Supplementary Material

Figure S1: The flow diagram shows the enrolment process

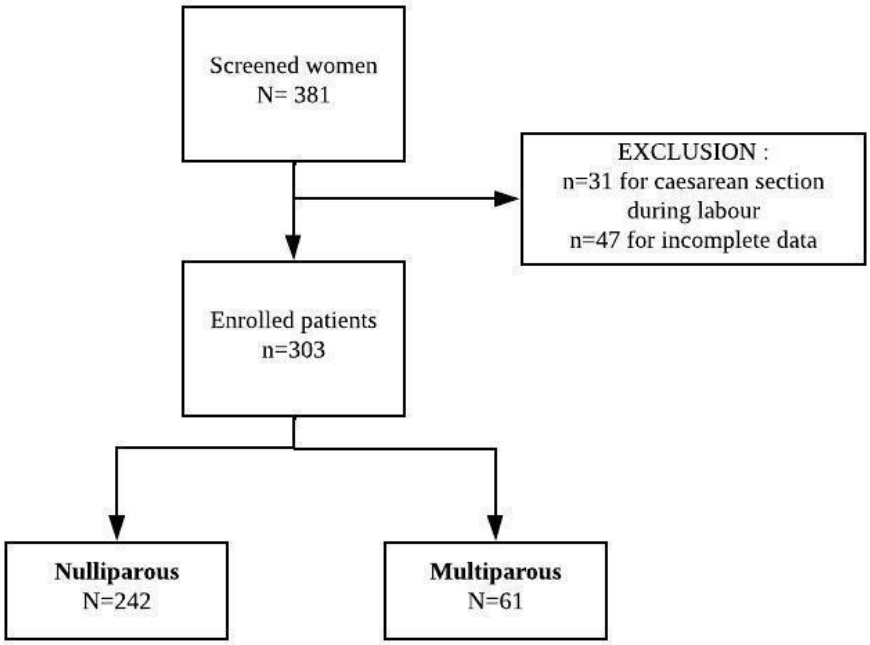
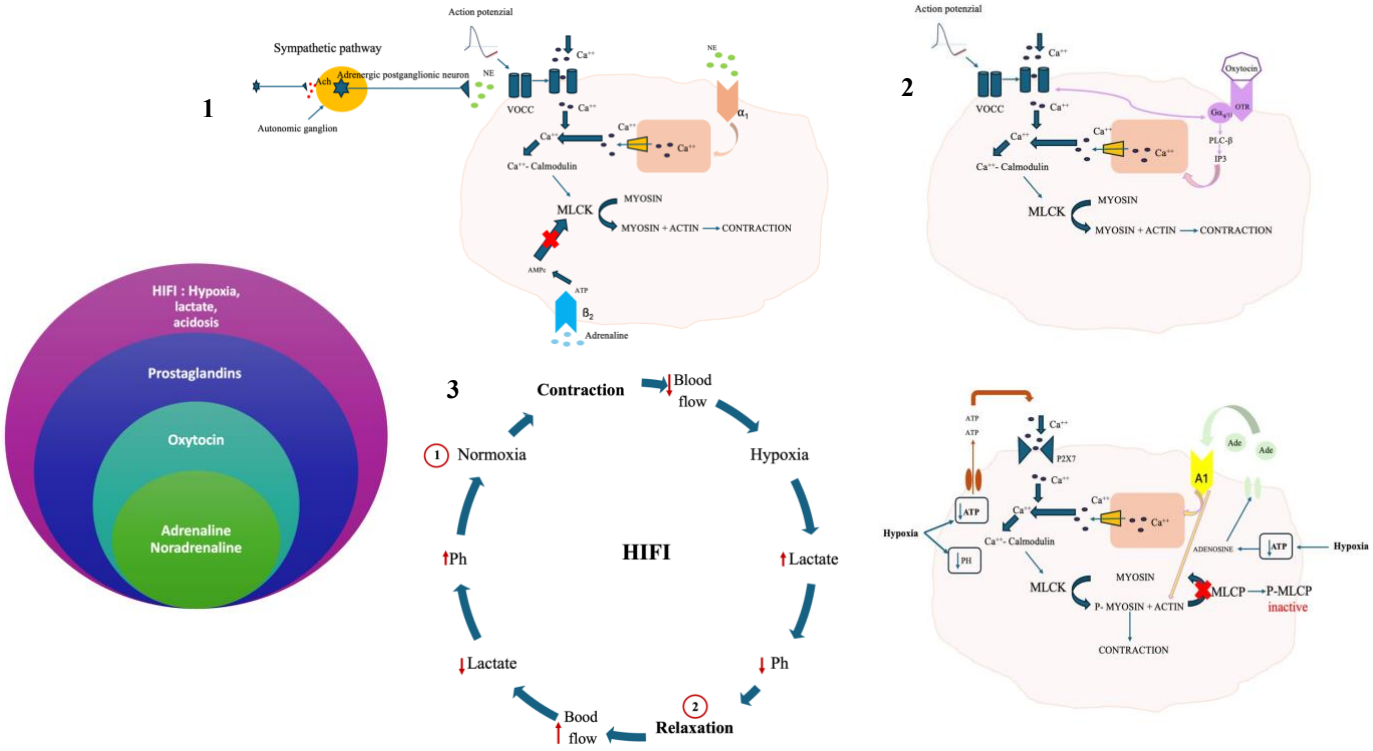


Figure S2: Contraction of the uterine smooth muscle



Rhythmic uterine contractions are controlled by several factors, including catecholamines, oxytocin, prostaglandins, and a complex process called hypoxic-induced force increase (HIFI).

1. In the smooth muscle cell, the release of norepinephrine (NE) from the postsynaptic fibre activates voltage-operated calcium channels (VOCC), promoting calcium ions entry into the cell[1]. The subsequent binding of calcium to calmodulin activates myosin light chain kinase (MLCK) by promoting the binding of actin and myosin. Norepinephrine, also excreted by the adrenal medulla, binds to alpha-1 receptors, promoting calcium release from the sarcoplasmic reticulum and the binding of Ca-calmodulin. In addition, adrenaline, also produced by the medulla, activates beta-2 receptors, leading to an increase in cAMP. This, in turn, activates protein kinase A (not shown in the figure) and causes the phosphorylation of MLCK by reducing the interaction between actin and myosin.

2. Oxytocin binds to its specific receptors, coupled to G protein. In the uterus, Gaq/11 activates phospholipase C-B, which hydrolyses phosphoinositide-bis-phosphate (PIP2) to inositol-triphosphate (IP3)[2]. The release of calcium from the sarcoplasmic reticulum is promoted by IP_3 so that calcium can bind to calmodulin [1]. Calmodulin activates MLCK, promoting actin-myosin binding. In addition, the Gaq/11 protein promotes the activation of VOCC. Furthermore, oxytocin has been observed to stimulate prostaglandin production, which sensitises the myometrium to oxytocin itself, increasing its receptors [3].

3. HIFI is a phenomenon in which the force of contraction in the uterus increases in response to a hypoxic state. During myometrial contraction, a period of transient hypoxia ensues, resulting in increased lactate concentrations, decreased pH, and smooth muscle fibrocellular relaxation. During the hypoxic phase of HIFI, ATP concentration also decreases. The efflux of ATP from the myometrial cells promotes the activation of P2X7 purinergic receptors. Additionally, ATP hydrolysis has been shown to stimulate A1 receptors. This promotes Ca release from the sarcoplasmic reticulum and facilitates actin-myosin interaction by inhibiting myosin dephosphorylation by myosin light-chain phosphatase (MLCP). Consequently, this series of events culminates in an augmentation of force during the ensuing contraction [4].