medical records as well as inferences about physiological causal relationships used in other previous studies, we consider that sufficient evidence is present to indicate that constriction of the trunk has an adverse effect on health.

ACKNOWLEDGEMENTS

The authors appreciate the help received from Dr. Noriyoshi Watanabe, who contributed greatly to the preliminary retrospective study of medical records and the development and design of the current study. The authors also acknowledge the advice and support from medical staff and pregnant women who participated in pilot tests in this center. We also appreciate the editorial support of Emma Barber of the Department of Education for Clinical Research at the National Center for Child Health and Development, Tokyo, Japan.

AUTHORS’ CONTRIBUTIONS

SK developed the intervention programs in this study. KT, SK, CN, AS and JSC conducted the preliminary retrospective study using medical records and analyzed the data. KT, SK, AS, JSC, NK, CN, HS, YN, TA, EI and YI participated in the design of this study. KT, SK, NK, HS, YN, TA and YI constructed the logistics of this study. KT and SK mainly wrote the first draft of the manuscript, and all authors reviewed and revised the manuscript and gave final approval for publication of this protocol. All contributors will have the right to access the final dataset of this study.
FUNDING STATEMENT
This work was supported by a grant from the National Center for Child Health and Development, Tokyo, Japan (Grant Number: 26-8).

ETHICS APPROVAL
The study protocol has been approved by the Institutional Review Board and Ethics Committee of the National Center for Child Health and Development in Japan (Approval Number 814).

COMPETING INTERESTS
We declare that we have no conflicts of interest.

REFERENCES
7. Takasu N, Furuoka S, Inatsugi N, et al. The effects of skin pressure by clothing on whole gut...


Figure 1  Summary of the study design

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**Introduction**

Background and rationale

6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

2-5

6b Explanation for choice of comparators


Objectives

7 Specific objectives or hypotheses

5

Trial design

8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

5

**Methods: Participants, interventions, and outcomes**

Study setting

9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

5

Eligibility criteria

10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

5-6

Interventions

11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

7-9

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)


11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)


11d Relevant concomitant care and interventions that are permitted or prohibited during the trial


Outcomes

12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

9-10

Participant timeline

13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

6,10
Sample size  14  Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations  ____10-11____

Recruitment  15  Strategies for achieving adequate participant enrolment to reach target sample size  ______6____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation  16a  Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions  ______6-7____

Allocation concealment mechanism  16b  Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Implementation  16c  Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions

Blinding (masking)  17a  Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  ____6-7____

Blinding (masking)  17b  If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods  18a  Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol  ____9-10____

Data collection methods  18b  Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols  ____9-10____
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 12 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 12-13 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | |

**Methods: Monitoring**

| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 13 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 13 |

**Harms**

| 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 11-12 |

**Auditing**

| 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | |

**Ethics and dissemination**

<p>| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 13-14 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 13-14 |</p>
<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
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<tbody>
<tr>
<td>26a</td>
<td>Consent or assent: Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)</td>
</tr>
<tr>
<td>26b</td>
<td>Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable</td>
</tr>
<tr>
<td>27</td>
<td>Confidentiality: How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial</td>
</tr>
<tr>
<td>28</td>
<td>Declaration of interests: Financial and other competing interests for principal investigators for the overall trial and each study site</td>
</tr>
<tr>
<td>29</td>
<td>Access to data: Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators</td>
</tr>
<tr>
<td>30</td>
<td>Ancillary and post-trial care: Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation</td>
</tr>
<tr>
<td>31a</td>
<td>Dissemination policy: Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions</td>
</tr>
<tr>
<td>31b</td>
<td>Authorship eligibility guidelines and any intended use of professional writers</td>
</tr>
<tr>
<td>31c</td>
<td>Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code</td>
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**Appendices**

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
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<tbody>
<tr>
<td>32</td>
<td>Informed consent materials: Model consent form and other related documentation given to participants and authorised surrogates</td>
</tr>
<tr>
<td>33</td>
<td>Biological specimens: Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable</td>
</tr>
</tbody>
</table>

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.*