Review article

Use of oxytocin for induction of labour

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Introduction

Oxytocin, a neuropeptide produced in the hypothalamus in a pulsatile manner and secreted through the posterior pituitary, is a powerful uterotonic which stimulates contractions of myometrial cells in the uterus and the myoepithelial cells around the mammary alveoli. Oxytocin has been long considered to have a central role in labour. The basal oxytocin levels gradually increase during pregnancy, and the oxytocin receptors in the uterine muscles also gradually increase in number and become increasingly sensitive to oxytocin in late pregnancy, mainly due to the increasing oestrogen level[1,2]. However, the onset of labour is a complex process which involves several processes such as structural remodeling ('ripening') of cervix, mediated by the interaction of nitric oxide with numerous cytokines and free radicals, followed by interlinked, harmonized changes in the levels of oestrogen, progesterone, prostaglandins, cortisol as well as their receptors. The ripening of the cervix merges in to the onset of labour with no clear demarcation inbetween[3,4]. Based on the assumption that an increase of oxytocin was responsible for the initiation of labour, and the fact that mammary stimulation resulted in release of oxytocin and uterine contractions, even Hippocrates (*cica* 400 BC), advised mammary stimulation (combined with mechanical dilatation of the uterine cervix), to artificially initiate labour, which is referred to as induction of labour (IOL). The use of "Pitocin", an extract from the posterior pituitary, was first described for IOL by Bell in 1909 but it was soon abandoned because of serious adverse effects including fetal death and ruptured uteri[5]. It was only in 1954 that the synthesis of oxytocin was first described by Vincent du Vigneaud, and he won a Nobel Prize for his efforts[6]. The use of synthetic oxytocin revolutionised the practice of IOL world wide, and it is widely used and popular. However, like in the case of any medication given to a human being, when using oxytocin, the principle of "*primum, non nocere*" – first do no harm enunciated by Hippocrates, must be kept in mind.

Maternal oxytocin levels during normal pregnancy and vaginal delivery

A recent systematic review carried out on the role of oxytocin in normal labour and vaginal delivery has shown that: basal oxytocin levels gradually increase during pregnancy; there is no evidence to support the hypothesis that physiologically, the onset of labour is

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triggered by a sudden rise of oxytocin levels; during labour the basal oxytocin levels increase further with pulses of oxytocin occurring with increasing frequency, amplitude, and duration, reaching a maximum frequency of three pulses per 10 minutes up to the end of the second stage of labour; the oxytocin pulses do not have a direct temporal association with uterine contractions; a four-fold rise of oxytocin levels occurs during vaginal delivery; and oxytocin is also released during the expulsion of the placenta[1]. The authors of this systematic review have also concluded that: some of the oxytocin peaks occurring during labour are probably spontaneous and of hypothalamic origin; oxytocin release in labour would promote prostaglandin release, further strengthening uterine contractions and labour progress; some of the oxytocin peaks, especially in advanced labour, are likely to be induced in response to activation of the Ferguson reflex[7]. In the Ferguson reflex, uterine contractions press the head of the fetus down against the cervix and vaginal wall, activating afferent sensory nerves which send impulses via the spinal cord to the brain, resulting in increased release of oxytocin into both the brain and circulation. Oxytocin released into the brain during labour and vaginal delivery induces many beneficial effects by its central actions within the brain. These include: stimulation of friendly social interaction; enhanced wellbeing; a positive mood; reduction of anxiety, pain and stress; and facilitating bonding with the neonate[1]. Epidural analgesia, by blocking the Ferguson reflex, may not only reduce oxytocin blood levels and progress of labour, but also abolish the beneficial central effects on the brain[1,8]. It has been observed that levels of oxytocinases, the enzymes that break down oxytocin, also increase 10- to 20-fold during labour. This may affect the half-life and metabolic clearance rate of oxytocin[9-11].

The uterus is innervated by the autonomic nervous system, which has a significant effect on the process of labour. There is evidence to suggest that parasympathetic activation promotes uterine contractility and increases circulation to the uterus and fetus, while sympathetic activation (e.g. from stressful, unfamiliar situations and surroundings, anxiety or fear) may trigger ineffective contractions and inhibit uterine circulation, or may in some cases give rise to long-lasting and more painful contractions[1,12]. Surroundings perceived as safe, familiar and friendly (eg. a woman's own home) and a supportive environment (eg. one to one nursing care and a lay labour companion of the woman's choice) are likely to promote endogenous oxytocin release by parasympathetic activation, and this could facilitate the progression of labour, as well as lead to the beneficial central actions caused by oxytocin.

Induction of labour with oxytocin

"Artificial initiation of uterine contractions which leads to progressive effacement and dilatation of the uterine cervix, and descent of the fetus", is the complete definition of IOL. Although IOL with oxytocin alone could be used in women with ruptured membranes, IOL with oxytocin alone is not recommended in women with intact membranes[13]. The aim should be to administer the minimum effective dose until adequate uterine contractions are established ie. at least three contractions per 10 minutes, each lasting at least 30 seconds, at the safest concentration, without adverse effects on the mother or her fetus. Oxytocin should be added to an intravenous infusion of normal saline, and large fluid volumes of very dilute oxytocin infusions should not be administered due to the risk of hyponatremia which could even lead to convulsions, mimicking eclampsia[14]. As the half-life of oxytocin is approximately 30 minutes, and about 40 minutes are needed for steady state plasma levels to be achieved after the commencement of an intravenous infusion, it is advisable to increase the oxytocin dose at intervals of about 40 minutes[11,15-20]. However, globally, the interval in between incremental doses varies from 15 minutes to 60 minutes, and starting doses as well as increments vary from 0.5 mU/min to 6mU/min. Stepwise (Arithmetical) incremental doses should be used rather than geometric increments (eg doubling), to reduce the risk of uterine over activity. Several low-dose as well as high-dose oxytocin regimens are used internationally, and there is no evidence to show which regimen is better.

The oxytocin protocol used in the Academic Obstetric Unit (AOU) at the Teaching Hospital Mahamodera, Galle (THMG), Sri Lanka, from 2006 up to date, has a high starting dose of 5mU/min, irrespective of parity and stepwise (arithmetical) increments at 40 minute intervals, until adequate uterine contractions are achieved, and then continued at that dose until delivery. If any woman was not having adequate uterine contractions at the maximum recommended dose for a particular woman, which depended on her parity, a failed IOL was diagnosed and a caesarean delivery was carried out (Table 1). If excessive uterine activity and or a non reassuring fetal heart rate pattern was detected,

the oxytocin dose was reduced or the infusion stopped altogether, a tocolytic administered (eg. Terbutaline 0.25 mg subcutaneously) and *in utero* fetal resuscitatory measures adopted, according to the circumstances. The adoption of this protocol in the AOU of THMG in 2006 resulted in improved birth outcomes in the unit[20]. It is important to note that the effects of any given dose of oxytocin in a specific woman is highly variable. While most women will respond to a dose of < 20 mU/min, a few will require >40 mU/min.

Table 1. Intravenous Oxytocin Infusion Protocol[20]

- Increase rate of oxytocin only to the point where good contractions are established
- (Duration 20 – 40 secs. with contraction free intervals < 3 minutes.)
- Maintain this rate. Reduce rate if contraction duration > 60 or contraction free interval < 1 min.
- Continue oxytocin at a higher concentration and dose after delivery

Time Hrs. mins	**500 ml N.Saline – Oxytocin units**	Drops / min (ml / min)	Dose mU / min	ml / hr	Total Vol. Infused -ml	Stage
0 - 0.40	**5 units (10 mU/ ml)**	10 (0.5)	5	30	20	I
0.40 - 1.20		20 (1.0)	10	60	60	II
1.20 - 2.00		30 (1.5)	15	90	120	III
2.00 - 2.40		40 (2.0)	20	120	200	IV
2.40 - 3.20		50 (2.5)	25	150	300	V
3.20 - 4.00		60 (3.0)	30	180	420	VI
4.00 - 4.40	**7.5 units (15 mU / ml) – New pack**	45 (2.25)	33.75	135	510	VII
4.40 - 5.20		50 (2.5)	37.5	150	610	VIII
5.20 - 6.00		55 (2.75)	41.25	165	720	IX
6.00 - 6.40		60 (3.0)	45	180	840	X
6.40 - 9.40	Multip – If not in established labour (cervical dilatation < 5 cm) with maximum dose above – Review. Continue maximum dose X 3 more hrs and Review again					XI
	Primips – If not in established labour (cervical dilatation < 5 cm) with maximum dose above – Review and continue as below					
6.40 - 7.20	**10 units (20 mU / ml) – New Pack – only Primips**	50 (2.5)	50	150	940	XII
7.20 - 8.00		55 (2.75)	55	165	1050	XIII
8.00 - 8.40		60 (3.0)	60	180	1170	XIV

Primips – If not in established labour (cervical dilatation <5 cm) with maximum dose above, Review and Continue maximum dose X 2 more hrs and Review again
If not in established labour (cervical dilatation < 5 cm) after another 2 hrs
= Failed induction ⟶ Caesarean delivery

Max. Concentration = 10u / 500ml (20 mU/ ml) – Rarely needed
Max. Dose and Rate = 60 mU /min (3ml / min, 60 dpm) – Rarely needed
Max. Duration = 11 hrs (Max Conc. reached in 6 hrs 40 mins in Multip, 8 hrs in Primips) – Rarely needed

Any given dose of oxytocin may result in sustained hypertonic uterine contractions and fetal hypoxia in one woman but no detectable effect on uterine contractility in another. Therefore, increments should be titrated against the uterine response, to achieve normal, physiological rates of labour progress for latent or active-phase, first stage of labour, keeping in mind that adverse effects of oxytocin on uterine activity and the fetus are exclusively dose-related. The focus must be essentially on the effects on uterine contractions and the fetus rather than the oxytocin dosage regimen.

Because oxytocin from the circulation does not pass the blood brain barrier, IOL with infusions of synthetic oxytocin do not give rise to the beneficial effects in the brain, as in the case of endogenous oxytocin[1,12]. Although recently there is a great interest on exploring the possibility outpatient IOL (ie. at the woman's own home) this would not be possible with oxytocin.

Pulsatile infusions of oxytocin

Unlike the episodic, narrow peaks of oxytocin observed in physiological labour, a continuous intravenous infusion of synthetic oxytocin would produce constant oxytocin levels in maternal blood, and may influence the pattern of uterine contractions and also contribute to the excessive uterine activity which could lead to fetal hypoxia by compromising the fetal blood supply[1,21]. In addition, prolonged exposure to synthetic oxytocin may desensitize oxytocin receptors, resulting in reduced contractility of the uterine muscles and an increased risk of postpartum haemorrhage (PPH)[22-23]. Furthermore, hypoxia and the accumulation of high concentrations of lactate in uterine muscle as a result of excessive uterine contractions, may also contribute to the increased risk of PPH[24]. As endogenous oxytocin from the hypothalamus is released in a pulsatile manner, several randomised controlled trials have been conducted to compare the effectiveness of pulsatile intravenous infusions versus continuous intravenous infusions. These trials have shown that: with pulsatile oxytocin regimens the total dose of oxytocin administered and the induction to delivery intervals are significantly reduced; excessive uterine activity is reduced; and there are no significant differences in caesarean delivery rates and outcomes for the baby[1,25-27]. Furthermore, it has been suggested that the pulsatile infusions may maintain myometrial receptor sensitivity and therefore maintain uterine contractility[28], thus not increasing the risk of PPH. Further research evidence is awaited, on the value of pulsatile intravenous oxytocin infusion regimens.

Discontinuing the oxytocin infusion in the active phase of the first stage of labour

It has been suggested that discontinuing the intravenous oxytocin infusion when the woman achieves 6cm dilatation of her cervix is better than continuing it. The postulated benefits include: reduction of uterine over activity and possible fetal compromise; reduction of total dose of oxytocin administered; and a possible reduction of caesarean delivery. However, the currently available research evidence is weak[29]. It is also possible that not continuing the intravenous oxytocin infusions may maintain myometrial receptor sensitivity like in pulsatile regimens and therefore not increase the risk of PPH. Further research evidence is awaited, on the value of stopping the oxytocin infusion in the active phase of the first stage of labour.

Safety concerns

The main risks of IOL with oxytocin are: uterine over activity leading to uterine tachystole (> 5 contractions for 10 mins) or uterine hypertonus (contractions lasting > 2 minutes), and non reassuring fetal heart rate patterns resulting from uterine over activity. The other well known and documented risks include: uterine rupture; PPH; maternal hypotension, tachycardia, arrhythmias, nausea, vomiting, headache, and flushing; water retention, hyponatraemia, myocardial ischaemia, seizures, and coma; and possible long-term adverse effects on behavioural development of children. However, as oxytocin continues to be widely used globally, and is also alleged to be misused, there is great concern regarding its use, and in fact it considered to be a "dangerous drug"[29]. Multiparous women carry a higher risk of uterine over activity, and if combined with scarred uteri, carry a higher risk of uterine rupture too.

Recommendations[20,30]

- All maternity units should have a protocol for oxytocin dosage, using an intravenous infusion pump, and a detailed, specific guideline on the procedures involved, as well as maternal and fetal monitoring.
- All intra partum care givers in a unit should understand and know the recommendations well, and they should be committed to follow same.
- After a risk benefit analysis is be carried out, there should be a clear indication to carry out IOL with oxytocin, as decided upon by an experienced specialist.

- Informed consent should be obtained from the patient.
- The membranes should be ruptured and the cervix favourable for induction (Modified Bishop Score ≥ 7/10).
- Pre induction cardiotocography (CTG) should be carried out for 20 minutes.
- One to one nursing care, and a lay labour companion of the woman's choice, should be available.
- Stepwise (arithmetical) incremental doses should be used rather than geometric (eg. doubling) increments, at 40-45 minute intervals.
- A partogram should be maintained.
- Continuous CTG monitoring is preferable.
- The dose of oxytocin should be increased and the intravenous infusion continued for two hours after the delivery.
- The use of oxytocin for IOL should be continuously monitored in all maternity units.

Conclusion

Synthetic oxytocin is widely used, globally, for IOL. However, its use has not been standardised, and there are allegations of it not being used properly and even abused at times. If used incorrectly, it can become a very dangerous medication, with serious adverse consequences to the mother and her fetus. Although endogenous oxytocin has additional, beneficial effects on the brain, these benefits are absent with exogenous oxytocin infusions. All maternity units should have a protocol for oxytocin dosage and a detailed, specific guideline on IOL with oxytocin, and it should be implemented under the direct supervision of an experienced specialist. It is important to have an interval of approximately 40 minutes between increments and to monitor the uterine contractions and the fetus carefully. The use of oxytocin for IOL should be continuously monitored in all maternity units.

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