



First Do No Harm: Intrapartum Calcium Loading During Oxytocic Induction of Labor

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Abstract

Pregnancy advancing beyond 40 completed weeks is associated with increased physical risk to both mother and fetus that increases concurrently with gestation. The recommended management for pregnancies approaching 42 weeks is a post-dates induction of labour. While induction often involves several stages, the majority of women are ultimately subject to exogenous oxytocin administration.

Stringent guidelines are in place for oxytocin administration, to control the known risks associated with the use of exogenous oxytocics. Despite these measures, exogenous oxytocin is the drug most commonly associated with adverse perinatal outcomes, and is attributable to approximately half of obstetric liability claims in the United States. Further, little research exists regarding the longitudinal effects of administration of exogenous oxytocin prior to or during birth.

Ionised calcium has been demonstrated to play a pivotal role in myometrial contractility through a variety of mechanisms, as demonstrated by the efficacy of calcium channel blockers as a tocolytic. Additionally, changes in calcium metabolism and sequestration during pregnancy and birth have the capacity to create a subclinical hypocalcaemia, affecting the process and progress of parturition.

This paper aims to review the known risks and benefits of labour induction and exogenous oxytocin administration, and to explore the potential for its longitudinal effects. Existing research regarding induction of labour and endogenous enhancement of parturient processes will be discussed, with a particular focus on the role of calcium in labour, its physiological contribution, and the efficacy of intrapartum calcium loading in the clinical setting. Overall this paper aims to reignite discussion as to the potential supportive role calcium may play in reducing the quantity of synthetic oxytocin administered in the management of prolonged pregnancy.

Keywords

Calcium; Induction; Oxytocin; Postdates; Pregnancy

Abbreviations

MAS: Meconium Aspiration Syndrome; IOL: Induction Of Labour; ARM: Artificial Rupture Of Fetal Membranes; ASD: Autism Spectrum Disorder; ADHD: Attention Deficit Hyperactivity Disorder; IP3: Inositol Triphosphate; SERCA: Sarco/Endoplasmic Reticulum Ca²⁺-Atpase; OASIS: Obstetric Anal Sphincter Injuries

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Introduction

Pregnancy with gestation beyond 42 weeks is considered prolonged, a situation commonly associated with increased risk to both mother and fetus [1-4]. Large-scale audits have revealed the risk is approximately 5.1 to 5.8 per 1000 at 43 weeks [2,5], however these figures vary widely in the literature. All reports demonstrate increased mortality and morbidity with gestation advancing beyond 40 completed weeks.

The pathogenesis of prolonged pregnancy is poorly described, largely due to the paucity of research in this area. While a 2012 study [6] demonstrated decreased inherent contractility in the post-term myometrium, little further advancement has been made. Perinatal statistics demonstrate that a paucity of scientific knowledge has reduced the efficacy of medical management in prolonged gestation [7].

A 2012 Cochrane review [8] found that induction of labour was associated with fewer perinatal deaths, a lower incidence of meconium aspiration syndrome (MAS), and a reduced incidence of caesarean section than expectant management. These findings are supported by other studies and suggest labour induction is effective in the management of risk associated with prolonged pregnancy [5,8-14]. The recommended management for prolonged pregnancy in Queensland, Australia is the Induction of Labour (IOL) [9]. Prolonged pregnancy is the most common indication for IOL, being responsible for up to 72% of induced births annually [7]. This may be undertaken with prostaglandins, artificial rupture of the fetal membranes and/or synthetic oxytocics. Induction is strongly recommended at 40 weeks plus 10 days, with the intent to deliver before 42 completed weeks [9].

Selection of induction method is decided after evaluation of the cervix as favourable. A woman with an unfavourable cervix will commence IOL with application of prostaglandins until a favourable cervix is established [9]. Artificial rupture of fetal membranes (ARM) follows, along with administration of exogenous oxytocics. Stringent guidelines [9] are in place for the management of women undergoing oxytocic IOL, including dosage, dilution, administration, titration and continuous assessment and monitoring of maternal and fetal wellbeing throughout this process. Such guidelines are necessary due to the known risks associated with the use of exogenous oxytocics for the induction of labour [9]. While developments in maternal and fetal monitoring have made the use of oxytocics safer, the potential for harm that these compounds present is largely underestimated [15]. Exogenous oxytocin is the drug most commonly associated with adverse perinatal outcomes and is attributed to approximately half of all paid obstetric liability claims in the US, and one of only twelve drugs listed as high-alert medications by the Institute for Safe Medical Practices in the United States [15].

Induction with oxytocics is also associated with a complex range of sequelae, including increased maternal requirements for analgesia and anaesthesia, increased incidence of maternal pyrexia [16] and a prolonged second stage which increases the risk of instrumental delivery, postpartum haemorrhage, placental retention, perineal trauma and obstetric anal sphincter injuries (OASIS) in the mother [17]. Instrumental delivery poses further risk to the infant including cephalohaematoma, craniofacial lacerations, subgaleal haemorrhage

and tentorial tears [17]. These prompt additional medical management of the infant, often resulting in invasive testing and administration of prophylactic intravenous antibiotics [18]. While risk management is paramount, little consideration is given to these procedures on the establishment of normal gut flora, breastfeeding or bonding in neonates. Furthermore, induction using an exogenous oxytocic infusion reduces the effectiveness of first line oxytocics for third stage management, necessitating the use of further measures such as ergot and prostaglandins to facilitate tonic uterine contraction and postpartum haemostasis [19].

While the immediate physical risks of labour induction to mother and infant are well understood, little research exists regarding the longitudinal effects of intra-partum administration of exogenous oxytocin. Research suggests that exposure to exogenous oxytocin may contribute to oxytocin receptor desensitisation and consequential reductions in endogenous oxytocin secretion and action that have been linked to increased neurodevelopmental risk [20-22]. Animal and human studies have established the importance of oxytocin to initiation, maintenance and facilitation of social behaviour [23-25] and perinatal oxytocin administration has been hypothesised to contribute to the development of Autism Spectrum Disorder (ASD) [22,26] and Attention Deficit Hyperactivity Disorder (ADHD) [21] particularly in male children. However more recent large population based studies have not supported earlier work in the context of ADHD [27] and urge caution in the interpretation of modest associations in Autism [26]. Importantly, the design of previous studies has not permitted the evaluation of dose and duration dependant effects of fetal oxytocin exposure and as such questions still remain as to the complex contributions of oxytocin to neural and social development, and use of exogenous oxytocics at such a pivotal developmental time may have the capacity to cause longitudinal damage as a result of epigenetic and environmental insult [20-22].

While the purpose of this paper is not to argue against the need for labour induction in prolonged pregnancy, it does serve to highlight the risk associated with utilising exogenous oxytocin. As such investigations into strategies which minimise the need for exogenous oxytocin in labour induction are warranted. One such method may be to enhance endogenous systems by revisiting intrapartum calcium loading as a means to reduce the amount of synthetic oxytocin necessary to produce a timely delivery in prolonged pregnancies.

Historically, physiological and obstetric investigation has determined that uterine activity and reactivity are augmented by calcium ions, and that absolute or relative quiescence, and/or reduced or absent sensitivity may also result from relative calcium insufficiency [28-34]. This has been used to medical advantage, with the use of calcium channel blockers as the primary to colytic in the management of preterm labour [35]. Continuing research demonstrates the importance of intracellular and extracellular calcium availability for parturient processes in mammals [36-43], and is becoming increasingly appreciated in homeostatic, simple and complex models in both animal and human research. However, little literature exists with regard to the mechanisms facilitating systemic calcium availability throughout the process of parturition [41] and as such remains poorly understood [44].

Calcium homeostasis in the non-pregnant individual is a relatively simple process, however it undergoes considerable change in the pregnant subject [44]. This results in lower maternal serum

levels due to calcium diversion to meet increased fetal demand [44], the blocking of bone resorption by increased estrogen [28] and haemodilution [45]. Additionally, maternal hypocalcaemia is enhanced by utero-placental calcium transport mechanisms [46]. This results in a fetal hypercalcaemia and corresponding maternal hypocalcaemia with a serum calcium trough evident during the third trimester [46].

Interactions between ionised calcium and acid-base balance at term play a role in parturient calcium availability on a systemic level. Hyperventilation during labour due to anxiety, fear, pain, abnormal breathing patterns and stimulation of the respiratory centre by progesterone results in a state of respiratory alkalosis [47,48]. This results in a shift in the acid base balance, causing an increased percentage of calcium ions to bind with albumin and create stable compounds, reducing ionic availability. Further, alkalosis inhibits tissue response to parathyroid hormone and results in a transient decrease in serum calcium concentration and contractility [47].

While the rudimentary role of calcium ions in smooth muscle contraction is well understood, several mechanisms additional to the binding of oxytocin to the oxytocin receptor (OXTR), triggering signalling pathways are thought to exist which are uterine specific [36-43,49]. These include prostaglandin pathways [36] membrane excitability [39], uterine pacemaker units [50] and calcium waves [51]. Research into many of these pathways is incomplete, however theorised actions are supported by the efficacy of calcium channel blockers (Nifedipine) [35] and oxytocin receptor antagonists (Atosiban) [52] in inhibiting labour, through the interruption of the flow of calcium ions into the contracting myometrium [35,53,54].

Ripening of the cervix is a prerequisite to normal labour, with endogenous prostaglandins released locally to soften the cervix prior to spontaneous parturition [55]. Addition of exogenous prostaglandins to cervical tissue mimics this response and is utilised during labour induction [55]. Calcium has been implicated as a primary factor in the regulation of prostaglandin synthesis in glomerular mesangial cells, [56] and while these findings are yet to be confirmed in the myometrium, it is clear that a complex relationship exists between calcium and prostaglandin synthesis. Additionally, functional studies of the role of prostaglandin receptors in myometrial contractility have determined that smooth muscle contraction is mediated through increased inositol triphosphate (IP3) turnover and calcium mobilisation, and is therefore dependent on calcium signalling [57,58].

The change from a quiescent to contractile uterus is largely due to the emergence of membrane oscillators at the time of labour which produce repetitive action potentials preceded by a depolarisation [50]. A model of this mechanism has been proposed which connects the known oxytocin receptor system and that of isolated smooth muscle contraction. It suggests that calcium influx is a major contributor to the rhythmic depolarisation of pacemaker areas playing a role in enhancing pacemaker potentials and facilitating myometrial contraction and coordination [50,59].

Further, calcium is considered to be the major charge carrier in the myometrium [59]. As pregnancy progresses, depolarisations change from short spikes to regular sustained activity, thereby promoting coordinated contractility [59]. Extra calcium channels are expressed as labour approaches and gap junction development facilitates carriage of electrical impulses [42,59]. To facilitate this calcium is released from the sarcoplasmic reticulum, however several

mechanisms for calcium influx from the extracellular environment have also been proposed which influence membrane excitability thereby contributing to contractility [49,59].

Action potentials and pacemaker areas combined cannot account for the shape of observed uterine contractions [51]. Intercellular calcium wave speed is thought to contribute to this process [51]. Calcium waves are specialised oscillations which are coordinated with respect to both time and place [60]. These waves may be either intra or intercellular, both of which have been demonstrated in cultured human myometrium [51,60,61]. These mechanisms are yet to be fully understood, however research demonstrates that calcium waves are a mode of tissue level communication in the myometrium, and may be considered separate to other contraction mechanisms.

Early *in vitro* experiments on guinea pig uterine tissue have found that spontaneous contractions may be augmented by calcium, and may be depressed or completely inhibited by diminishing calcium [29,31]. A drop in ionised calcium concentration inhibited Myometrial response to oxytocin, with no response elicited when calcium was removed from the environment altogether [29]. Conversely, raising calcium ion concentration in the solution resulted in a marked increase in response to oxytocics [29].

These results are further supported by research using isolated human myometrium, which demonstrated an increase in myometrial tension with stimulation of intracellular calcium release. This response was greatly augmented by the presence of extracellular calcium [37]. Further, the increased expression of sarco/endoplasmic reticulum Ca²⁺-ATPase (SERCA) isoforms found in labouring compared to quiescent myometrium highlights the physiological importance of ionised calcium during parturition [41]. Combined with the finding of poor intrinsic contractility in the postdates myometrium being related to intracellular calcium transients, research suggests that calcium loading in postdates induction of labour may be beneficial in the change from a quiescent to contractile uterus [6].

The use of calcium with exogenous oxytocin is common in the parturient bitch and is administered routinely in clinical cases of primary uterine inertia [62]. Prevention and management of this condition have been investigated, with researchers finding that decreased availability of physiologically active calcium plays an important role in its pathogenesis, and that forceful uterine contractions are dependent on free ionised calcium into myometrial cells [47]. This is supported clinically, in that uterine inertia in the parturient bitch is resolved by slow intravenous administration of calcium gluconate, despite total serum calcium being within normal reference range [31,47] and that calcium loading augments the rate, amplitude and coordination of contractions in the bitch [31], ewe [63] and the rabbit [30,32]. It was also determined that the minimal effective dose of exogenous oxytocin produced greater results when administered with or after calcium compared with oxytocin administration alone.

Two mid twentieth century studies with differing protocols administered a calcium gluconate pre-load prior to administration of oxytocics [33,34]. Considerable ethical issues taint these studies, however the physiological principles appear sound and the results a foundation for further research. The first of these studied the effect of a calcium gluconate preload in a cohort comprising of 123 social and 6 therapeutic inductions. It was reported that the women experienced labours with shorter average duration and lower morbidity than a comparable population experiencing spontaneous labour and birth

[33]. This author determined that an increase in ionised calcium is necessary for spontaneous onset at term, that alteration of the ratio of ionised to non-ionised calcium may have been responsible for the increase in uterine contractility, and that calcium gluconate given intravenously was a definite aid to producing normal and efficient uterine contractions [33]. A subsequent Canadian study utilised an alternative methodology to study the effect of this preload on 200 women undergoing induction for a variety of indications at gestations ranging from 32 - 40 weeks [34]. This author also reported a shorter average length of labour duration in both primiparous and multiparous women compared to the existing norm. No maternal mortality or neonatal deaths attributable to induction were recorded in either study [33,34]. However, these studies are subject to design flaws and ethical considerations. The stringent testing processes applied today which ensure the safety and efficacy of a newly developed product were not historically applied, and as such oxytocics were utilised with little awareness of safe dosage and administration. Further, most patients birthed under the influence of scopolamine, thereby effectively inhibiting cognitive and psychological influences on the progress of labour [33].

Despite this promising early research, no further mention of calcium loading in induction of labour protocols has been found. Current induction protocols indicate that this research was never fully integrated into clinical either practice or fell out of favour; however the available literature does not indicate which the case is or why.

Discussion

Pregnancy beyond 42 weeks gestation poses increased risk of morbidity to both mother and fetus - risk which is managed by induction of labour in the post-dates period. Ultimately, most of these women are subject to exogenous oxytocin administration. While induction of labour has demonstrated outcomes superior to those of expectant management, the risk of uterine rupture during induction with oxytocin is nearly double that of fetal demise due to prolonged pregnancy. While guidelines exist to limit this risk, exogenous oxytocin remains the drug most commonly associated with adverse perinatal outcomes.

Adequate availability of ionised calcium is necessary to facilitate all mechanisms of parturition from ripening of the cervix via prostaglandins to every known aspect of uterine contractility. Given that the efficacy of fundamental functions such as oxytocin receptor binding, simple smooth muscle contraction, membrane excitability, endogenous pacemakers, and calcium wave propagation and signalling is markedly affected by the absence of calcium, logic dictates that even a subclinical hypocalcaemia may have major effects on the normality and progress of parturition. Alterations in calcium function, metabolism and sequestration during pregnancy and birth have the capacity to contribute to such a physiological state and thereby inhibit pivotal parturient processes.

Historical research in Theriogenology and Obstetrics has demonstrated the efficacy of intra-partum calcium loading in the augmentation and coordination of contractions in uterine inertia and labour induction. However, despite the continuation of this clinical practice in animals and the promising early research in human subjects, the physiological role of calcium in labour and the potential for intra-partum calcium loading to improve induction outcomes in women appears to have been grossly overlooked.

Bioethical standards require that healthcare providers are guided

by the principle of non-maleficence - "first, do no harm". While the purpose of the paper is not to argue against the need for labour induction, the use of exogenous oxytocin to manage prolonged pregnancy introduces a considerable range of consequences both known and unknown in nature. Our current medical knowledge does not encompass long term sociological and psychological effects of exogenous oxytocin on mothers, infants, or the dyad as a whole. Conversely, the effects of hypercalcaemia, hypocalcaemia and calcium administration are well known, and present an opportunity to enhance endogenous parturient systems. Further research regarding intrapartum calcium loading is warranted, and may reduce the quantity of synthetic oxytocin required to produce a timely delivery under these circumstances.

Summary

Pregnancy of gestation beyond 42 weeks is considered prolonged, a situation commonly associated with increased risk to both mother and fetus. Induction of labour is strongly emphasized at 40 weeks plus 10 days with the intent to deliver before 42 completed weeks, reducing associated risk. Current induction protocols require the use of exogenous oxytocin, introducing risks both known and unknown in nature. This paper suggests that enhancing endogenous systems may reduce synthetic oxytocin use resulting in decreased associated risks and increased efficacy of induction. In particular, research regarding calcium availability has been discussed, and introduces an argument for intra-partum calcium loading in the oxytocin induction of labour.

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