BMJ Open

Double-blind, randomised, placebo-controlled trial to evaluate the effectiveness of late gestation oral melatonin supplementation in reducing induction of labour rates in nulliparous women: the MyTIME study protocol

Zoe Bradfield ,[1,2] Scott W White,[3,2] Miranda Davies-Tuck ,[4] Mary Sharp,[2] Jane Warland,[5] Emily Callander,[6] Lesley Kuliukas,[1] Monique Rose,[1,2] Amber Pettitt,[1] Kylie Ekin,[1] Dorota A Doherty,[3] JA Keelan[3]

To cite: Bradfield Z, White SW, Davies-Tuck M, *et al*. Double-blind, randomised, placebo-controlled trial to evaluate the effectiveness of late gestation oral melatonin supplementation in reducing induction of labour rates in nulliparous women: the MyTIME study protocol. *BMJ Open* 2025;**15**:e090370. doi:10.1136/bmjopen-2024-090370

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-090370).

Received 24 June 2024
Accepted 08 January 2025

For numbered affiliations see end of article.

Correspondence to
Dr Zoe Bradfield;
Zoe.Bradfield@curtin.edu.au

ABSTRACT

Introduction Around the world, rates of induction of labour (IOL) among nulliparous mothers have increased in the last 10 years. In Australia, rates have increased over the last decade by 43%, from 32% to 46%. There is growing concern about the rapid rise in IOL before 41 weeks for nulliparous women without medical complications because of the associated increased rates of caesarean section, reduced satisfaction with birth, and birth trauma. Melatonin potentiates the action of oxytocin and may promote the spontaneous onset of labour; therefore, we will test the hypothesis that exogenous melatonin supplementation in late pregnancy will reduce the rate of labour induction by 30% or more.

Methods and analyses This is a double-blind, randomised, placebo-controlled trial in nulliparous pregnant women to reduce IOL rates. We will randomise 530 women to receive either 3 mg oral melatonin or placebo daily from 39^{+0} weeks' gestation until they give birth. The primary endpoint will be IOL rate after 39 weeks post enrolment. Secondary endpoints will include the following: interval between administration of trial medication and birth; a range of maternal and neonatal outcomes, including birth outcomes; breastfeeding on discharge, at 10 days and at 2 months; maternal satisfaction; child developmental outcomes at 2 months of age; and cost-effectiveness of melatonin compared with standard care. All data will be analysed by intention to treat.

Ethics and dissemination The study is approved by the Western Australia Health Central Human Research Ethics Committee (RGS0000006283). Trial findings will be disseminated through conference presentations and peer-reviewed publications.

Trial registration number The trial has been prospectively registered on the Australian New Zealand Clinical Trials Registry as ACTRN12623000502639 on 17/05/2023.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first registered randomised double-blind, placebo-controlled clinical trial investigating the effect of melatonin to improve the onset of spontaneous labour.
⇒ Substudy findings from participants with gestational diabetes mellitus and exploration of child developmental outcomes, not previously undertaken in trials including melatonin supplementation in pregnancy, broaden the utility of trial data and are strengths.
⇒ The trial is conducted within one health service area which may limit generalisability; however, this area is large, encompassing four separate sites, various models of care and all capability levels of maternity care (primary through to quaternary) minimising the impact of this selection bias.
⇒ Singular health service governance over such a large variety of settings supports protocol implementation and compliance and reduces variability, improving trial quality.

INTRODUCTION

There is growing concern around the world about the rapid rise in induction of labour (IOL) before 41 weeks, in the absence of maternal or fetal complications, because of the risk of iatrogenic harm to the mother and baby.[1–6] Obstetric intervention in late pregnancy has inexorably risen over recent decades, more than is accounted for by changing population complexity and risk factors. In Australia, for example, the rate of IOL has increased by 43% over the past decade, from 32% to 46%.[7] This has occurred without a demonstrated reduction in stillbirth, particularly for women without identified risk factors, and with a clear increase

in early-term birth (37–38 weeks) which is known to be harmful to subsequent childhood neurodevelopment.[8] In particular, there is concern about the possible increased incidence of caesarean section, neonatal intensive care unit (NICU) admission and adverse longer-term neurodevelopmental outcomes for children born prior to 39 weeks or after 41 weeks.[2–6 9] Other perinatal morbidity indicators are also rising, including episiotomy, postpartum haemorrhage, maternal sepsis, and maternal and neonatal birth trauma.[4 7 10–12] The association between IOL and increased rates of caesarean section is clear from population studies but this conflicts with the findings of clinical trials, most famously the ARRIVE trial, which show reductions in caesarean section with IOL compared with expectant management.[3 13] In a recent systematic review and meta-analysis, the effect of IOL on caesarean section overall remains unclear.[14]

The WHO guidelines indicate that, for those women whose pregnancies are not complicated, IOL prior to 41 weeks is not recommended.[15] For pregnant women without medical complication, the most common reason for IOL is prolonged pregnancy beyond 42 completed weeks.[7] Recent evidence from studies around the world reveals that, among women, the broad acceptability of IOL is low[2 16] and may increase the risk of traumatic stress.[17] There is limited evidence regarding the long-term perinatal outcomes of IOL. One Australian retrospective cohort study showed increased incidence of hospital admission for ear, nose, throat and respiratory complaints and sepsis up to 16 years of age.[4] A retrospective cohort study in the Netherlands revealed an association between IOL and reduced offspring school performance which, although small in magnitude, is of clinical relevance when occurring at a population level.[11]

The backdrop of conflicting practice, guidelines and ad hoc translation of evidence to practice sees a clinical landscape that is confusing to women and practitioners alike. The dilemma for clinicians and pregnant women is founded in balancing (i) the risks of causing iatrogenic short- and long-term harm associated with non-medically indicated IOL versus (ii) the risks of poorer perinatal outcomes with later or no intervention. The solution to be investigated in this study is a simple, cost-effective and widely accessible approach that seeks to optimise and potentiate maternal physiology in late term to improve rates of spontaneous births after spontaneous onset, thereby reducing the need for IOL.

Induced by circadian cycles of light and darkness, maternal melatonin levels naturally peak at night under the influence of circadian control and trend upwards during pregnancy.[18] Melatonin levels rise in response to falling daylight and peak between 23:00 hours and 04:00 hours.[19] From 24 weeks' gestation, the uterine muscles begin a diurnal pattern of contraction, two-thirds of which occur at night, under the influence of nocturnal melatonin levels.[18] These contractions are largely imperceptible to the mother but increase in strength and frequency as the pregnancy progresses to late term. Recent in vivo observations and ex vivo findings demonstrate synergistic actions between melatonin and oxytocin demonstrating that melatonin sensitises myometrial cells to oxytocin, driving pulsatile contractions of the uterine muscles.[20–22] Since most (72%) spontaneous labour occurs at night,[23] which is when maternal serum melatonin levels peak,[19] the synergistic action between melatonin and oxytocin is a natural and feasible link to test in this clinical trial.

Contemporary environmental and lifestyle factors are known to negatively impact upon endogenous melatonin production and release. Exposure to blue light through screens and mobile devices, sleep disturbance, shift work and changes to lifestyle factors such as diet and exercise can all decrease melatonin synthesis and release.[20 24 25] A clinical trial conducted in the USA examined the melatonin levels of late-term pregnant women who were exposed to short-wave light (known to inhibit endogenous melatonin levels). Investigators monitored uterine activity and melatonin levels before, during and after the intervention. Uterine activity and melatonin levels were reduced by more than 50% in those who were exposed to the short-wave light intervention. After intervention was withdrawn, serum melatonin levels restored to baseline and the uterine activity continued. These findings highlight the sensitivity of melatonin release to environmental triggers and the impact of melatonin on uterine contractility. Investigators concluded that exogenous melatonin may be a useful addition to the care of late-term pregnancy, to counter the influence of environmental changes, or as an adjuvant to labour.[20] In a recent observational study, this understanding was applied and further extended in a study conducted on women with late-term pregnancies. In Türkiye, melatonin levels were obtained from 362 women of varying gestations from term (40 weeks) to late term (42 weeks). Lower melatonin levels were highly predictive for prolonged pregnancy without labour. Higher melatonin levels were found in term and post-term women who laboured spontaneously. Investigators concluded that melatonin could be considered as a therapeutic agent to support effective labour.[26] These studies point to the role melatonin may play in spontaneous onset of labour and uterine contractility and thus provide support for the use of melatonin in this trial.

Rationale

In many Organisation for Economic Co-operation and Development (OECD) nations around the world, rates of IOL have increased sharply in the last decade.[5 6 27] Despite escalated investment and medical intervention, rates of stillbirths, neonatal deaths and maternal mortality remain largely unchanged. Conversely, rates of some maternal and neonatal morbidity indicators have increased.[7 28] Despite its rising prevalence, IOL is not a benign intervention, associated with increased risk of caesarean section in nulliparous mothers, birth trauma and signals for potential longer-term childhood impacts.[2 4 7 10–12] Contemporary changes to human behaviour and environments that increase light exposure can interfere with melatonin

synthesis and release which may contribute to prolonged pregnancy.[20 24 25] Melatonin supplementation is known to be safe in pregnancy.[18 29–32] Late-term supplementation with melatonin may optimise maternal physiology and reduce the need for IOL by promoting the spontaneous onset of labour.

Aim

The aim of this clinical trial is to determine if oral supplementation with 3 mg melatonin nightly from 39 weeks' gestation in nulliparous women will reduce IOL rates.

METHODS AND ANALYSIS

This protocol has been developed using an approved template for Clinical Trials, which is based on Therapeutic Goods Administration guidelines, Standard Protocol Items: Recommendations for Interventional Trials guidelines and WHO recommendations.

Study design

This study is a phase 3 placebo-controlled double-blind, randomised clinical trial. Trial design with nested substudies is shown in figure 1.

Substudies

It is widely understood that melatonin plays an important role in supporting the onset and continuation of sleep.[33] There is also emerging evidence that melatonin plays a role in regulating blood glucose levels.[34 35] Two substudies investigating impact on women's sleep (MyTIME+Sleep) and blood glucose control (MyTIME+Sweet) are embedded within the trial design (figure 1).

Trial timeline

The planned timeline is January 2024–January 2027.

Study setting

The trial will be conducted within Women and Newborn Health Service (WNHS), the largest maternity service in Western Australia. The service cares for around 8000 women per year giving birth across the Perth metropolitan area as well as tertiary referral care for women from around Western Australia, the largest area health service in the world. Care is provided through a range of settings and models including (i) a quaternary/tertiary referral maternity hospital (King Edward Memorial Hospital (KEMH)); (ii) a secondary maternity service (Osborne Park Hospital); (iii) primary birthing services offered through the state's only stand-alone birth centre (Family Birth Centre); and (iv) publicly funded home-birth programme (Community Midwifery Program).

Participants

Pregnant nulliparous women at 39 weeks' gestation who meet inclusion criteria booked to birth at one of the settings within the WNHS. Other inclusion and exclusion criteria are detailed in table 1.

While not a specific criterion for inclusion, clarification is offered that women with gestational diabetes mellitus (GDM) (not taking metformin or insulin) are able to be included in this trial. Women who require the aid of a language interpreter are able to be included in this trial.

Recruitment and informed consent

Eligible potential participants will be approached at the various sites by a clinical trial midwife at their routine 36-week antenatal appointment who will provide them with information about the trial. If the potential participant is interested, the participant information form will be given to them to read and consider. Information will also be provided upon an eligible potential participant contacting the study team, if they hear about the trial from a recruitment poster or other source.

At the potential participant's routine week 38 antenatal appointment, if they are willing to participate, they will provide written informed consent to the trial with a study staff member.

A subset of n=30 participants will be invited to participate in the MyTIME+Sleep substudy (n=15 from each of the melatonin and placebo groups). Participants will be asked to give permission for a trial midwife to visit their home at night to collect pre/post-melatonin bloods and cord blood after birthing. Melatonin measurements are for ascertaining the efficacy of the intervention in elevating maternal circulating melatonin levels. Participants will also wear an actigraphy device (Axivity Model AX3) to provide objective sleep data.

All participants with diet-controlled GDM will be asked to participate in the MyTIME+Sweet substudy. It is anticipated that up to 150 women may be eligible to participate during the planned trial data collection period of 2 years. Substudy participation involves wearing a (trial supplied) continuous glucose monitor (CGM) for the trial duration. Those who do not wish to wear a CGM may continue in the trial with routine GDM care undertaking a four-point profile involving a finger prick blood glucose test four times a day.

Participant retention is expected to be high, due to the strong consumer interest in this trial and short intervention duration.

Randomisation and blinding

Participants will be randomised to melatonin or placebo in a 1:1 ratio. Randomisation will be stratified by model of care (continuity or non-continuity), GDM, and MyTIME+Sleep substudy enrolment. Computer-based block randomisation will occur in varied block sizes of two, four, six and eight participants according to the strata.

A statistician will prepare the randomisation sequence for the trial, which will be implemented electronically using the Research Electronic Data Capture (REDCap) randomisation module, which blinds the trial staff enrolling participants from the assigned allocation. Only

Figure 1 Study schematic. ASQ, ages and stages Questionnaire; GDM(d), gestational diabetes mellitus (diet-controlled); IP, investigational product; PK, pharmacokinetic; QOL, quality of life;

Table 1 Inclusion and exclusion criteria

Inclusion	Exclusion
Nulliparous	Women with indications for induction of labour (IOL) or caesarean section prior to 40 weeks and 10 days because of medical and/or obstetric complications
Singleton, live pregnancy	Any known fetal congenital abnormality or compromise/condition that would necessitate admission to neonatal intensive care unit after birth
Cephalic presentation	Women with diagnosed fetal death in utero at recruitment
No clinical indication for IOL at time of recruitment	Any known sensitivity or adverse reaction to melatonin or excipients in melatonin formulation
Awaiting onset of spontaneous labour	Fetal growth restriction (abdominal circumference or estimated fetal weight <10th centile) with abnormal dopplers
Not planning a scheduled birth before 41 weeks' gestation unless subsequently indicated	Women with gestational diabetes mellitus taking metformin or insulin, or those with type I or II diabetes
Age 16 and over	Unable/unwilling to follow direction in participant information and consent form
Able to provide written informed consent to participate in the clinical trial	Unable to provide informed consent (mentally, legally, cognitively incapacitated)
	Co-recruitment in another trial where there are competing pharmaceutical or nutritional interventions
	Currently taking a medication known to influence melatonin pharmacokinetics or bioavailability

the unblinded pharmacy team will be aware of the allocation to facilitate dispensing.

Study intervention

The study intervention is melatonin slow release (3 mg) encapsulated tablet administered orally in the evening. Placebo is selected as a comparator to provide a comparison point. Both the melatonin and placebo will be compounded for the purpose of this double-blind trial, to ensure the tablets will be identical in appearance, weight, shape and colour as to remain indistinguishable from each other.

At enrolment, participants will be automatically randomised and trial medication dispensed. Those enrolled in the MyTIME+Sweet substudy will be fitted with CGM to monitor pre-intervention and intra-intervention blood glucose control. Those enrolled in MyTIME+Sleep substudy will wear an actigraphy device and arrange for pre-intervention and intra-intervention blood collection at night. On the night of the 39th week, participants will receive a daily text message reminder to take trial medication in the evening and complete a medication diary in the morning. Texts will continue every evening until the participant indicates that baby has been born.

There will not be any dose changes. Participants may discontinue the study medication due to clinician assessment of adverse events or participant choice.

Outcomes

Primary

IOL rate after 39 weeks.

Secondary

- Interval between administration of trial medication administration and birth.
- Gestational age at birth.
- Duration of labour.
- Analgesia use during labour or birth.
- Mode of birth.
- Indication for mode of birth.
- Interval between administration of trial medication and IOL or caesarean section.
- Estimated blood loss after birth.
- Shoulder dystocia, requiring at least one recorded manoeuvre.
- Severe perineal trauma.
- Maternal plasma melatonin levels (substudy).
- Apgar scores at 5 min.
- Maternal and cord blood biomarkers of inflammation and oxidative stress.
- Baby birth weight.
- Admission to NICU within the first 24 hours of life, primary reason for admission and length of stay if admitted.
- Mother and baby total length of stay.
- Breastfeeding on discharge, Y/N, Exclusive Y/N.
- Perinatal mortality.
- Maternal intratrial participation satisfaction.
- Sleep duration.
- Sleep quality rating (self-reported).
- Maternal blood glucose levels for GDM mothers before and during trial medication use.
- Blood glucose levels for neonates of GDM mothers.

- Trial satisfaction and breastfeeding at 10 days postpartum.
- Ages and stages questionnaire assessing child developmental outcomes at 2 months of age.
- Breastfeeding survey at 2 months.
- Cost-effectiveness of melatonin compared with standard care.

A preplanned analysis of the primary and secondary outcomes stratified by GDM status and model of care will also be performed.

Maternal and pregnancy characteristics

The following characteristics will be collected and may be considered in modelling: maternal date of birth, weight and height at time of booking; Aboriginal or Torres Strait Islander (Australian Indigenous people); maternal self-reported ethnicity, country of birth and language spoken at home; length of time in Australia; body mass index at booking; medical conditions including diagnosis of anxiety or depression; gravidity and parity; medications in pregnancy; substance use in pregnancy; sexually transmitted infections in pregnancy; alcohol intake in pregnancy; tobacco or vaping in pregnancy; group B streptococcus screening results; Edinburgh Postnatal Depression Scale scores; family domestic violence screening; previous blood donation; number of antenatal visits; setting of labour and birth; antenatal complementary therapies discussed with care providers and recorded in the perinatal database; and special child health referral.

Sampling and data collection

Data will be obtained from various sources: STORK (the clinical perinatal database used by maternity services within WA public health services), maternal medical record (via digital record or paper file), directly from the participant (in person or via questionnaire), directly from clinicians, blood tests and wearable devices. NEObase (the neonatal admissions database at KEMH) will be accessed only if required for neonatal safety reporting.

Participant data collected will be entered into REDCap for analysis. Data collected, signed consents and questionnaire responses will be stored within REDCap, which is only accessible to the study team via individual password-protected accounts. Clinical trial records will be securely retained for a minimum of 25 years from the completion of the trial. Data will regularly be monitored internally by the investigator team.

A total sample size of 530 women (~265 per group) will attain 80% power to detect this clinically relevant reduction of induction rate (30%) in the melatonin group (OR of 0.57) while using logistic regression analysis with adjustment for the stratification factors and other relevant covariates at alpha=0.05. This sample size is also inflated to account for a 10% loss to follow-up (Power and Sample Size Program for Windows, V.2019).

Statistical analysis

Data will be analysed on intention-to-treat basis. Binomial and logistic regression analyses will be performed on primary endpoint and other binary outcomes. Linear and/or Cox proportional hazards regression will be used to examine group differences between the continuous and time to event outcomes. Melatonin adherence will be assessed and, if applicable, supplementary analyses on the adherent subgroup and per treatment received will also be performed. All hypothesis tests will be two-sided with alpha=0.05. Data analyses will be performed using STATA statistical software (V.16). A single blinded interim safety analysis will be conducted when 50% of the participants (n=265) have been recruited.

A within-trial cost-effectiveness analysis will be conducted to compare differences in costs and Quality Adjusted Life Year (QALYs) (QALYs) of women receiving melatonin supplementation compared with those receiving standard care. Costs and QALYs will be compared using generalised linear models. A modelled cost-effectiveness analysis will then be conducted to assess cost-effectiveness and budget impact with population-level implementation and projecting to a 5-year time horizon to estimate long-term cost-effectiveness.

Safety events

Monitoring, assessment and reporting of adverse events within the trial will occur as per the National Health and Medical Research Council Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (2016). All safety events will be assessed regardless of causal relationship. Identification of safety events may occur via alert from the participant and/or observed by the researcher and/or clinical staff, and/or identified in the course of other trial-related procedures.

Oral melatonin is known to be safe for pregnant women and babies. There are no anticipated risks from taking oral melatonin during pregnancy, and published accounts of clinical studies in pregnant populations do not report serious adverse reactions or safety concerns. Recent cohort studies researching melatonin supplementation in the general population have reported encouraging pharmacotherapeutic findings, including regulation of hypertension, protection against maternal and neonatal oxidative stress, neuro-regulation and neuro-protection. However, as with any pharmaceutical, there is risk of a participant experiencing an unexpected, previously unknown adverse reaction or hypersensitivity to melatonin. Safety events will be reported from randomisation up until 24 hours after the final administration of melatonin/placebo. This reporting period was selected as it more than covers five half-lives of the study drug.

All safety events assessed as possibly, probably or definitely related to the trial medication and all serious safety events will be followed up to resolution, or until they are assessed as stabilised but unlikely to resolve.

The admission of a baby to the NICU within 24 hours after the final maternal administration of melatonin/

placebo will be reported as a serious adverse event. Prolonged hospitalisation for a reason unrelated to trial participation, such as social reasons or planned hospitalisation for the purpose of birth, will not be reported. However, if birth complications result in prolonged hospitalisation, this will be reported.

Data and safety monitoring committee

A data and safety monitoring committee (DSMC) will be established as melatonin is not currently approved for use in pregnancy, or to promote onset of spontaneous labour. The DMSC will review study progress, recruitment and adverse events. The committee will be comprised of an independent obstetrician, neonatologist, midwife, biostatistician and pharmacist. The DSMC will determine the trial stopping rules and suggest any changes to the protocol which may be required. The composition of the DSMC will be described in the DSMC charter.

Data will be presented without linkage to any participant identifiers. Data will also remain blinded to the DSMC members. If a safety signal is apparent, the DSMC will request for data to be unblinded. Data will be provided to the DSMC 6 monthly, or at request of the committee, the Sponsor (Curtin University) or the Human Research Ethics Committee (HREC). An interim safety analysis will also be carried out at 50% recruitment, and results will be provided to the DSMC for review.

The WA Health Central HREC, WNHS Research Governance Office (RGO) and the Sponsor will be notified of DSMC findings at each safety assessment.

Trial discontinuation

The trial may prematurely, permanently or temporarily cease recruitment if the Principal Investigator (PI), DSMC, or the Sponsor believe there are issues pertaining to participant welfare and safety; a serious breach of trial protocol; or a recommendation from the DSMC that the trial should cease or be re-evaluated.

If the trial is ceased prematurely, the Sponsor, WA Health Central HREC and WNHS RGO will be immediately informed.

Unblinding

The trial may be unblinded in the following circumstances: to make clinical treatment decisions when a suspected unexpected serious adverse event occurs, and the intervention must be known; at the request of the DSMC; and at the conclusion of the trial to determine intervention effectiveness as per study protocol.

If individual unblinding is required, it will be completed by a member of the investigator team using the REDCap Code Break module.

Public involvement

Considerable engagement with consumers has informed the project conceptualisation and development. Our pretrial consumer data indicate high acceptability and strong maternal demand for this proposed innovative trial, with 90% of women (n=172) surveyed indicating they would be interested in participating if this trial were available to them.[36]

We have a consumer representative as a member on our trial team who was involved in the successful grant application and has contributed to the review and design of this study at each stage. Consumer involvement is embedded at every stage of this trial and will continue through to knowledge translation. The mutual investment of consumer representation in the conduct of this Randomised Controlled Trial (RCT) supports knowledge translation and capacity to influence maternity policy.

Ethics and dissemination

The study is approved by the WA Health Central HREC (RGS0000006283) and will be carried out in accordance with the approval conditions of the HREC. The trial will also be carried out in accordance with all applicable guidelines set out by the National Health and Medical Research Council (NHMRC) and in line with Good Clinical Practice principles. Any protocol changes will be submitted to the HREC prior to implementation.

Aggregate trial findings will be disseminated through conference presentations and peer-reviewed publications. Trial findings will also be provided to all participants. We will also co-design a consumer facing infographic containing key data from this trial to be disseminated via the trial consumer representative with established national and international networks. We will also ensure opportunities for the consumer representative to join communication of trial findings to clinicians through established professional networks.

DISCUSSION

IOL has increased without clear evidence of improvement in perinatal outcomes for those mothers who do not have a medical indication for induction.[1–6] It is plausible that contemporary environmental and lifestyle factors may have an inhibitory impact on synthesis and release of melatonin,[20 24 25] a hormone shown to be involved in spontaneous labour.[19 26] Melatonin supplementation may potentiate late-term maternal physiology and reduce the need for IOL in women who do not have a medical indication for intervention. If so, this affordable, accessible, off-patent medication would constitute an acceptable alternative to IOL which carries risk of iatrogenic harm. Melatonin is known to be safe in pregnancy [18 29–32] and offers a range of potential health benefits and may play a role in supporting spontaneous labour.[19 26]

Trial status

The trial commenced recruitment in January 2024. Two years has been allocated for recruitment based on service data.

This publication is based off study protocol V1.3 dated 13 June 2024.

Author affiliations
[1]Curtin University - Perth Bentley Campus, Perth, Western Australia, Australia
[2]King Edward Memorial Hospital for Women Perth, Subiaco, Western Australia, Australia
[3]The University of Western Australia, Perth, Australia
[4]The Ritchie Centre, Hudson Institute of Medical Research, Melbourne, Victoria, Australia
[5]The University of Adelaide - North Terrace Campus, Adelaide, South Australia, Australia
[6]School of Public Health, University of Technology Sydney, Ultimo, New South Wales, Australia

X Miranda Davies-Tuck @DaviesTuck and JA Keelan @jeff_keelan

Contributors ZB conceptualised the trial. ZB, JAK, SWW, MS, MD-T, JW, LK, DAD, EC, KE, MR, and AP designed and wrote the trial protocol and make up the steering committee for the trial. ZB is responsible for the overall content as the guarantor.

Funding This work is supported by the Medical Research Future Fund grant GNT#2023945, Curtin University, WNHS, and the Women & Infants Research Foundation.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Zoe Bradfield http://orcid.org/0000-0002-1013-0461
Miranda Davies-Tuck http://orcid.org/0000-0003-1918-5538

REFERENCES

1 Acsqhc A. *The fourth Australian atlas of healthcare variation*. Sydney: ACSQHC AIHW, 2021.
2 Adler K, Rahkonen L, Kruit H. Maternal childbirth experience in induced and spontaneous labour measured in a visual analog scale and the factors influencing it; a two-year cohort study. *BMC Pregnancy Childbirth* 2020;20:415.
3 Butler SE, Wallace EM, Bisits A, *et al*. Induction of labor and cesarean birth in lower-risk nulliparous women at term: A retrospective cohort study. *Birth* 2024;51:521–9.
4 Dahlen HG, Thornton C, Downe S, *et al*. Intrapartum interventions and outcomes for women and children following induction of labour at term in uncomplicated pregnancies: a 16-year population-based linked data study. *BMJ Open* 2021;11:e047040.
5 Haavaldsen C, Morken N-H, Saugstad OD, *et al*. Is the increasing prevalence of labor induction accompanied by changes in pregnancy outcomes? An observational study of all singleton births at gestational weeks 37-42 in Norway during 1999-2019. *Acta Obstet Gynecol Scand* 2023;102:158–73.
6 McCarthy CM, Meaney S, McCarthy M, *et al*. Induction of labor: reviewing the past to improve the future. *AJOG Glob Rep* 2022;2:100099.
7 Aihw. *Australia's mothers and babies*. Canberra: Australian Institute of Health and Welfare, 2022.
8 White SW, Newnham JP. Is it possible to safely prevent late preterm and early term births? *Semin Fetal Neonatal Med* 2019;24:33–6.
9 Yin W, Döring N, Persson MSM, *et al*. Gestational age and risk of intellectual disability: a population-based cohort study. *Arch Dis Child* 2022;107:826–32.
10 Health Alo, Welfare. *Maternal deaths*. Canberra: AIHW, 2023.
11 Berger BO, Jeffers NK, Wolfson C, *et al*. Role of Maternal Age in Increasing Severe Maternal Morbidity Rates in the United States. *Obstet Gynecol* 2023;142:371–80.
12 Lin L, Ren L-W, Li X-Y, *et al*. Evaluation of the etiology and risk factors for maternal sepsis: A single center study in Guangzhou, China. *World J Clin Cases* 2021;9:7704–16.
13 Grobman WA, Rice MM, Reddy UM, *et al*. Labor Induction versus Expectant Management in Low-Risk Nulliparous Women. *N Engl J Med* 2018;379:513–23.
14 Dong S, Bapoo S, Shukla M, *et al*. Induction of labour in low-risk pregnancies before 40 weeks of gestation: A systematic review and meta-analysis of randomized trials. *Best Pract Res Clin Obstet Gynaecol* 2022;79:107–25.
15 WHO Guidelines Approved by the Guidelines Review Committee. *WHO recommendations: Induction of labour at or beyond term*. Geneva: World Health Organization, 2018.
16 Declercq E, Belanoff C, Iverson R. Maternal perceptions of the experience of attempted labor induction and medically elective inductions: analysis of survey results from listening to mothers in California. *BMC Pregnancy Childbirth* 2020;20:458.
17 Nagle U, Naughton S, Ayers S, *et al*. A survey of perceived traumatic birth experiences in an Irish maternity sample - prevalence, risk factors and follow up. *Midwifery* 2022;113.
18 McCarthy R, Jungheim ES, Fay JC, *et al*. Riding the Rhythm of Melatonin Through Pregnancy to Deliver on Time. *Front Endocrinol (Lausanne)* 2019;10:616.
19 Olcese J, Lozier S, Paradise C. Melatonin and the circadian timing of human parturition. *Reprod Sci* 2013;20:168–74.
20 Rahman SA, Bibbo C, Olcese J, *et al*. Relationship between endogenous melatonin concentrations and uterine contractions in late third trimester of human pregnancy. *J Pineal Res* 2019;66:e12566.
21 Sharkey JT, Puttaramu R, Word RA, *et al*. Melatonin synergizes with oxytocin to enhance contractility of human myometrial smooth muscle cells. *J Clin Endocrinol Metab* 2009;94:421–7.
22 Sharkey JT, Cable C, Olcese J. Melatonin sensitizes human myometrial cells to oxytocin in a protein kinase C alpha/extracellular-signal regulated kinase-dependent manner. *J Clin Endocrinol Metab* 2010;95:2902–8.
23 Martin P, Cortina-Borja M, Newburn M, *et al*. Timing of singleton births by onset of labour and mode of birth in NHS maternity units in England, 2005-2014: A study of linked birth registration, birth notification, and hospital episode data. *PLoS One* 2018;13:e0198183.
24 Mitsui K, Saeki K, Tone N, *et al*. Short-wavelength light exposure at night and sleep disturbances accompanied by decreased melatonin secretion in real-life settings: a cross-sectional study of the HEIJO-KYO cohort. *Sleep Med* 2022;90:192–8.
25 Rahman SA, Wright KP, Lockley SW, *et al*. Characterizing the temporal Dynamics of Melatonin and Cortisol Changes in Response to Nocturnal Light Exposure. *Sci Rep* 2019;9:19720.
26 Yurtcu N, Çalışkan C, Çelik S. Serum Melatonin as a Biomarker for Assessment of Late-term and Postterm Pregnancies in Women without Spontaneous Onset of Labor. *Z Geburtshilfe Neonatol* 2021;225:499–505.
27 Swift EM, Gunnarsdottir J, Zoega H, *et al*. Trends in labor induction indications: A 20-year population-based study. *Acta Obstet Gynecol Scand* 2022;101:1422–30.
28 Flood M, McDonald SJ, Pollock W, *et al*. Incidence, trends and severity of primary postpartum haemorrhage in Australia: A population-based study using Victorian Perinatal Data Collection data for 764 244 births. *Aust N Z J Obstet Gynaecol* 2019;59:228–34.
29 Carloni S, Proietti F, Rocchi M, *et al*. Melatonin Pharmacokinetics Following Oral Administration in Preterm Neonates. *Molecules* 2017;22:2115.
30 Tarocco A, Caroccia N, Morciano G, *et al*. Melatonin as a master regulator of cell death and inflammation: molecular mechanisms and clinical implications for newborn care. *Cell Death Dis* 2019;10.
31 Vine T, Brown GM, Frey BN. Melatonin use during pregnancy and lactation: A scoping review of human studies. *Braz J Psychiatry* 2022;44:342–8.
32 Wei S, Smits MG, Tang X, *et al*. Efficacy and safety of melatonin for sleep onset insomnia in children and adolescents: a meta-analysis of randomized controlled trials. *Sleep Med* 2020;68:1–8.
33 Costello RB, Lentino CV, Boyd CC, *et al*. The effectiveness of melatonin for promoting healthy sleep: a rapid evidence assessment of the literature. *Nutr J* 2014;13:106.
34 Patel R, Parmar N, Pramanik Palit S, *et al*. Diabetes mellitus and melatonin: Where are we? *Biochimie* 2022;202:2–14.
35 Pourhanifeh MH, Hosseinzadeh A, Dehdashtian E, *et al*. Melatonin: new insights on its therapeutic properties in diabetic complications. *Diabetol Metab Syndr* 2020;12:30.
36 PSANZ. Oral. *J Paediatr Child Health* 2023;59:4–54.