Melatonin to Prevent Brain Injury in Unborn Growth Restricted Babies

Verified by: Monash University, September 2012

First Received: September 7, 2012 | Last Updated: September 26, 2012

Phase: Phase 4 | Start Date: September 2012

Overall Status: Recruiting | Estimated Enrollment: 12

Brief Summary

Skip to Participation Criteria

Official Title: "A Pilot Study of Maternally Administered Melatonin to Decrease the Level of Oxidative Stress in Human Pregnancies Affected by Intrauterine Growth Restriction."

Intrauterine growth restriction is the term used to describe a condition where an unborn baby does not reach its optimum size. In the short and long term, intrauterine growth restricted babies have a higher risk of serious disease and even death. It is well established that very low levels of oxygen in the baby's blood can harm the baby's health through a state known as oxidative stress. Currently, there is no established treatment available to treat intrauterine growth restriction or its complications. In experimental animal studies however, the naturally occuring hormone, melatonin, has been shown to significantly reduce oxidative stress and improve health of the unborn babies that have suffered from intrauterine growth restriction. This study aims to find out if the use melatonin twice per day throughout pregnancies affected by intrauterine growth restriction will lower the level of oxidative stress experienced by the unborn baby. If this is the case melatonin may help protect the unborn baby from damage caused by oxidative stress, this will be studied in a separate future study.

- Study Type: Interventional
- Study Design: Endpoint Classification: Safety/Efficacy Study, Intervention Model: Single Group Assignment, Masking: Open Label, Primary Purpose: Treatment
- Study Primary Completion Date: October 2014

Interventions Used in this Clinical Trial

- Drug: Melatonin
  - 4mg prolonged release melatonin oral tablets twice daily

Arms, Groups and Cohorts in this Clinical Trial

- Experimental: Melatonin
  - Women with IUGR will take 4mg prolonged release melatonin oral tablets twice daily. Treatment will occur as soon as the diagnosis of intrauterine growth restriction is made and the patient has been enrolled to this study until birth. The overall duration of treatment will vary due to the nature of intrauterine growth restriction.

Outcome Measures for this Clinical Trial

Primary Measures

- Oxidative stress in the umbilical artery
    - Time Frame: Once, at birth.
      Safety Issue?: No

Secondary Measures

- Oxidative stress in maternal venous serum
    - Time Frame: Once within one week before start treatment and once per week during the treatment period (estimated to be an average of 4 weeks).
      Safety Issue?: No
- Fetoplacental Doppler studies
    - Time Frame: Once within one week before start treatment and twice per week during the treatment period (estimated to be an average of 4 weeks).
      Safety Issue?: No
- Placental oxidative stress
    - Time Frame: Once, at birth.
      Safety Issue?: No
- Gestational age at birth.
    - Time Frame: Once, at birth.
      Safety Issue?: No
- Composite neonatal outcome.
    - Time Frame: Participants will be followed for the duration of hospital stay, up to 12 months.
      Safety Issue?: No

Criteria for Participation in this Clinical Trial

Inclusion Criteria

- Estimated fetal weight <10th percentile in combination with abnormal fetoplacental Doppler studies.
- Singleton pregnancy.
- Live fetus.
- Gestational age: from 23+0 weeks until 34+0 weeks.
- Normal fetal anatomy on ultrasound.
- Confirmed gestational age.
- No indication for immediate delivery.
- Basic understanding of the English language.
- 18 years or older.
- Consent obtained.

Exclusion Criteria

- Fetal demise.
- Multiple pregnancy.
- Known abnormal karyotype.
- Presence of any congenital abnormality.
- Unknown duration of pregnancy.

- IUGR attributable to non-placental factors.

Gender Eligibility for this Clinical Trial: Female

Minimum Age for this Clinical Trial: 18 Years

Maximum Age for this Clinical Trial: 45 Years

Are Healthy Volunteers Accepted for this Clinical Trial: No

Clinical Trial Investigator Information

- Lead Sponsor
  - Monash University
- Provider of Information About this Clinical Study
  - Principal Investigator: Nicole Alers, MD – Monash University
- Overall Official(s)
  - Nicole O Alers, MD, Principal Investigator, The Ritchie Centre, Monash Institute of Medical Research, Monash University
  - Euan M Wallace, MBChB MD FRCOG FRANZCOG, Principal Investigator, Southern Health, The Ritchie Centre, Monash Institute of Medical Research, Monash University
  - Graham Jenkin, BSc PhD, Principal Investigator, The Ritchie Centre, Monash Institute of Medical Research
  - Suzanne L Miller, BSc PhD, Principal Investigator, The Ritchie Centre, Monash Institute of Medical Research
- Overall Contact(s)
  - Nicole O Alers, MD, +61416000539, nicole.alers@monash.edu

Additional Information on this Clinical Trial

Information obtained from ClinicalTrials.gov on October 29, 2012

Link to the current ClinicalTrials.gov record. – http://clinicaltrials.gov/show/NCT01695070

Study ID Number: U1111-1133-4541

ClinicalTrials.gov Identifier: NCT01695070

Health Authority: Australia: Human Research Ethics Committee

Source

Trial to prevent brain injuries in babies

October 19, 2012

Brooke Lumsden

Wonders of science ... Melatonin is a powerful natural antioxidant that can help prevent brain injuries, researchers say.

World-first clinical trials have started in Victoria after Australian researchers discovered that melatonin, a naturally occurring hormone, may prevent brain injuries in unborn babies.

The injuries, which can be caused during pregnancy or labour, can lead to such conditions as intellectual disabilities, epilepsy, and learning and behavioural problems. It can also lead to cerebral palsy, which is the most common physical disability in childhood, with an Australian baby born with the condition every 15 hours.

> If successful, the melatonin supplements are something that may become a routine part of pregnancy care

The trials, being conducted at Southern Health's Monash Medical Centre and The Ritchie Centre at the Monash Institute of Medical Research, are being offered to women carrying growth restricted babies, which occurs in approximately 1 in 20 pregnancies.

"Women are identified when they are seen clinically and thought to have a small baby on board," says leading obstetrician and Director of the Ritchie Centre, Professor Euan Wallace. "They are then referred to us for an ultrasound scan. If this confirms a small baby then we offer the treatment."

The cause of these brain injuries during pregnancy is an excess in free radicals, which leads to oxidative stress. For growth-restricted babies, Wallace says that the most common cause is a placenta that hasn't developed properly, and therefore doesn't provide the baby with enough oxygen.

“This happens from the very beginning of pregnancy and is not usually related to anything the women has or has not done,” he explains.

Although melatonin is mostly known for regulating our body clock to assist with sleep, it is also a powerful natural antioxidant which is able to change the dangerous free radicals into a form that isn’t harmful to our bodies.

“We believe, based on our research to date, that melatonin prevents oxidative stress in the developing baby's brain at a critical stage of brain development or at the time of birth,” Wallace says.

Based on this research, the current trials involve expectant mothers taking melatonin tablets in order to provide the antioxidant to their unborn babies. Each pregnancy is then monitored carefully and cord blood and placenta is taken for testing after the birth of the baby. As the level of free radicals has shown to be higher in the umbilical cord blood in growth restricted babies, this will provide researchers with indicative results of the trials. Experiments have already been conducted with sheep, with the melatonin supplements successfully correcting the oxidative stress in foetal lambs.

In a linked study by the Ritchie Centre, research has indicated that melatonin can also prevent these brain injuries in babies who are asphyxiated during labour, most commonly caused by obstruction of the umbilical cord. This affects more than 1 million babies worldwide each year, even those whose mothers have the healthiest pregnancies.

In this case, the melatonin would be given directly to the baby shortly after birth. This study is still in the experimental phase, in which researchers have been administering the melatonin to newborn lambs for approximately the last 18 months, but Wallace says the team hopes to move to clinical trials with humans in 2013.

An added benefit to these trials is that they have also shown an improvement in the lambs’ ability to feed. This is due to the protection the melatonin gives the brain, which Wallace hopes will also be true in human babies.

Another advantage is that there are no adverse side effects, as melatonin is produced naturally by our bodies.

This ground-breaking research is a collaborative effort involving the work of scientists, obstetricians, paediatricians, radiologists, and midwives, work which Professor Wallace says is very exciting.

“It is hard work - trying to unravel the mysteries of human brain development, how this can go wrong and how we can prevent that. The thought of preventing even one child developing cerebral palsy is thrilling,” he says.

If successful, the melatonin supplements are something that may become a routine part of pregnancy care, the way that many women now take folic acid to help prevent spina bifida. If this is the case, however, Wallace says it is still further down the track as there is still so much to be learned.