

Oxytocin augmentation: Poison or potion in the multipara?

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Abstract

Oxytocin is one of the most commonly used drugs in obstetric practice but it is also the drug associated with the most preventable adverse events in childbirth. In this review we look at the use of oxytocin augmentation in the multigravida. We look at the concept of whether the multigravida is different to the primigravida. We provide a differential diagnosis for poor progress in the multigravida and look at the use of the partogram. Oxytocin recommended regimens are discussed and we look at how one can measure the effects of oxytocin. We summarize the evidence for the use of oxytocin in augmentation of the multigravida and then provide strategies to avoid problems if oxytocin is used in the multigravid patient. We conclude that the multigravida is very different to the primigravida and that use of oxytocin for augmentation in the multigravida should be strongly discouraged. If used, one should seriously consider the risks associated with oxytocin augmentation in the multigravida which includes uterine rupture. Use needs to be decided on a senior consultant level and it should only be used with continuous fetal monitoring, intrauterine pressure monitoring and only after all other causes of poor progress in the multigravida have been excluded. Consent, with explanation of all the risks associated with augmentation, should be obtained from the mother before augmentation is initiated. If oxytocin is going to be used for augmentation in the multigravida there must be a standardized protocol, there must be a doctor on site who is able to perform emergency caesarean section and who is available to respond to all emergencies. A low-dose, low-frequency dosing regimen should be used with weaning to the lowest dose necessary to maintain contractions.

Introduction

O'Driscoll and Meagher stated in their textbook of "Active management of labour" in 1986 that there are fundamental differences between a first and all subsequent births and that these differences are so great that they warrant the statement that the primigravida and the multigravida behave as different biological species.¹ If this is true, should we approach labour in the same way, and, should we be using the same methods to stimulate the uterus in primigravid and multigravid woman? Oxytocin is one of the most commonly used drugs in obstetric practice with 32% of woman receiving it during labour.² It has been associated with adverse events and medical negligence³ and it remains the drug most commonly associated with preventable adverse events during childbirth.⁴ In 2007 the Institute for Safe Medication Practices added intravenous oxytocin to their list of high-alert medications.⁵

In a recent survey of specialists registered with the South African Society of Obstetricians and Gynaecologists, 91% answered that they would use oxytocin to augment labour in a nulliparous woman and 33% stated that they would use

oxytocin for the same purpose in the multigravida. With regard to dosage regimens, 33% said that they would use the same regimen as used for a primigravida and 66% said that they would use a lower regimen.⁶ In 2009 Bentov et al. sent a questionnaire sent to all chairpersons of obstetrics and gynaecology departments in Israel and found that 85% of the chairpersons allowed the use of oxytocin augmentation for grand multiparous patients.⁷ In this review we will look at the evidence for using oxytocin as augmentation in the multigravid patient.

Definitions

As the management of labour depends to a large extent on the assessment of uterine activity, it is essential that the terminology is accurately defined.

In 2008 the National Institute of Child Health and Human Development arranged a workshop on electronic fetal monitoring.⁸ Uterine contractions were quantitated as the number of contractions during a 10-minute window, averaged over a period of 30 minutes. Contraction frequency alone was regarded as a partial assessment of uterine activity. Other parameters such as duration, intensity, and relaxation time between contractions were regarded as equally important in clinical practice. They used the following terminology to describe uterine activity:

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- Normal: up to 5 contractions in 10 minutes, averaged over a 30-minute window.
- Tachysystole: >5 contractions in 10 minutes, averaged over a 30-minute window.
- Characteristics of uterine contractions: They further recommended that tachysystole should always be qualified as to the presence or absence of associated FHR decelerations and that the term tachysystole applies to both spontaneous and stimulated labor. Lastly, they stated that the terms hyperstimulation and hypercontractility are not defined and should be therefore not be used.

Minimally effective uterine activity is defined as 3 contractions per 10 minutes averaging greater than 25 mm Hg above baseline.⁹

Augmentation of labour is the stimulation of contractions when spontaneous contractions have failed to result in progressive dilatation of the cervix or descent of the fetal head.

Is the multigravid patient a different species?

Duration of labour

Labour in the primigravida is most distinctive due to its longer duration, with an average rate of cervical dilatation of at least 1.5 cm/hour. The active phase in the primigravid patient is longer as inefficient uterine action is common and genital tract has never been stretched before. The normal duration of labour in a primigravida varies from 5.6 to 18 hours.¹⁰

In a multigravida the average rate of dilatation is at least 1.2 cm/hour and the active phase of labour is comparatively shorter as inefficient uterine action is extremely rare and the genital tract has been stretched.¹

Normal duration of the active phase in a multigravid patient should be 4 to 5 hours with a maximum duration that should not exceed eight to nine hours.¹¹ In a retrospective review of nearly 7,000 women with minimal intervention, the mean length of the second stage of the active phase of labour was 54 minutes for nulliparous women and 19 minutes for multiparous women.¹² In a primigravida the diagnosis of a prolonged second stage should be considered when the second stage exceeds 3 hours if regional anesthesia has been administered or 2 hours if no regional anesthesia is used compared to the multigravida where the diagnosis can be made when the second stage exceeds 2 hours with regional anesthesia or 1 hour without regional anaesthesia.⁹

Cephalopelvic disproportion versus obstructed labour

The term "cephalopelvic disproportion" should be restricted to the primigravida and for woman who have never given birth vaginally. It can only be used when the functional capacity of the pelvis is not known. Obstructed labour occurs in a multiparous patient who has already proved the functional capacity of the pelvis.

Obstructed labour in the multiparous patient is a different clinical entity to cephalopelvic disproportion and has far more serious consequences. The physiological response to cephalopelvic disproportion in the primigravida is atony. Multigravid patients respond to obstructed labour with an increase in contractions which can lead to severe complications for both the mother and child including uterine rupture.¹³⁻¹⁶

Rupture of the uterus

Uterus rupture in the primigravida who has not had misoprostol is a rare occurrence even when oxytocin is used. Rupture in the multigravida is a more common phenomenon. In the 5th CESDI report a focus group on cases involving a ruptured uterus without scarring showed that 12 women suffered from a ruptured uterus, 11 of these women were parous and most had high parities.¹⁷

Secondary arrest in uterine action

Secondary arrest in uterine action in the primigravid patient can be due to cephalopelvic disproportion but is most commonly associated with inefficient uterine action and oxytocin can safely be used.

Secondary arrest in the multiparous patient is a different entity and is usually associated with obstructed labour. Giving oxytocin in this scenario commonly leads to severe complications for the mother and fetus which also includes uterine rupture.¹⁸

Inefficient uterine contractions

Inefficient uterine contractions are common in a primigravid patient but very rare in a multigravid patient. Slow progress in the second stage of labour in a parous woman should never be assumed to be due to inefficient uterine action.

Partogram in the multigravid patient

In 2004 Van Bogaert published an audited series from a South African district hospital of 1398 partograms of spontaneous labours in multigravidas that resulted in vaginal delivery. The results of the audit indicated that the norms of the usual-care partogram did not reflect the facts of multigravid labour. He stated that the potential benefits of customizing the multigravid partogram included better distinction between normal and abnormal labour and more timely intervention ensuring the best pregnancy outcome for both the mother and baby.¹¹

Differential for poor progress in the multipara

To be able to assess the progress of labour in the multigravida, one should be aware of the following very important definitions, rules and guidelines. A differential to follow is the following;

Multiparous cervix

When a woman is seen during apparent labour, one of the first things to consider is whether she is in true labour. A multiparous cervix can easily be mistaken with a dilated cervix and this may lead to the false diagnosis of labour.

The rule of the four P's:

- Patient: assess hydration, pain relief and emotional support
- Passenger: Abnormal fetal lie or presentation:
 - Abnormal presentations include
 - occiput posterior position
 - brow presentation
 - face presentation
 - breech presentation.

Abnormal lies include transverse or oblique

Causes of abnormal lie or presentation can be divided into maternal, fetal or placental reasons

Maternal reasons include

- pelvic tumours such as ovarian masses or fibroids
- pendulous abdomen which causes anterior displacement of the uterus and therefore prevents engagement

Fetal reasons include

- an abnormally large baby where the head cannot engage. This can be caused for example by poorly controlled diabetes mellitus
- multiple pregnancy
- congenital abnormalities of the fetus which include hydrocephalus and other central nervous system abnormalities
- polyhydramnios
- preterm labour
- intra-uterine death

Placental reasons include

- an abnormally shaped placenta: lobata or succenturiata
- abnormally large placenta
- an abnormally short umbilical cord
- placenta praevia

3. Power: Inadequate uterine contractions are very uncommon in multiparous patients and another cause should be sought.
4. Passage: The passage has already been proven in a multiparous patient.

ACOG suggests that before augmentation is considered, an assessment of the maternal pelvis, cervix, fetal position, station, and well-being should be performed. If any of these abnormalities are found, it should be specifically addressed to ensure the optimal outcome of labour.⁹

Measuring the effects of augmentation

Measuring the effects of oxytocin on the uterus

At present there are only inexact technical means of measuring the effects of oxytocin on the uterus.¹⁹ There are two options namely internal or external monitoring. Internal monitoring makes use of an intrauterine catheter. External monitoring includes palpation and external tocodynamometry. In a randomized trial of 250 patients undergoing labor augmentation with contractions monitored by either external tocotransducers or intrauterine catheters, there were no significant differences between the groups regarding length of labour, dose of oxytocin, hyperstimulation, caesarean section rates or neonatal outcome.²⁰ ACOG guidelines state that despite this intrauterine pressure catheters may be beneficial for women when the evaluation of contractions is difficult because of such factors as obesity or lack of one-on-one nursing care or when response to oxytocin is limited.⁹ There have been no recent advances in measuring uterine activity.

Electronic fetal heart rate monitoring and augmentation

No overwhelming evidence has identified the most effective method of fetal heart rate surveillance when oxytocin is used for augmentation.⁹ The RCOG guidelines suggest that if oxytocin is being used for augmentation of labour, continuous electronic fetal monitoring should be used.²¹

Oxytocin

History

In 1895 Oliver and Schafer reported that extracts made from a pituitary gland extract caused a rise of blood pressure in anaesthetized animals when injected intravenously. This extract was made by grinding the pituitary gland of cattle in acetone to remove water and fat. Three years later Howell demonstrated that this activity was confined to the posterior lobe. Dale, in 1906, was the first to describe that this extract stimulated uterine muscle. For many years there was controversy on whether post-pituitary extract contained one or more active principles, and in 1928 Kamm et al. settled the dispute by separating two active preparations. Bell was the first to use post-pituitary extract in obstetric practice, and in 1909 he reported its efficacy in the treatment of post-partum haemorrhage. Two years later Hofbauer suggested its use in the treatment of uterine inertia. Bourne and Burn in 1927 used this extract for prolonged labour due to sluggish pains provided that the patient was primiparous with dilatation nearing completion. Reid (1946) and Eastman (1947) were the first to use this extract for prolonged labour in the primigravida.²² In 1953 the characterization and biosynthesis of oxytocin was described by du Vigneaud et al.²³ A Nobel prize was awarded for this discovery.²⁴

Production

Oxytocin is a hormone that is synthesized by the posterior pituitary gland and is secreted directly into the blood stream in a pulsatile manner. Synthetic oxytocin is an analogue of this hormone.

Pharmacology

Synthetic oxytocin is an octapeptide which has a half life of 3 to 10 minutes. Uterine response to oxytocin is within 3 to 5 minutes of intravenous administration and a steady state is reached at approximately 40 minutes after drug initiation or dose change.^{25,26} Oxytocin has a very unpredictable therapeutic index and the effects of any given dose of oxytocin in a specific woman may range from sustained hypertonic contractions and fetal asphyxia to no discernible effect on uterine contractility.¹⁹ Another important aspect is the down regulation of oxytocin receptors with increasing high dosages of oxytocin.

Warnings

Oxytocin has been added to the list of high-alert medications designated by the Institute for Safe Medication Practices.²⁷ A high alert medication is one that bears a heightened risk of harm when they are used incorrectly and that may require special safeguards to reduce the risk of error.¹⁹ Reports of adverse outcomes with the use of oxytocin has also led the Food and Drug Administration to place a black box warning on oxytocin stating that it should only be used for medically indicated inductions and augmentations of labor and not used for the elective induction of labour.²⁵

Side effects

Uterine hyperstimulation and water intoxication are the most commonly reported side effects. Uterine hyperstimulation is associated with uterine rupture and precipitous birth which may lead to traumatic injuries. Water intoxication is due to the

antidiuretic effect of oxytocin which results in absorption of water from the distal tubules of the kidneys. It can occur when more than three litres of salt free fluid are administered via the intravenous route and can result in convulsions, coma and death. Arrhythmias and blood pressure changes have also been described.

Fetal distress can be due to overstimulation of the uterus with oxytocin. If fetal distress occurs the oxytocin infusion should be immediately stopped and tocolysis should be given. If there is no improvement the fetus should be delivered within 30 minutes.²¹ Adverse neonatal effects associated with oxytocin include neonatal seizures, hyperbilirubinemia and retinal hemorrhage.

Dosage regimens for augmentation

A commonly used standardized oxytocin infusion protocol was described by Hayes et al. in 2008. They suggested using a uniform concentration. In this regime 10 international units (IU) of oxytocin is injected in one liter of normal saline which results in a concentration of 10 mU/mL. The same concentration could be made by putting 2.5 IU of oxytocin in 250 mL of normal saline. This initial infusion rate is started at 12 ml per hour which would give a dosage of 2 mU/min. They suggest that the dose adjustments should be based on the half-life of oxytocin and the time it takes to reach a steady state. Using the longer half-life of 10 minutes they suggest that the dose should be increased at 45 minute intervals. The maximum infusion rate is set at 16 mU/min or 96 ml per hour which is a level approximately 3 times that of the normal physiologic oxytocin level in spontaneous labor.²⁵

The RCOG guidelines from 2001 for induction of labour recommend a starting dose of 1–2 mU per minute which should be increased at intervals of 30 minutes or more. The minimum dose possible of oxytocin should be used. They suggest that the maximum dose should not exceed 32 mU per minute. Standardized dilutions and dose regimens include 30 IU in 500 ml of normal saline; hence 1ml/hr = 1milliunits per minute or 10 IU in 500 ml of normal saline; hence 3ml/hr = 1milliunits per minute.²¹

There is debate as to whether high dose or low dose regimens should be used. The ACOG guidelines state that the current data available does not support the notion that low-dose oxytocin regimens are superior to high-dose regimens for augmentation of labor. Low-dose regimens are associated with less uterine hyperstimulation and lower maximum doses. They state that high-dose regimens may be used for multiparous women, and that a wide variety of oxytocin regimens may be used for labor augmentation provided proper precautions are met.⁹ A number of authors disagree with this and feel that a low dose regimen is safer.²⁵ There is consensus that whatever regime is used it must be standardized and there must be a strict protocol that is adhered to by all staff.²⁸

Looking at the evidence for oxytocin in the multigravida

We performed a Medline and Google scholar search using the words LABOUR OR LABOR AND OXYTOCIN AND MULTIGRAVID OR MULTIGRAVIDA, OXYTOCIN AND AUGMENTATION and OXYTOCIN AND MULTIGRAVIDA OR MULTIGRAVID. We searched the Cochrane library using the

same search strategies.

Theobald et al. in 1948 published the first report of the use of a posterior pituitary extract therapy in 110 patients of which 49 were multigravid. They found that very few patients needed a maximum dose of more than 5 mU/min, regardless of parity.²²

In 1982 Gibb looked at the outcome of spontaneous labour in 847 consecutive multigravid patients admitted in spontaneous labour. Normal labour occurred in 88.5%. 98 patients were augmented with oxytocin. 12 patients did not improve with augmentation. 7 were delivered by caesarean section of which one was for a potentially preventable uterine rupture. The greatest neonatal morbidity was in the group with primary dysfunctional labour that did not improve with augmentation.²⁹

In 1983 Seitchik and Castillo studied the effect of oxytocin on multiparous patients in apparent spontaneous true labour with arrest of first stage labour resulting from uterine hypocontractility who then had a vaginal delivery. They excluded all woman who did not have vaginal delivery. All the patients had their membranes ruptured at least one hour before oxytocin was started. They compared using a computer which provided numerical analysis of contractility using a low dose oxytocin regimen with an initial dose of 1 mU/min. The dose was increased by 1 mU/min at intervals of not less than thirty minutes if the computer- defined level of myometrial activity was reached until a dose of 4 mU/min was reached. The dose was maintained at 4 mU/min for one hour and then was increased slowly. The control group did not labour with computer monitors and the oxytocin regimen was of the registrar's choice. 28 patients laboured with the computer and 32 patients were in the control group. They concluded that quantification of uterine contractility was a useful but imperfect technique for identifying hypocontractility and guiding oxytocin treatment in multiparous patients. They felt that the initial dose should not exceed 1 mU/min as 18% of the patients responded to this dose and that the rate of incrementation should not exceed 1 mU/30 minutes. They anticipated that 90% of patients would have cervical dilatation with doses of 1 to 4 mU/minute.³⁰

In 1988 Reddi looked at the intra-uterine pressure in 116 multigravid patients at term in spontaneous labour. They found a wide range of levels for patients who progressed normally and for patients whom had delay in cervical dilatation but if they looked at the means of the patients who failed to progress, the mean was lower. 54 women progressed normally. Of the patients treated with oxytocin 32 delivered vaginally and 23 patients had operative delivery.³¹

Ben-Aroya et al. published a retrospective case control series in 2001 on oxytocin use in grand-multiparous patients during the years 1989-97. 11 075 grand-multiparous women were identified and only 424 received intravenous oxytocin for augmentation. All of the women were monitored for fetal heart rate and uterine contractions. They found no significant differences between the oxytocin and the control groups in the rates of placental abruption, intrapartum fetal death, postpartum hemorrhage, uterine rupture, fetal distress, meconium-stained liquor, Apgar scores less than 7 at 5 min, Caesarean section rates, retained placentas and vaginal and cervical lacerations. They did find a significant increase in the rate of vacuum deliveries in the augmented group (3.5% vs.

1.4%, respectively; $p = 0.001$).³²

Selin did a retrospective study in 2000 to 2001 to investigate the use of oxytocin for augmentation in a Swedish hospital. He reviewed the data from 1263 singleton term pregnancies in spontaneous labour. Oxytocin was administered to 75% of primiparous patients and 38.1% of multiparous patients and the main conclusions were that oxytocin augmentation was undertaken in an unstructured manner, some women were inadequately treated and others were treated unnecessarily. Oxytocin recipients with labour dystocia underwent operative delivery to a higher extent than oxytocin recipients without labour dystocia and this suggested that the main reason for caesarean section was the underlying problem of labour dystocia rather than the oxytocin augmentation itself.³³

A number of case reports have described the danger of oxytocin augmentation and use in the multigravid patient. Siddiqui et al. in 2002 described a case of uterine rupture of an unreparable uterine rupture in a multigravid woman with an unscarred uterus who was augmented with oxytocin. The fetus survived but the woman needed a hysterectomy.¹⁶ Mazzone et al. published a case report in 2006 of a multigravid woman who had a spontaneous uterine rupture after induction with misoprostol and oxytocin.¹⁴ Dane et al. in 2008 reported a case of a multigravid woman who had a spontaneous uterine rupture after oxytocin use. Laparotomy and a hysterectomy were performed. The patient died 30 min after surgery.¹³ Sweeten et al. published a case series in 1995. Both cases of uterine rupture were associated with low-dose oxytocin augmentation in unscarred uteri. Both spontaneous and ruptures of previous unscarred uteri were associated with fetal bradycardia and uterine tachysystolic monitor contraction patterns that occurred at the onset of the second stage of labour.¹⁵

In the Cochrane Library we identified 3 reviews of interest. The reviews "High dose versus low dose oxytocin for augmentation of labour" and "Oxytocin versus placebo or no treatment for slow progress in the first stage of spontaneous labour" are still in the protocol phase.

Wei et al. reviewed "The Effect of Early Oxytocin Augmentation in Labour". The conclusions were that early oxytocin for augmentation in labour is associated with an increase in spontaneous vaginal delivery. For every 20 patients treated by early oxytocin augmentation, one additional spontaneous vaginal delivery was expected. They included nine trials comprising 1 983 women. Women in the early oxytocin group did have a higher incidence of an unpleasant experience and an increased chance of being dissatisfied with pain in labour. The risk of tachysystolic contractions was increased substantially with early oxytocin use. They also stated that the meta-analysis was relatively underpowered to detect rare serious maternal and neonatal adverse outcomes owing to the small sample sizes in most trials. In the trials included in this review only three trials looked at multiparous woman. The total number of multiparous woman included was only 112.³⁴

Avoiding problems with oxytocin

Errors involving the use of oxytocin are commonly dose related and often involve the lack of early recognition and

appropriate treatment of excessive uterine activity. Other errors include the mistaken administration of IV fluids with oxytocin for IV fluid resuscitation. Inappropriate elective induction of women who are less than 39 completed weeks' gestation can also lead to the incorrect use of oxytocin.⁵

Miller³⁵ in 2009 suggested the following points to improve safety

- The use a standardized, multidisciplinary protocol that clearly outlines the role of physicians, midwives, and nurses.
- A doctor on site who is able to perform an emergency caesarean section, who is aware of all patients receiving oxytocin and is available to respond to emergencies.
- Staff must be educated especially with reference to the differences in uterine activity in the different phases and stages of labour.
- The primary focus of oxytocin use must be attaining adequate uterine activity.
- Uterine muscle function must be promoted through adequate hydration and use of positioning.
- A low-dose, low-frequency dosing regimen to maximize pharmacologic dose response and avoid tachysystole.
- Isotonic intravenous fluids must be used with oxytocin to avoid hyponatraemia.
- The lowest dose possible must be used with weaning to the lowest dose necessary to maintain contractions.
- There must be intervention on any episodes of tachysystole and hypertonus must be avoided.
- If coupling and tripling of uterine contractions occur, oxytocin must be discontinued for 30–60 min, administer an intravenous fluid bolus (isotonic), and encourage the woman to adopt a side-lying position.
- Consider the use of intrauterine pressure catheters when uterine activity seems adequate to palpation but is not resulting in labour progress or in cases where it is difficult to evaluate uterine activity with palpation and external monitoring.
- Electronic fetal heart rate monitoring should be used when augmenting with oxytocin as this will help with early detection of suspicious or pathological fetal heart rate patterns associated with tachysystole.

Conclusion

Slow progress is common in the primigravida and uncommon in the multigravid patient.

Primigravid patients respond to disproportion with atony while multigravid patients respond with increased contractions. If misdiagnosed this can lead to an increased risk of uterine rupture with serious complications.

The evidence for using oxytocin in the multigravida is scanty and there is one meta-analysis which includes only 112 multigravid women. Most of the reports on oxytocin use in the multigravida are retrospective case control series. There are a number of case reports describing uterine rupture with the use of oxytocin in the multigravid patient.

The use of oxytocin for augmentation in the multigravida is discouraged unless it is used for a specific reason. If oxytocin is used it should only be used with well trained adequate staff, intrauterine pressure monitoring and continuous fetal monitoring.

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