# Preventing Preterm Birth The Human Uterus is Enigmatic

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# **Human Prematurity**

- Birth before the 37<sup>th</sup> completed week of gestation. [10% of US pregnancies]
- The majority of preterm birth follows idiopathic preterm labor.
- The signals that initiate term labor in women are incompletely known.
- There are no FDA approved tocolytics available to allow the foetus to remain in the womb until term.
- In order to develop new tocolytics we need to understand how quiescence is maintained during gestation.



#### HEALTHY MOMS. STRONG BABIES.

#### 2022 MARCH OF DIMES REPORT CARD

The 2022 March of Dimes Report Card continues to elevate the latest data on infant and neonatal outcomes and maternal risk factors. We continue to provide updated measures on preterm birth, infant mortality, social drivers of health, rates of low-risk Cesarean births and inadequate prenatal care. This year we include an update to our social drivers of health by including the Maternal Vulnerability Index (MVI).

This year's report card highlights a worsening state of maternal and infant health with increases in preterm birth and low-risk Cesarean births. Additionally, the health equity gap continues to increase among these outcomes. Comprehensive data collection and analysis of these measures inform the development of policies and programs that move us closer to health equity. As in previous years, the Report Card presents policies and programs that can help improve equitable maternal and infant health outcomes for families across the country.

# **UNITED STATES**

PRETERM BIRTH GRADE

## PRETERM BIRTH RATE 10.5%







D

F

Preterm birth rate of 11.2 to 11.4%.

Preterm birth rate greater than or

equal to 11.5%.

Preterm is less than 37 completed weeks of gestation, based on obstetric estimate of gestational age.

Grades assigned by March of Dimes Perinatal Data Center.

Puerto Rico is not included in the United States total.

Source: Preterm birth rates are from the National Center for I lealth Statistics, 2021 final natality data and U.S. Territories natality data.



# <u>Newborn Morbidity Risk</u> <u>Consequences</u>

- Retinopathy of Prematurity
- Respiratory Distress Syndrome
- Chronic Lung Disease
- Intraventricular Hemorrhage
- Necrotizing Enterocolitis
- Severe Brain Injury

## Long Term

- Developmental Delay
- Blindness
- Cerebral Palsy
- Mental Retardation
- Deafness
- Sensory Deficits

# What can relax uterine contractions?

## The Human Uterus is Denervated at Term



Axons innervating the uterus travel in the hypogastric nerves and terminate in the thoracolumbar spinal cord segments (T10–L2).

Adrenergic innervation of the myometrium is selectively denervated during pregnancy. Suggesting that non-neuronal mechanisms regulate contraction/relaxation of the smooth muscle.

# Physics! - Laplace's Law and the Uterus

#### In the uterus:

When the muscle in the wall of the uterus contracts the wall tension, T, increases

An increase of wall tension increases pressure, P, in the lumen *T and P are not linearly related*The value of pressure also depends on the radius of the vessel

$$P = \frac{2T}{r} =$$
Stretch



#### **Might Stretch Underlie Uterine Quiescence?**



The smaller the radius, the greater the pressure for a given wall tension (preterm pregnancies?)

## Smooth Muscle Relaxation Canonical Thinking.....Nitric Oxide (NO) The 1998 Nobel Prize in Physiology or Medicine



Most of what is assumed regarding the signaling of NO to relax smooth muscle has been developed in vascular or GI smooth muscle.

NO Signaling in uterine smooth muscle is different.



### cGMP accumulation has no effect on

# NO-mediated Relaxation is Blunted in Human PTL



- NO relaxed spontaneous contractions in term laboring (•) myometrium. K<sub>1</sub> = 1 μM.
- In PTL, the K<sub>1</sub> was 10 times higher and relaxation was significantly blunted (
  , 26% vs. 86% relaxation).
- In a set of tissues from the same patients, NO relaxed oxytocin (OT, 100 nM) contractions over 5 min (AUC, ▼).
- In OT stimulated PTL tissues (◆) NO produced only 12% relaxation (K<sub>1</sub> = 10<sup>-5.5</sup> M) compared to control (p = 0.6), while in term laboring tissues, NO was equieffective as when spontaneous contractions were measured.

What signaling mechanism can explain the effect of NO to relax uterine smooth muscle, and explain the dysfunctional relaxation in PTL?

## **NO Relaxes Myometrium by S-nitrosation**



Relative expression profile of the human uterine smooth muscle S-nitrosoproteome in disparate states of pregnancy.

The endogenous NO-donor that nitrosates proteins is S-nitroso glutathione (GSNO).

Differential expression suggests that S-nitrosation is regulated and that Preterm Tissues are disparate from term tissues.

Myometrial Smooth muscle GSNO-mediated relaxation signaling is an exception to the Nobel Dogma

# No-donors Relax Agonist-evoked Contractions: K<sup>+</sup> Channel Antagonists Block Relaxation



- Relaxation of pregnant human myometrium is insensitive to guanylyl cyclase blockade.
- Toxins known to block K<sup>+</sup> channels prevent NO-mediated relaxation.
- What K<sup>+</sup> channels in the human myometrium explain relaxation to NO?

# A Role for K<sup>+</sup>-Channels?

- •Since blockade of potassium channels can alter the relaxation responses to NO in uterine smooth muscle, what K<sup>+</sup>-channels are associated with myometrial relaxation?
- •Knowledge that a channel with unique properties including activation by stretch had been cloned from the fly captured our attention.
- •We were the first to describe the regulation of two-pore K<sup>+</sup>-channel TREK-1 in human myometrium.

### **Tarantula Toxin GsMTx-4 Blocks SAC Channels**



# TREK-1 is a Stretch-Activated Potassium (K<sup>+</sup>) Channel



# Highlights

- Nervous innervation cannot explain uterine contraction/relaxation.
- NO-mediated relaxation is cGMP independent.
- NO relaxes myometrium via S-Nitrosation.
- Protein S-Nitrosation is pregnancy state specific.
- Human preterm laboring tissues fail to relax well to NO-stimulation.
- S-nitrosation explains dysfunctional relaxation in preterm tissues.
- Stretch-activation may reveal new targets for tocolytic drug development.
- What SAC are present in human myometrium?

## Buxton Lab: The Myometrial research Group





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