

Unexpected Role of Nitric Oxide Signals in Myometrial Relaxation: A Promising Therapeutic Approach in Preterm Birth Prevention

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Pregnancy is normally an '*anticipation boosted happiness*' to all pregnant women, but it can also be a time of uncertainty. Ideally, full-term pregnancy lasts 40 weeks in pregnant women, however some women have concerns about 'preterm birth' that occurs between 20 to 37 weeks of pregnancy due to regular contraction/relaxation of smooth muscles in uterus leading to preterm labor followed by early delivery¹. Preterm labor is difficult to predict and it occurs mostly in women with no known risk factors. Preterm birth is the major underlying cause for new born morbidity and mortality. About 1 in 10 babies is born prematurely each year in United States that occurs mainly due to preterm labor on its own or after premature rupture of fetal membranes². Preterm babies are not fully developed at the time of birth and have serious health-related complications including difficulty in breathing, feeding, disabilities in learning as well as injury to eyes and intestine³.

There are several factors that may increase the women risk for preterm birth. The major risk factor for preterm birth is a previous preterm birth. Nearly 22% of women with previous preterm delivery had similar preterm problems during their subsequent pregnancy. Certain other risk factors for preterm birth includes twin pregnancy, history of cervical procedures, uterine abnormalities, uterine bleeding, microbial infections, polyhydramnios (excess amount of amniotic fluids) and abdominal surgery⁴. Though, preterm labor is a complicated and often unpredictable series of events, still research is ongoing to discover predictable

markers that can help to predict the risk of preterm delivery⁵. Certain test such as ultrasound measurement of cervix length and determination of fetal fibronectin concentration in woman may be helpful in some settings to predict the risk of preterm birth^{6,7}. Even if we knew the risk of preterm birth in every case, we could not prevent it at the present time.

The primary goal of preterm birth treatment is to delay early delivery through administration of tocolytic medications that can slow or stop preterm labor for optimally 48 h. Steroids (glucocorticoid) are often administered during preterm labor to accelerate the development of preterm infant's lung that would facilitates the production of surfactant and prevents the collapse of alveoli⁸. In general, there are no obvious treatment available to prevent preterm labor that allow a fetus to remain in the mother's womb until term. While effective treatment can be achieved only by gaining a better understanding of uterine muscle relaxation and contraction pathways that will offer a major novel therapeutic approach to prevent preterm labor.

As the first discovered gaseous signaling molecule, nitric oxide (NO) plays essential role in number of cellular processes. It has been known that NO regulates vascular smooth muscles relaxation by stimulating cytosolic guanylate cyclase to produce cyclic-guanosine 3',5'-monophosphate (cGMP), which leads to vasodilation⁹. However, the role of NO on uterine smooth muscle (myometrium) relaxation

remained unknown for several years. Recently, Buxton and Barnett have elegantly studied the mechanisms of uterine smooth muscle relaxation and discovered the unexpected role of NO in human myometrial relaxation. This study has uncovered an exciting connection between biochemical differences in NO-induced S-nitrosation of crucial proteins that mediate muscle activity and the outcome of these differences in the effect of NO-donor on both term and preterm myometrial relaxation¹⁰. This is also the first study that measured the ability of NO to relax preterm vs term pregnant human myometrium. Buxton and Barnett research findings have confirmed that targeting the major fundamental biochemical differences in preterm tissues in response to NO signals might be a promising therapeutic approach for prospective treatment of preterm labor.

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